NICE National Institute for Health and Care Excellence

# Highly Specialised Technology Evaluation

# Afamelanotide for treating erythropoietic protoporphyria [ID927]

# Evaluation Report

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

# Afamelanotide for treating erythropoietic protoporphyria [ID927]

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*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

## Final evaluation document

# Afamelanotide for treating erythropoietic protoporphyria

## 1 Recommendations

1.1 Afamelanotide is not recommended, within its marketing authorisation, for preventing phototoxicity in adults with erythropoietic protoporphyria (EPP).

1.2 This recommendation is not intended to affect treatment with afamelanotide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### Why the committee made these recommendations

EPP is a condition in which exposure to light causes painful and debilitating reactions in the body. Because there is no treatment, people try to avoid light. This limits their ability to do normal daily activities, and leads to feelings of social isolation, anxiety and poor quality of life.

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.

The cost-effectiveness estimates for afamelanotide are all very much higher than the range normally considered acceptable for highly



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specialised technologies. This is despite taking into account the impact the condition and technology have on quality of life, 'disability', and likely non-health-related benefits such as improving employment and study options, and the fact that afamelanotide is an innovative treatment.

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.

# 2 The condition

2.1 Erythropoietic protoporphyria (EPP) is a genetic disorder. It is caused by impaired activity of the enzyme, ferrochelatase. The condition results in excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma and red blood cells. EPP is a cutaneous porphyria, and the major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and some types of artificial light. The skin may become painful, swollen, itchy and red, and skin erosions can also occur. A phototoxic reaction typically lasts between 2 days and 3 days. However, it can last 10 or more days, with severe pain and loss of sleep. These symptoms, along with anxiety and social isolation because of sunlight avoidance, can have a profound impact on quality of life. Over time, light exposure can cause thickening of the skin on the knuckles and scarring on the face. A small proportion of people with EPP may have important complications related to liver and gallbladder function.

# 3 The technology

3.1 Afamelanotide (Scenesse, Clinuvel) activates the synthesis of eumelanin mediated by the MC1R receptor. Eumelanin contributes to photoprotection by: strongly absorbing UV and visible light (acting as a filter); antioxidant activity; and inactivating the superoxide anion and increasing the availability of superoxide dismutase to reduce oxidative stress. Afamelanotide has a UK marketing authorisation under

'exceptional circumstances' for 'the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)'. It is administered as a subcutaneous dissolving implant. One implant is administered every 2 months before expected and during increased sunlight exposure, for example, from spring to early autumn. Three implants are recommended annually, depending on the length of protection needed, and the maximum recommended dose is 4 per year. Treatment with afamelanotide would be life-long. The marketing authorisation stipulates that afamelanotide should only be prescribed by specialist clinicians in recognised porphyria centres, and that it should only be given by a clinician trained and accredited by the marketing authorisation holder to insert the implants.

3.2 The most common side effects with afamelanotide seen in clinical trials were nausea and headache, and discolouration, pain and redness at the implant site. These were generally mild and affected about 1 in 5 of people. Afamelanotide is contraindicated for people with reduced liver or kidney function. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 Afamelanotide has not been launched in the UK, but the company has stated that the cost of an implant will be £12,020 (excluding VAT).

# 4 Consideration of the evidence

The evaluation committee (see section 6) 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). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

## *Nature of the condition*

### Burden of disease

4.1 The committee heard from patient experts that phototoxic reactions can be triggered by even a few minutes of exposure to light, particularly when light is at its most intense on sunny days in the summer, and the reaction itself can last for days. The patient experts described the pain during a reaction as intense, intolerable and not relieved by pain medication. Furthermore, the pain is neuropathic, meaning that even a light touch to the skin during a reaction exacerbates the pain. Patient experts also reported an all-encompassing tiredness associated with a phototoxic reaction. Sometimes, the phototoxic reactions are accompanied by redness and swelling but often there are no external signs. The committee acknowledged that phototoxic reactions can be associated with intense pain and extreme tiredness that lasts for days.

4.2 People with erythropoietic protoporphyria (EPP) report the symptoms of phototoxic reactions as being debilitating, preventing them from being able to do day-to-day activities. They also say that, without anything to treat the pain or the phototoxicity, their only option is to wait for the phototoxic reaction to stop and their bodies to heal. The patient experts explained that, because phototoxic reactions are unbearable, they will do anything it takes to prevent them. In the absence of any treatment that prevents phototoxicity, this involves avoiding light. The patient experts reported that they constantly assess the light conditions and measures they need to take to minimise the risk of a phototoxic reaction. This, and the fear of a phototoxic reaction, are major and constant causes of anxiety. People with EPP report that they often turn down invitations to activities or events, which leads to feelings of social isolation and compromises family life because they cannot take part in outdoor activities or go on holidays. A patient expert explained that his children cannot understand why he cannot join in, which leads to guilt and depression. The patient experts stated that they have had to adapt their

careers to manage the measures they need to take to avoid light. The British Porphyria Association stated that its members reported choosing jobs that are indoors with minimal travel and even night jobs to minimise light exposure. A study from Holme et al. (2006) reported that most people with EPP were in employment or education but that 47% (n=66/127) of those in work felt their choice of profession had been influenced by their condition. Education choices are similarly affected. The British Porphyria Association stated that, for some families, the children may take on caring for a parent with EPP or other responsibilities that the parent cannot do because of their EPP. It also noted that EPP can place a financial burden on families because of loss of earnings and the expense of measures to protect against sun exposure. The committee heard from a clinical expert that EPP either causes debilitating pain if people with the condition try to live a normal life, or anxiety and isolation if they try to avoid the pain by staying indoors. Testimonies received during consultation emphasised the extent of the burden of the condition, including the physical pain from light exposure, and the severe anxiety and social isolation from having to avoid light. The committee was clear that EPP can have a far reaching impact on the lives of patients and their families, resulting in poor quality of life.

### Current treatments

4.3 The committee heard that there is no effective treatment for the underlying cause of EPP, to protect against phototoxicity or to relieve pain caused by it. 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 and associated adverse effects (such as an increased risk of death from lung cancer and cardiovascular disease with beta carotene, and an increased risk of developing skin cancer with narrow band UVB). Light avoidance and covering the skin are the only options available to people with EPP. A clinical expert noted that light blocking creams like Dundee cream do not provide complete blocking of light and are also not ideal because they are

noticeable on the skin. The committee concluded that there is no effective treatment for preventing phototoxicity caused by EPP, so there is an unmet need for an effective treatment.

### Diagnosis

4.4 The committee noted that, like many rare conditions, people with EPP have experienced delays in getting a diagnosis. The British Porphyria Association stated that the median age of diagnosis is 22 years, although for most people the age of onset of EPP is at birth or soon after; 1 reason is that awareness and knowledge of the condition is very low, both among the public and in general medical practice (outside of specialist porphyria centres). People with EPP have reported that other people not understanding their experience, when it is not accompanied by external signs of phototoxicity, has led them to feeling isolated and it means they have often had the condition without support for years. The committee concluded that delay in the diagnosis of EPP is a problem, and could result in people with the condition developing automatic behaviour over time to avoid light and so phototoxic reactions.

### Variation in symptoms

4.5 The committee discussed the variation in symptom severity in people with EPP. A clinical expert stated that most people (around 70) under his care have 'classical' EPP. These people could have between 2 minutes and 40 minutes of sun exposure before experiencing a phototoxic reaction. However, the pain severity and duration of a phototoxic reaction are similar among these people. The clinical expert noted that he had treated around 16 people with mild EPP, who could be in very strong sunshine for several hours without a phototoxic reaction. Both clinical experts stated that people with mild EPP may not need, or choose, to have afamelanotide. The company stated that it is not possible to measure the severity of EPP. The committee acknowledged that there is some variation in how long people with EPP can be exposed to sunlight without

a reaction. It concluded that any variation in patient experience of the condition was unclear because of a lack of data.

## *Impact of the new technology*

### Clinical benefits and uncertainties

4.6 The committee discussed the evidence available for afamelanotide, noting that there were 4 randomised placebo-controlled trials (CUV017: 100 patients and 12-month duration; CUV029: 76 patients and 9-month duration; CUV030: 77 patients and 6-month duration; CUV039: 94 patients and 6-month duration ). The committee noted that, although the trials were designed so that the patients would not know what they were having, some patients may have known they were having afamelanotide because it caused their skin to tan. The committee understood that CUV039 was the pivotal trial and this was carried out in the US. It noted that the other trials had included people from the UK and other European countries. It also noted the view of the clinical experts that the trials were generalisable to clinical practice in England. The committee was disappointed and concerned to note that the company submission did not include complete trial details, such as full baseline data. It meant that the ERG was unable to independently assess the methods and reliability of the clinical-effectiveness assessment of afamelanotide in the clinical trials. The committee understood that the ERG had, where possible, extracted data from publications available to supplement the information available in the company submission. The ERG pointed out 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. The company highlighted that it had been through a long and complex regulatory process and, based on input from patient and clinical experts, afamelanotide had been granted a marketing authorisation under exceptional circumstances. This was because the EMA recognised that the comprehensive data on the efficacy and safety required for a regular marketing authorisation could

not be generated but that the benefit-risk balance based on the evidence available was favourable. The company stated that the evaluation committee should not reopen the conclusions made by the EMA's Committee for Medicinal Products for Human Use about the efficacy of afamelanotide. 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. 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 population health gains 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.

4.7 The committee noted that the clinical trial results indicated a relatively small but statistically significant increase with afamelanotide compared with placebo in the median amount of time a person could spend in daylight (between 10:00 and 15:00) without pain (CUV029: 5.63 hours with afamelanotide and 0.75 hours with placebo, p=0.006; CUV039: 69.4 hours and 40.8 hours respectively, p=0.044), and a decrease in the median number and severity of phototoxic reactions (CUV029: 77 reactions with afamelanotide and 146 with placebo, p=0.04). The data on severity are not reported because the company has deemed them to be commercial in confidence. It heard from patient experts and the British Porphyria Association that even small benefits such as being able to spend an extra few minutes in daylight or having fewer phototoxic reactions could have a large impact on people's lives. For example, a few minutes may allow a person with EPP to get into a shop or travel to work. A patient expert also explained that a few minutes in full daylight would typically equate to many more minutes, and even hours, in dappled light (shade). This would mean people with EPP would be in a much stronger

position to manage their lives without being debilitated by the disease. The comments received following consultation strongly echoed these statements. Additionally, the committee understood that the company considered conditioned light avoidance behaviour was a likely reason the trial outcomes showed relatively small benefits with afamelanotide. The committee was aware that, in the trials, patients were asked to voluntarily expose themselves to light and the duration of light exposure was measured. It agreed that conditioned light avoidance could have impacted on the trial results, but it was unclear to what extent. The committee heard from a patient expert who had had afamelanotide that it had taken time to unlearn this behaviour and increase the amount of time spent in light. It understood that, with time, it was possible that conditioned light behaviour could be unlearnt, but it was unclear how long this would take and whether it would vary from person to person. A clinical expert stated that the length of the clinical trials may have been too short for patients to have changed this ingrained behaviour. 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. The committee concluded that the trials had shown relatively small benefits with afamelanotide, and that clinical and patient experts believed the effects would be greater than those seen in the trials.

4.8 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. A clinical expert stated that the increase in the first 6 months was important, and speculated that the climate in Switzerland and Italy may have contributed towards the

stabilisation in scores beyond 6 months. The committee was aware that, in the trial, there was also an improvement in quality-of-life scores in the placebo arm; the company explained that this was likely because EPP is a neglected disorder and the opportunity to enrol in a trial would have provided patients hope for the first time. The committee considered that these results were in contrast to the discussions around the impact of conditioned light avoidance. The committee concluded that afamelanotide was likely to improve quality of life but the true size of any improvement was uncertain.

4.9 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. The committee was convinced that patients valued the benefits of afamelanotide but remained concerned that no data were available to quantify this impact. It heard from the company that the issue was of a lack of scientific tools to capture the true impact of the disease and so the benefit of afamelanotide, rather than a lack of data. The company and experts stated that an indicator of the effectiveness of afamelanotide was the compliance rate of about 94% despite the cost and time associated with travel for treatment. The committee appreciated the compliance rate was high but noted that it was not a quantifiable marker of effectiveness. It concluded that, although there was a substantial difference between patient and clinical expert testimonies and trial

outcomes and although it believed afamelanotide did offer a clinical benefit, the size of the benefit remained uncertain.

### Quality of life

4.10 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 from clinical experts that these measures were not appropriate for capturing the quality of life of people with EPP. The committee further noted that the company had developed a condition-specific quality-of-life questionnaire called the EPP-QoL, but that this had not been fully validated. The committee noted that, to be appropriately validated, it should be suitable to support labelling claims granted by the EMA and the US Food and Drug Administration. Furthermore, the EPP-QoL had been modified while the trials were ongoing and data were being collected, and some questions were removed. The company stated that it had consulted with EPP experts to develop the EPP-QoL, but was unable to provide the committee with a response to whether it had used standard methods for developing and validating this tool. The committee was particularly concerned that a question relating to capacity to go to work or school was removed from the EPP-QoL, and that there were no questions relating to the impact of pain, because these aspects were stated by people with EPP to be of great importance to them. The company stated that it had not included a question on how pain affected patient's quality of life because it was not considered to be comprehensive in describing symptoms during a reaction. Following consultation, the company also stated that, because patients avoid light, it is rare for them to experience pain and so it would not yield useful results. The committee appreciated the nuances of capturing the burden of the condition because of light avoidance but, based on extensive patient testimonies, it maintained that pain was an important outcome. A clinical expert added

that, because of small numbers of patients, there was a limit to how much the tool could be optimised, and that additionally seasonal variations were important in interpreting the results. They explained that, ideally, a quality-of-life assessment should be done during each of the 4 seasons to capture these variations. The committee considered that any quality-of-life measure should capture the aspects of the condition that affect a person's quality of life and, for EPP, this should capture quality of life during and between phototoxic reactions. It also considered that the EPP-QoL did not appear to capture some aspects of EPP that people with the condition and their clinicians report as important. However, the committee was aware of the substantial feedback from stakeholders that EPP-QoL is a relevant tool. The committee concluded that it would take the EPP-QoL into account in its decision-making but that, without full and appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide.

4.11 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 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. 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. Following consultation, clinical experts stated that the DLQI had not been validated

specifically for EPP, whereas the EPP-QoL was developed by experts in EPP and queried the committee's preference for DLQI. The committee noted that DLQI data from the trials had shown a modest but not statistically significant improvement in quality of life with afamelanotide and, in a large observational study, it had been shown to be sensitive to the impact of EPP on people with the condition. The committee noted that the same issue seen with EPP-QoL on seasonal variations (see section 4.10) applied to the interpretation of DLQI scores. Importantly, the committee explained that the DLQI could be mapped, using a validated algorithm, to EQ-5D to generate utility values to be used in a cost-effectiveness model. 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 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. The committee concluded that results based on DLQI were relevant to its decision-making, alongside results based on EPP-QoL.

## *Cost to the NHS and value for money*

### Company's model

4.12 The committee discussed the company's model and noted that a large amount of information relating to the model structure and assumptions was considered confidential by the company. The committee was disappointed that this meant that its discussions and decisions on the model could not be fully described publicly. It noted that the modelled benefits were based on pooled trial data on EPP-QoL collected at 4 months. It also noted that data were collected at 6 months, although from a smaller proportion of the trial population, but these data had not

been presented by the company. The committee considered that the longer follow-up data could be useful to see, particularly because it heard from a clinical expert that the benefits of afamelanotide may take time to become apparent if people adapt their conditioned behaviour gradually. The committee noted that the company had stratified the data to represent mild, moderate and severe disease by splitting the EPP-QoL scores into 3 equal ranges. It heard that, in the absence of validated cut-offs for EPP severity using the EPP-QoL, the company considered the arbitrary division of the EPP-QoL into thirds to be the fairest approach. The committee considered the validity of the EPP-QoL to be uncertain (see section 4.10) and concluded that the company's arbitrary approach to stratifying disease severity added to this uncertainty.

4.13 The committee noted that the company's analyses estimated disability-adjusted life years (DALYs) averted, and the incremental cost-effectiveness ratios (ICERs) were presented as cost per DALY averted. The company stated that, because of the unique nature of the condition and because there was of a lack of available robust data from which to derive utility values, it did not support using utility values to quantify quality of life. Rather, the company noted it was more appropriate to consider the impact of EPP and afamelanotide on people's quality of life in terms of disability. The committee noted that the NICE interim process and methods guide of the Highly Specialised Technologies Programme states that benefits of a technology should be expressed as utility values to determine the impact of a technology on quality and quantity of life, that is, quality-adjusted life years (QALYs) gained. It stated that using QALYs was in the NICE reference case (that is, the preferred methods to be applied consistently across evaluations), and that this was important to allow consistent evaluation across therapy areas. 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. The committee noted, however, that it could consider non-reference case

methods alongside those in the reference case if there is a strong enough 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. The committee questioned further why the company preferred to map from other diseases that may not be fully representative of EPP rather than directly use patient-level quality-of-life data collected in EPP trials. The committee understood from the company that it needed a proxy condition to derive disability weights because these were not available for EPP (see section 4.15). However, it did not consider that the company had made a strong case for using disability weights to justify the added uncertainty of using a proxy condition rather than direct trial data.

4.14 At the second evaluation meeting, the company stated that it did not consider the DALY approach to be more appropriate than QALYs. Rather, it considered that no approach was entirely suitable to reflect the complexities in EPP, and that the DALY model was its attempt to present an alternative approach. The committee was aware that the ERG had provided a simple adaptation of the company's model, which showed that the differences between the DALY and the QALY did not matter in this instance because both approaches produced similar results and so would not affect the committee's conclusions. The committee concluded that, although it would take a DALY-based model into account in its decision-making, its preferred approach was the one aligned with the NICE reference case.

4.15 The committee noted that, in its DALY-based framework, the company had used disability weights from the World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) to model the disability associated with mild, moderate or severe EPP. However, because the GBD survey had not asked about EPP, the company had used weights for a proxy condition it considered similar to EPP in its modelling. The committee noted that the company considered the proxy condition to be confidential. It appreciated similarities between some

important aspects of the conditions but was aware of other important aspects that were not similar. The committee stated that it was unclear about the extent to which the proxy condition reflected the disability associated with EPP and whether it was valid to assume that the disability associated with mild, moderate or severe disease in the proxy condition would correspond with mild, moderate or severe EPP. Furthermore, it reiterated its concerns about the uncertainties surrounding the stratification of people with mild, moderate and severe EPP based on EPP-QoL data collected in the trials (see section 4.12). The committee concluded that the proxy condition used by the company may not fully capture the experience of people with EPP, and the assumption that it is similar to EPP in general and at different levels of severity was not sufficiently robust.

### ERG's exploratory analyses

4.16 The committee discussed the alternative approach taken by the ERG in its exploratory base case to model the benefits of afamelanotide. That is, using DLQI data from one of the clinical trials and mapping this to EQ-5D to derive utility values using a published algorithm. 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. 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.

### Treatment duration

4.17 The committee noted that the company assumed in its modelling that the benefits of afamelanotide would be immediate and would remain constant for the whole year, including after the last implant. It also noted that the ERG had tested some assumptions around this in sensitivity analyses. These included analyses around how long it would take for a person to experience the benefits of afamelanotide and how long the treatment effects of afamelanotide would persist after the last implant of the year. The committee considered that it was likely that it would take some time before patients would experience the benefits of afamelanotide, not least because time would be needed to unlearn conditioned behaviour associated with light avoidance. The clinical experts described how the protective antioxidant effect of afamelanotide needed time to build up after the first implant but would persist for a period of time after the last implant. The committee noted the lack of data to support these assumptions. However, on balance, it concluded that the ERG's analyses assuming that the effect of afamelanotide would build up over the first 2 months (as the ERG had modelled in its base case), and that the treatment effect would slowly decrease over 6 months after the last implant, used plausible assumptions.

### Dosage of afamelanotide

4.18 The committee discussed the likely use of afamelanotide in clinical practice. It was aware that the marketing authorisation recommended administering an implant every 2 months before expected, and during increased, sunlight exposure from spring to early autumn, and recommended a maximum of 4 implants per year. 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 (based on what had been seen in

expanded access and commercial distribution of the drug across the expected EPP population; this number is not reported because the company has deemed it to be commercial in confidence) but had provided no detail on whether it was generalisable to people using afamelanotide in clinical practice in England. The committee concluded that it should take into account that people may have up to 4 implants in its decision-making.

### Cost-effectiveness results

4.19 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained. The committee discussed the QALY gains associated with afamelanotide, noting that EPP is not associated with a reduced life expectancy and, as such, afamelanotide does not extend life. The QALY gains were therefore driven by improvements in quality of life, which were relatively modest in both the company's base case and ERG's exploratory analyses. The undiscounted incremental DALYs in the company's base case and the ERG's estimated incremental QALYs based on the company's use of a proxy disease cannot be reported because the company has stated that these are commercial in confidence. Over the life-time of a patient, the undiscounted QALYs gained with afamelanotide in the ERG's exploratory base case were 0.56, and did not exceed 0.8 in the ERG's sensitivity analyses. The committee recalled that there was uncertainty around the utility estimates (and the disability estimates in the company's model), and that the full benefits of afamelanotide were not quantified. However, it concluded that accounting for this was unlikely to result in an incremental QALY gain of at least 10.

The committee concluded that the criteria for applying a QALY weight was not met.

4.20 The committee noted that the following key ICERs were all over £100,000 per QALY gained:

- the company's base case: £278,471 per DALY averted (£278,386 per QALY gained when converted to a QALY-based ICER using the ERG's simple QALY adaptation)
- the ERG's exploratory simple QALY adaptation using utilities from the literature for the company's proxy condition: £1,726,802 per QALY gained
- the ERG's exploratory base case assuming 3 implants per year, gradual onset and 2-month attenuation of the relative treatment effect (see sections 4.17 and 4.18): £1,605,478 per QALY gained
- the ERG's exploratory base case with the committee's preferred assumptions on gradual onset and 6-month attenuation of the relative treatment effect: £1,343,359 per QALY gained
- the ERG's exploratory base case assuming 2 implants per year: £1,337,494 per QALY gained
- the ERG's exploratory base case assuming a maximum of 4 implants per year: £1,785,957 per QALY gained.

The committee concluded that the ICERs based on its preferred methods and assumptions were likely to be between £1,343,359 and £1,785,957 per QALY gained. The committee noted that the ICERs based on EPP-QoL, and 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. The committee considered this to be very similar to the ERG's exploratory base-case ICERs.

### *Impact of the technology beyond direct health benefits and on the delivery of the specialised service*

4.21 The committee discussed the impact of afamelanotide beyond its direct health benefits and the testimony of the patient experts. It noted that people with EPP might alter their career plans to accommodate the effects of their disease and might be unable to take up enhanced career opportunities. The committee considered that people who had already taken a certain career path because there had historically been no treatment options would not necessarily change career if they had afamelanotide, but appreciated that it would allow them the freedom to pursue more opportunities. Additionally, people diagnosed with EPP starting out in their careers may not need to alter their preferred career plans to accommodate managing their EPP. Furthermore, the committee was unclear about the financial implications of these career choices. It acknowledged that afamelanotide reduced phototoxic reactions in the clinical trials and that this could affect a person's ability to work and study. However, 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. It also noted that only 1 scenario reduced the ICER from £278,471 per DALY averted in the company's base case to less than £100,000 per DALY averted. This was based on the assumption that people having afamelanotide receive 90% of the mean wage whereas people having standard care earned only 10% of the mean wage. The committee noted that this assumption was very strong and was not in keeping with the findings on choice of occupation from Holme et al. (2006; see section 4.2). The committee concluded that afamelanotide would have an impact beyond direct health benefits but that quantifying this was difficult. It concluded that it was highly unlikely the impact would be sufficient to overcome the committee's concerns about value for money

(see section 4.20), and also unlikely to bring the most plausible ICERs to a level considered to be an acceptable use of NHS resources.

### Managed access agreement

4.22 Following consultation, the British Association of Dermatologists queried the possibility of developing a managed access agreement (MAA) to address the uncertainties. The committee noted that it could consider an MAA proposal if all stakeholders collaborated to develop and support it. The committee noted that it had not been presented with a proposal but discussed whether a proposal could potentially address the 2 main elements of an MAA:

- Data collection to reduce uncertainty at the end of the MAA: the committee was aware of the significant uncertainties in this evaluation and discussed whether further data collection would address the uncertainties. It heard from the company that there was a lack of appropriate instruments to enable robust data collection and it was not in support of redesigning clinical studies. The company also highlighted that the EMA considered it to be unethical to conduct further clinical trials in patients. Instead, the company stated that they intend to collect post-authorisation safety data and to validate the EPP-QoL tool and use it to collect further data in the UK. 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.

- Sharing of financial risk during the MAA: the committee noted that an MAA would typically include financial components that would apply while it is in force to share the financial risk with the NHS. The company stated that it offered a single price across countries and there was no scope for this to differ in England. However, it was willing to enter into discussions with NHS England to cap

financial risk to the NHS. The committee considered this in the context of the cost-effectiveness estimates discussed in section 4.20. The committee was aware that these estimates (ranging between £1,343,359 and £1,785,957 per QALY gained) were very much above what could be considered an acceptable use of NHS resources, making it highly unlikely that afamelanotide has a plausible potential to be considered cost effective.

## *Conclusion*

4.23 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 without a phototoxic reaction 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. 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 substantial difference between the trial results and the expert testimonies, anecdotal evidence of those present at the meeting, and the consultation comments. The committee agreed that afamelanotide was effective and that the true benefit 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. On balance, it concluded that the ERG's modelling approach was more plausible than the company's because it used trial data in a more direct way. The committee also concluded that it was unclear on how to interpret the non-validated EPP-QoL data and proxy-condition weights, which the company had used to model the benefits of afamelanotide. It concluded that the ERG's exploratory results were also highly uncertain because the

benefits of afamelanotide may not have been fully captured by the DLQI measured in the clinical trials.

4.24 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. It also considered that afamelanotide did not meet the criteria for QALY weighting to be applied, even if qualitative evidence on the extent of benefit and impact beyond direct health benefits was taken into account. The committee considered that an MAA would not have the plausible potential to reduce the uncertainties identified during the evaluation or to reduce the financial risk to the NHS. The committee was therefore unable to recommend afamelanotide for use in the NHS in England.

# 5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
May 2018

# 6 Evaluation committee members and NICE project team

## *Evaluation committee members*

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## *NICE project team*

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Mary Hughes, Aminata Thiam**
Technical Leads

**Raisa Sidhu**
Technical Adviser

**Joanne Ekeledo**
Project Manager

ISBN: [to be added at publication]

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**HIGHLY SPECIALISED TECHNOLOGY EVALUATION**

**APPEAL HEARING**

# Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927]

# Decision of the panel

## Introduction

1. An appeal panel was convened on 30 July 2018 to consider an appeal against NICE's final evaluation determination, to the NHS, on afamelanotide for treating erythropoietic protoporphyria (EPP) [ID927].

2. The appeal panel consisted of:

| | |
|---|---|
| • Prof Jonathan Cohen | Chair |
| • Mr Tom Wright | Non-executive director |
| • Dr Biba Stanton | NHS representative |
| • Mr Uday Bose | Industry representative |
| • Mr Colin Standfield | Lay representative |

3. None of the members of the appeal panel had any competing interests to declare.

4. The panel considered appeals submitted by the British Association of Dermatologists, the International Porphyria Patient Network, the British Porphyria Association and CLINUVEL (UK) Ltd.

5. The British Association of Dermatologists (BAD) was represented by:

| | |
|---|---|
| • Dr Robert Sarkany | Consultant Dermatologist |
| • Prof Lesley E Rhodes | Professor of Experimental Dermatology, Honorary Consultant Dermatologist, Director of the Photobiology Unit |

6. The International Porphyria Patient Network (IPPN) was represented by:

| | |
|---|---|
| • James Rawnsley | EPP patient representative |
| • Emily MacKenzie | Brick Court Chambers |
| • Dr Jasmin Barman-Aksözen | Co-founder and Vice-Chair of the International Porphyria Patient Network |

7. The British Porphyria Association (BPA) was represented by:

| | |
|---|---|
| • John Chamberlayne | BPA Chair |
| • Dr Geoff Sloan | EPP patient representative |

8. CLINUVEL (UK) Ltd was represented by:

| | |
|---|---|
| • Lachlan Hay | General Manager, CLINUVEL (UK) Ltd |
| • Marie Manley | Sidley Austin LLP |
| • Sarah Love | Brick Court Chambers |

9. In addition, the following individuals involved in the evaluation were present and available to answer questions from the appeal panel:

| | |
|---|---|
| • Dr Peter Jackson | Highly Specialised Technologies (HST) Evaluation Committee Chair |
| • Mrs Sheela Upadhyaya | Associate Director – HST, NICE |
| • Mr Meindert Boysen | Centre for Health Technology Evaluation Director, NICE |
| • Miss Aminata Thiam | Technical Lead, NICE |
| • Mr Francis Pang | HST Evaluation Committee Member |
| • Mr Jeremy Manuel | HST Evaluation Committee Member |

10. The appeal panel's legal adviser Alistair Robertson was also present.

11. Two members of the NICE appeals panel (Mr Christopher Rao and Prof Ruairidh Milne) were present as observers but did not participate in any of the discussions of the appeal panel, or in the decision-making.

12. Under NICE's appeal procedures, members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

13. There are two grounds under which an appeal can be lodged:

1) **<u>Ground One</u>: In making the assessment that preceded the recommendation, NICE has:**
   **(a) Failed to act fairly; and/or**
   **(b) Exceeded its powers.**

2) **<u>Ground Two</u>: The recommendation is unreasonable in light of the evidence submitted to NICE.**

14. The Vice Chair of NICE (Dr Rosie Benneyworth) in preliminary correspondence had confirmed that:

- The British Association of Dermatologists (BAD) had potentially valid grounds of appeal as follows: Ground 2.

- The International Porphyria Patient Network (IPPN) had potentially valid grounds of appeal as follows: Grounds 1(a), 1(b) and 2.

- The British Porphyria Association had potentially valid grounds of appeal as follows: Ground 2.

- CLINUVEL (UK) Ltd had potentially valid grounds of appeal as follows: Grounds 1(a) and 1(b).

15. The evaluation that is the subject of the current appeal provided advice to the NHS on the use of afamelanotide for the treatment of EPP.

16. EPP is a genetic disorder. It is caused by impaired activity of the enzyme, ferrochelatase. The condition results in excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma and red blood cells. EPP is a cutaneous porphyria, and the major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and some types of artificial light. The skin may become painful, swollen, itchy and red, and skin erosions can also occur. A phototoxic reaction typically lasts between 2 days and 3 days. However, it can last 10 or more days, with severe pain and loss of sleep. These symptoms, along with anxiety and social isolation because of sunlight avoidance, can have a profound impact on quality of life.

17. During the appeal hearing, Dr Sloan, Dr Barman-Aksözen and Mr Rawnsley gave personal testimony about their experience of EPP as patients. They emphasised the profound suffering caused by EPP and the pervasive impact of the disease on their lives. They also discussed their own experiences of treatment with afamelanotide. The panel found their testimony powerful and moving, and would like to thank them all for their particular efforts to attend the hearing. The panel also wishes to acknowledge the arrangements made by NICE to ensure that patients were not exposed to direct sunlight during the hearing.

18. Before the appeal panel inquired into the detailed complaints, the following preliminary statements were made: Emily MacKenzie on behalf of the International Porphyria Patient Network (IPPN), John Chamberlayne on behalf of the British Porphyria Association (BPA), Dr Robert Sarkany on behalf of the British Association of Dermatologists (BAD), Sarah Love on behalf of CLINUVEL (UK) Ltd and Dr Peter Jackson on behalf of the evaluation committee.

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

**Appeal by International Porphyria Patient Network (IPPN)**

**Appeal Ground 1a.1: The committee failed to act fairly by demonstrating consistent discrimination against IPPN as a stakeholder group**
(This appeal point was named IPPN 1a6 in initial correspondence and during the hearing).

19. Dr Barman-Aksözen, for IPPN, stated that the specific circumstances of this evaluation made the involvement of her organisation as a consultee vital. Specifically, it was important for the committee to hear evidence on the long term experience of treatment with afamelanotide in a real world setting, and this is available only from international patients.

20. Ms MacKenzie, for IPPN, explained that the IPPN had participated as a stakeholder at the scoping stage but had then been told by NICE that they could not be a consultee for the remainder of the process. It was only after protracted correspondence that they were once again recognised as a consultee. Despite this, they did not have the opportunity to participate in the second meeting of the committee held on 20 February 2018.

21. Mrs Upadhyaya, for NICE, agreed that the IPPN had been consulted during scoping before being excluded and later readmitted as consultees. She explained that the rationale for this initial exclusion had been that they might not have access to UK patients. In response to questions from the panel, she agreed that the process guide does not specifically exclude international organisations as consultees but said that patients with experience of the UK system are generally preferred as patient representatives.

22. It was pointed out during the hearing that the IPPN was represented by patients from the UK at the scoping meeting.

23. Dr Jackson, for NICE, said that the Chair of the evaluation committee is responsible for selecting which of the patient and clinical experts nominated by consultees should attend the second committee meeting. Given that the size of meetings is limited, he would usually prefer patients from England as they know the English health service well and, of particular importance for this appeal, experience the weather in this country. He said that IPPN had been able to comment at all stages of the process and that their input had been very helpful.

24. In response to a question from the panel, Dr Barman-Aksözen, for IPPN, said she hoped the final decision of the committee would have been different if an IPPN patient representative had been able to participate in the second committee meeting because they would have highlighted additional information about patients' experience from long term treatment. She also confirmed that the BPA and IPPN are the only patient groups for EPP that she is aware of.

25. The appeal panel concluded that the IPPN had an important role to play in this evaluation. Whilst recognising that UK patient representatives are often the most appropriate to include, in this particular case, the panel judged that the lack of UK patients with experience of long term treatment with afamelanotide made it important to include international patients. In addition, for this rare disease where there are only two patient groups who represent UK patients with EPP (BPA and IPPN), it would seem logical to include both of these patient groups as consultees throughout the process. The panel did not accept that the IPPN suffered discrimination, and noted that the IPPN did have opportunities to contribute to the evaluation process. However, the appeal panel judged that excluding the IPPN from the second committee meeting was an unfair approach, as they had an important contribution to make.

26. The appeal panel therefore upheld the appeal on this point.

**Appeal by CLINUVEL (UK) Ltd**

**Appeal Ground 1a.1: NICE acted unfairly by failing to give the Company an opportunity to discuss and negotiate its proposed MAA to NHS England before presenting it**

(This appeal point was named CLINUVEL 4 in initial correspondence and during the hearing).

This part of the appeal was held in private at the request of the appellant.

27. Sarah Love, for CLINUVEL, stated that the use of Managed Access Agreements (MAAs) as part of the highly specialised technology (HST) evaluation process is relatively new and pointed out the HST process guide does not set out in detail the procedural details regarding MAAs. She argued that the company was therefore reliant on advice given by NICE about the procedure to follow. She went on to say that because an MAA is a multi-party agreement, it seems unlikely that a company could arrive at an acceptable MAA alone, in the absence of an iterative process. Ms Love stated that the process that occurred did not allow CLINUVEL a fair opportunity to propose an acceptable MAA. In particular, she stated that NICE told the appellant that they would facilitate a meeting with NHS England and then did not follow through on that assurance.

28. Sarah Love, for CLINUVEL, went on to state that in CLINUVEL's opinion, the MAA the company submitted did address both of the concerns expressed by the committee in paragraph 4.22 of the FED concerning data collection and the sharing of financial risk.

29. Ms Love went on to state that NICE invited CLINUVEL to submit an MAA on 13 April 2018. She argued that if the high Incremental Cost-effectiveness Ratios (ICERs) in the FED were an insurmountable barrier to an acceptable MAA, this invitation should not have been made so that CLINUVEL did not waste time and resources pursuing it.

30. Lachlan Hay, for CLINUVEL, provided a detailed timeline of the interactions between NICE and CLINUVEL regarding an MAA, as set out in an appendix to their original appeal letter. He stated that the company was keen to engage with the process of negotiating an MAA and emphasised that the company were expecting NICE to facilitate a discussion with NHS England before submission of the proposed MAA and the publication of the FED.

31. Maria Manley, for CLINUVEL, said that the only meeting between NICE, NHS England and CLINUVEL took place on 30 May 2018 (after publication of the FED). She stated that this meeting consisted of feedback on a decision that had already been made by NICE and NHS England rather than an opportunity for CLINUVEL to engage with a collaborative process.

32. Meindert Boysen, for NICE, stated that NICE is aware that NHS England will not consider an MAA unless there is plausible potential for that MAA to resolve uncertainty in a way that leads to NICE being able to make a decision to recommend a technology as cost-effective. He said that the committee were

aware of the company's policy of only offering a single price for their product and that they do not offer discounts. In this case, NICE had to consider how far away the key ICERs in the FED were from the usual threshold for cost-effectiveness in the HST process. He said that the committee concluded that this distance was so great that it was implausible that any data collected in an MAA could lead to a decision to recommend the technology. Whilst it is not for NICE to seek a change in the price of a product, this was an option that was open to the company throughout the process.

33. In response to questions from the panel, Mr Boysen said that NICE is not a "gate-keeper" to NHS England, and that a company can approach NHS England directly to discuss an MAA.

34. In response to further questions, Mr Boysen said that an MAA was indeed mentioned at the committee meeting of 20 February 2018 by the British Association of Dermatologists and that NICE offered to help the company to understand what NHS England's expectations might be. However, soon after that it became apparent that an MAA did not have plausible potential to result in a decision to recommend the technology.

35. Sheela Upadhyaya, for NICE, said that during the teleconference between NICE, CLINUVEL and NHS England on 30 May 2018, CLINUVEL were advised that they needed to respond to the concern in the FED about the lack of plausible potential for afamelanotide to be considered cost-effective. Meindert Boysen, for NICE, said that if CLINUVEL had offered a proposal that led to plausible potential for afamelanotide to be cost-effective this would have "opened a door" to an MAA that could then attempt to address uncertainties in the evidence base.

36. In response to questions from the panel, Lachlan Hay said that CLINUVEL have always been consistent and transparent about their policy of only offering a single price for their product and that they do not offer discounts. He said that CLINUVEL understood the ICERs to be the material driver of the decision not to recommend the product. However, the company believed the issue of sharing financial risk during the MAA had been addressed by their proposal.

37. The appeal panel concluded as follows:

38. Although the appeal panel had some sympathy with the company's view that there had been a lack of clarity regarding the procedure surrounding the development of MAAs, they did not feel that this was sufficient to make out the ground of appeal.

39. The question is whether the final decision was arrived at fairly. A company must know, during an evaluation, what all of the material drivers of a decision are. The key moment to consider is the moment at which the committee takes its final decision: at that point, has the company been made aware of all of the material drivers, has it had a chance to address them, and has whatever submission it has made informed the committee? Furthermore, the panel were clear that the

company would have had the opportunity to approach NHS England directly at any time. The panel was satisfied that the FED contained adequate reasoning for why an MAA was not judged appropriate, in particular the fact that it was highly unlikely that afamelanotide had plausible potential to be considered cost-effective. CLINUVEL were aware that cost-effectiveness was a material driver for the decision that an MAA was not appropriate, which was clear some time before the finalisation of the FED, and CLINUVEL had opportunities to address this. The appeal panel therefore concluded that CLINUVEL were not disadvantaged by any lack of clarity concerning the MAA procedure and that overall the process followed was fair.

40. Therefore the panel dismissed this appeal point.

**Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.**

**Appeal by International Porphyria Patient Network (IPPN)**

**Appeal Ground 1b.1: The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward**
(This appeal point was named IPPN 1b2 in initial correspondence and during the hearing).

41. In their appeal, the IPPN state that they raised a concern about the equalities impact of the decision during the consultation process. They state that the committee responded by simply stating that “no potential equalities issues have been identified” without providing further justification of this.

42. During initial scrutiny, there was some discussion on whether this was a valid point of appeal. It was accepted on the grounds that another appellant (CLINUVEL) argued that the committee’s decision does not take proper account of equality issues and was put to the appeal panel on this basis. The appeal panel therefore considered this appeal point together with CLINUVEL 1b.1 and this decision letter will deal with these two points together in the section below.

**Appeal by CLINUVEL (UK) Ltd**

**Appeal Ground 1b.1: NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities**
(This appeal point was named CLINUVEL 5 in initial correspondence and during the hearing).

43. Sarah Love, for CLINUVEL, argued that:

(a) NICE is a public authority within the meaning of the Equality Act 2010;
(b) EPP constitutes a disability under the meaning of the Act;
(c) The method used by the evaluation committee to determine cost effectiveness is a 'provision, criterion or practice' within the meaning of the Act;

(d) In this case, the practice adopted was to treat the incremental cost effectiveness ratios (ICERs) as effectively determinative of the committee's decision;
(e) ICERs are derived from quality of life measures, and there is no suitable measure to capture quality of life in EPP;
(f) Therefore use of ICERs (based on such measures) to determine the decision discriminated against all patients with EPP (not just a subset of that group). It put them at a substantial disadvantage to others who do not have EPP, as there is no metric that can produce an accurate ICER. People without EPP could expect to have a treatment for their (different) condition evaluated using metrics that adequately assess that treatment's impact on patients' quality of life, whereas people with EPP could not;
(g) Accordingly reasonable adjustment(s) are required;
(h) The reasonable adjustment to be made in the circumstances would have been to recommend afamelanotide subject to a Managed Access Agreement. Even if NICE was not prepared to go that far, NICE should have changed the methodology adopted.

44. Ms Love emphasised that equalities concerns had been raised by both BPA and IPPN during the consultation, but that the response to these concerns in the documents did not address them adequately. She stated that there was no evidence of the committee considering the need to make a reasonable adjustment to their usual methodology in order to meet their duties as a public authority under the Act. She argued that there was no evidence of consideration of the committee's obligations under the public sector equality duty.

45. Ms Love referred to the High Court judgment in the case of *R(Eisai) v NICE* [2007] EWHC 1941 (Admin), and in particular to the need for proper consideration to be given to NICE's duties as a public authority to promote equal opportunities and to have due regard to the need to eliminate discrimination. Although that case was subsequently considered by the Court of Appeal, Ms Love explained that this part of the High Court judgment was undisturbed by that subsequent consideration.

46. The appeal panel's legal adviser drew the appeal panel's attention to paragraph 92 of the *Eisai* judgment and the "series of simple questions that the appeal panel could have asked both the appraisal committee and themselves" set out in that paragraph. The appeal panel found these instructive and put them to the committee, in particular asking in terms: "has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?"

47. Dr Peter Jackson, for NICE, stated that the HST process was specifically set up to address the particular challenges faced by rare diseases. He commented that measuring outcomes is generally challenging in all rare diseases that the HST evaluation committee considers. He stated that the ICERs were an important factor, but not the only factor in the committee's decision. He explained that they are "an element that gives structure to our thinking. They are one of the things that we think about, and an important thing, but not the only thing we think about".

48. Meindert Boysen, for NICE, said that NICE had completed an Equality Impact Assessment for the evaluation that was signed off on 12 March 2018 but that this was not published on the NICE website or otherwise provided to any other party in error. He apologised for this.

49. Meindert Boysen, for NICE, said that NICE has consistently implemented their positive duty to make reasonable adjustments to protected groups in the way recommendations are implemented, but has not typically considered this relevant to making a recommendation in the first place. He explained this by saying "If we are saying no to everyone, then there is no particular issue within the group and no need to make adjustments".

50. Jeremy Manuel, for NICE explained that the HST process itself was established in response to potential discrimination faced by sufferers of rare diseases. He felt that the same arguments used with regard to afamelanotide in this appeal point (concerning the complexities of capturing the full benefits of treatment) could potentially be applied to any rare disease. He argued that if a different method had been used in this particular case, it could be unfair to those with other rare conditions.

51. In response to the question "has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?" Dr Jackson replied that the committee did not consider EPP as a disability in the meaning of the Act. In response to a request for clarification from the panel, Dr Jackson elaborated by saying that they had interpreted "disability" as referring to a patently visible disability, and that it would be problematic if every disease before them were regarded as a disability.

52. The appeal panel concluded as follows.

53. The panel took the view that EPP very clearly meets the definition of a disability under the Equality Act 2010. It is also clear that NICE is a public authority as defined in the Act. The panel accepted that the Interim Process and Methods of the HST Programme[1] is NICE's institutional response to the problem of highly specialised technologies in respect of which outcomes are difficult to measure and where reliance solely on ICERs would be unreasonable. It is itself a reasonable adjustment made for the benefit of people with rare diseases. In particular, the appeal panel noted paragraph 41 of that document, which states that:

> *41. The Evaluation Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Evaluation Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers*

[1] 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

*and clinical experts who have used the technology being evaluated or are familiar with the relevant condition. In evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions.*

54. However, in this case, the panel were not able to consider the Equalities Impact Assessment said to have been completed by NICE as this had not been published and was not available to either the appellants or the panel. The panel could not see evidence of consideration of NICE's duties under the Act with respect to the use of afamelanotide in EPP specifically, elsewhere in the documents provided. Furthermore, the evaluation committee confirmed during the hearing that they had *not* taken into account any anti-discrimination legislation in reaching their decision. Irrespective of whether ICERs were indeed determinative of the committee's decision, or whether the use of ICERs in this way would constitute a discriminatory "provision, criterion or practice", the panel therefore concluded that NICE had not demonstrated adequate consideration of the legal obligations placed on it as a public authority.

55. The appeal panel therefore upheld the appeal on this point and on the linked IPPN Ground 1b.1 (see paragraph 42). The appeal panel suggests that the Committee may wish to seek further guidance from the Institute, if the Committee considers that it is required, on the relationship between the HST Process Guide and any specific need for reasonable adjustment(s) in relation to a particular cohort of people sharing a protected characteristic.

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

**Appeal by British Association of Dermatologists**

**Appeal point Ground 2.1: The NICE committee have not taken into account the full range of factors.**
(This appeal point was named BAD 2.4 in initial correspondence and during the hearing).

56. Professor Lesley Rhodes, for the British Association of Dermatologists (BAD), stated that real world evidence, clinical expertise and photobiological science were ignored by the committee. She argued that the following factors were not taken seriously by the committee: clinicians' views on the dramatic benefits of afamelanotide, the testimony of non-UK patients, and the evidence of efficacy provided by the high rate of long term compliance with treatment in the observational study Biolcati et al 2015: Br J Dermatol 72:1601.

57. Professor Rhodes stated that conditioned light avoidance probably resulted in the clinical trials under-estimating the benefit of treatment compared with that seen in the longer term.

58. Professor Rhodes also stated that the photo-provocation test used in the clinical trials showed a highly significant increase in light tolerance with treatment.

59. Jeremy Manuel, for NICE, said that all patient and clinician testimony was taken seriously by the committee, who spent time discussing the potential wider benefits of treatment for patients' lives and activities.

60. Dr Jackson, for NICE, said the committee had considered whether conditioned light avoidance was likely to have resulted in the clinical trials substantially under-estimating the benefit of treatment. They concluded that this was unlikely, because in the observational study by Biolcati et al (2015) there was a substantial improvement in quality of life over the first 6 months of treatment with no additional substantial change thereafter.

61. The appeal panel concluded that both the FED and the responses of the evaluation committee during the hearing indicated that the committee had considered the full range of factors put forward by the BAD in this appeal point. Whilst opinions might differ on whether all these factors were given sufficient weight by the committee, the panel judged that the committee's approach to weighing up the importance of all these factors was reasonable.

62. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.2: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide**
(This appeal point was named BAD 2.1 in initial correspondence and during the hearing).

*And*

**Appeal point Ground 2.3: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide**
(This appeal point was named BAD 2.5 in initial correspondence and during the hearing).

63. These two grounds of appeal from BAD, together with IPPN 2.2, (see paragraphs 84-85) overlapped to the extent that it was difficult to disentangle separate points, and they have been considered together in this decision letter.

64. Professor Rhodes disputed the committee's view that the clinical trial results suggest "small" benefits with afamelanotide. She stated that the average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). She argued that this increase puts patients with EPP who are on treatment into the normal range for this measure. (She quoted data that showed that healthy indoor workers spend an average of 22 minutes in the sun between 10am and 3pm). She also pointed out that the figure of approximately 10 minutes extra per day of sun exposure represents an <u>average</u> daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest.

65. James Rawnsley, for IPPN, explained that for a patient with EPP, a small absolute change in the number of minutes in the sun could be life-changing. He commented that when he took part in the trial he was able to spend a whole day outside in the sun without any reaction, but that sometimes the feedback in his trial diary about how much time he had actually spent in the sun appeared less positive because of poor weather or his own work commitments.

66. Dr Jasmin Barman-Aksözen, for IPPN, referred to data from an observational study by Biolcati et al (2015) which found improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first six months of treatment.

67. Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.

68. Dr Jackson stated his view that the differences in minutes per day of time in the sun found in the randomised controlled trials were indeed numerically small. He mentioned that the European Medicines Agency (EMA) had also referred to the magnitude effect of afamelanotide seen in the clinical trials in this way. In response to a question from the panel he stated that there is no established minimally important difference for the outcome measures used in the trials, including minutes per day of time in the sun. However, he emphasised that the committee did not intend to imply that the overall benefit experienced by patients was small[2].

69. The appeal panel concluded as follows:

70. Whilst the panel noted Dr Jackson's comment that the term "small benefits" was intended to refer to the randomised trial results rather than the overall benefit of treatment, it also noted that this term was used repeatedly both in the FED and during the hearing. The panel was persuaded by Professor Rhodes' argument that whether an increase of 10 minutes represents a small or a large change can only be interpreted with regard to the normal range for this measure. The panel noted that FED paragraph 4.7 cites differences in the amount of time spent in daylight and decreases in phototoxic reactions that would not necessarily sound small to someone reading the document. The panel judged that describing these differences as small lacks face validity. Whether or not this choice of words was relevant to the final recommendation made, it is important that the FED describes the results of the trial data in a way that appears to "add up". Overall, the panel concluded that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide.

71. The appeal panel therefore upheld the appeal on these two points (and IPPN point 2.2, see below paragraph 85).

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[2] The panel noted a minor typographical error in the FED, page 5 paragraph 4.2 where "47% (n=66/127") should read 47% (n=60/127)" as written in the original Holme paper.

**Appeal by International Porphyria Patient Network (IPPN)**

**Appeal point Ground 2.1: The committee failed to act fairly by not acknowledging the evidence provided in patient testimonies and by expert physicians on the overwhelming clinical benefit**
(This appeal point was named IPPN 1a1 in initial correspondence and during the hearing).

72. Dr Jasmin Barman-Aksözen, for IPPN, emphasised the importance of patient testimonies for understanding the real world impact of rare and poorly understood conditions like EPP. She illustrated this with her own powerful personal testimony. She said that every patient treated with afamelanotide reports life-changing benefits.

73. James Rawnsley, for IPPN, also described very eloquently the devastating impact that EPP has had on his own life, and the dramatic benefits he experienced with treatment.

74. Emily MacKenzie, for IPPN, said that the committee themselves acknowledge that the existing measures of quality of life used in EPP (the DLQI and EPP-QOL) are unsatisfactory. Ms MacKenzie said that the committee also acknowledge in the FED that the trials are likely to have under-estimated the true clinical benefit of treatment. She argued that this means patient and physician testimony should have been given greater weight but this was not done. She expressed concern that the committee were "paying lip service" to acknowledging the importance of patient and expert testimony, whilst at the same time demonstrably preferring the trial data.

75. Ms MacKenzie referred to paragraph 41 of the HST process guide which requires the committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical experts. She argued that the committee had rejected evidence from patient and clinician testimony simply because these factors could not be quantified. She stated that it was inappropriate to use patient testimony only at the stage of judging whether the usual threshold for an ICER could be applied flexibly. Rather, patient testimony should have been given greater weight throughout the process as an alternative approach to one based on economic modelling.

76. Ms MacKenzie referred to paragraph 46 of the HST process guide regarding QALY weighting. She rejected the committee's conclusion that even accounting for the patients' and clinicians' testimony would be unlikely to result in an incremental QALY gain of at least 10, as being based on "woefully inadequate data".

77. Ms MacKenzie referred to paragraph 55 of the HST process guide, which concerns the circumstances in which the usual ICER threshold can be "flexed". She stated that in this case there is a strong reason to indicate that there are substantial uncaptured benefits. She argued that the committee have not shown evidence that they took this into account in making their final decision not to recommend treatment.

78. Dr Peter Jackson, for NICE, explained that the HST evaluation committee have substantial experience in evaluating treatments for rare diseases where because of small sample sizes it is indeed often more challenging to capture all the benefits of treatment with quantitative tools. He said that the HST evaluation committee must apply a rigorous approach to evaluating information from patient and clinician testimonies. This would include consideration of the range of responses, how respondents were elicited and any potential biases. In response to a question from the panel about whether the patient and clinician testimony was unusually compelling and uniform in this case, Dr Jackson replied that the HST evaluation committee very commonly sees a similar picture of very positive responses with technologies that come before them. When the committee looked at descriptions of EPP in the literature, they felt that while the testimony of the nominated patients and clinicians was very powerful, this might not be a complete picture. Dr Jackson said the committee have considerable experience of using a process of deliberative discussion to gauge patient testimony against that from other diseases, but acknowledged that the nature of this discussion can be hard to capture in a simple description.

79. Dr Jackson stated that whilst the committee recognised the limitations of the outcome measure used to assess quality of life for the economic model (the DLQI) they certainly did not accept it was so flawed that it could not be useful. The DLQI has been widely validated in other conditions. Scores on the DLQI correlate with both biochemical and clinical measures of the severity of EPP, and are sensitive to the impact of EPP on quality of life.

80. Asked by the panel what the committee thought were the most likely reasons for the apparent discrepancy between the trial results and the patient testimony, Dr Jackson gave a detailed response but concluded that they had not reached a satisfactory explanation. He said that the committee had therefore put these two pieces of information together as best they could in reaching a decision.

81. The panel asked about how the committee had incorporated patient and clinician testimony into their decision making. Dr Jackson said that they discussed each factor that had been raised (such as impact on occupational functioning) in detail. They had then considered to what extent this would allow them to "flex" the standard ICER threshold for HSTs (as set out in paragraph 55 of the HST process guide). In response to a question from the panel, Dr Jackson said that the ICERs were an order of magnitude away from the usual threshold. The committee had therefore concluded that, whilst the quantitative data was likely to have underestimated the benefit of treatment, it was not plausible that it had been underestimated to the extent that the treatment could plausibly be cost-effective.

82. The appeal panel concluded that there was evidence both from the FED and the committee's responses during the hearing that they had carefully considered the patient and clinician testimony. The panel judged that the committee had shown detailed consideration of the strengths and limitations of different sources of information as well as possible reasons for apparent discrepancies. The committee clearly stated the process they had used to incorporate patient and clinician testimonies into their final decision, and this process was judged by the panel to be reasonable.

83. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.2: The evidence provided shows that the benefit is significant and not small, as assessed by the committee**
(This appeal point was named IPPN 2.1 in initial correspondence and during the hearing).

84. This appeal point overlapped with BAD Appeal points 2.2 and 2.3 to the extent that it was difficult to disentangle separate issues. They were discussed together at the hearing and considered together by the panel (paragraphs 63-71).

85. The appeal panel therefore upheld the appeal on this point.

**Appeal point Ground 2.3: The evidence provided of the measured trial outcome shows that the treatment is highly effective**
(This appeal point was named IPPN 2.2 in initial correspondence and during the hearing).

86. Dr Jasmin Barman-Aksözen, for IPPN did not accept the perception that there was a discrepancy between the randomised trial results and patient testimony. Rather, she argued that the trial results concur with patient testimony in showing that afamelanotide is highly effective. She highlighted the points made by Dr Rhodes (paragraph 64) about how the absolute change in minutes of sunlight per day should be interpreted.

87. The appeal panel concluded as follows;

88. As described in paragraph 70 of this decision letter, the panel was persuaded by the specific arguments made by Professor Rhodes and Dr Barman-Aksözen (paragraphs 64 and 86). It is for this reason that the panel concluded that it was not reasonable for the committee to describe the magnitude of benefits seen in the trial as "small" and thus upheld appeal points BAD 2.2, BAD 2.3 and IPPN 2.2.

89. However, insofar as it differs at all from IPPN 2.2, this appeal point seems to go further in stating that the trial outcomes showed the treatment to be "highly effective".

90. It should be noted that it is not for the appeal panel to draw its own conclusions on the evidence presented, but only to comment on the reasonableness of the conclusions reached by the committee. From the totality of the evidence presented, the panel were confident that it was reasonable for the committee not to have described the trial evidence as showing that afamelanotide was "highly effective".

91. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.4: The evidence provided shows that quality of life before treatment is low and under treatment with afamelanotide increases dramatically and sustainably**
(This appeal point was named IPPN 2.3 in initial correspondence and during the hearing).

92. Dr Jasmin Barman-Aksözen, for IPPN, emphasised the data from the observational study by Biolcati et al (2015) which found improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first six months of treatment. Dr Barman-Aksözen expressed concern that these findings had not been given sufficient weight by the committee (or perhaps had been misinterpreted by the committee) because no further improvements were seen after six months (even though the improvements were sustained).

93. Dr Barman-Aksözen argued that the EPP-QOL was a more appropriate tool to measure quality of life in EPP than the DLQI because it is disease-specific and designed with input from patients and clinical experts. She said that the EPP-QOL is sensitive to treatment effects and can even detect differences in quality of life between summer and winter. She expressed concern that the DLQI fails to capture non-skin components of EPP such as fatigue and that it has not shown to be sensitive to treatment effects.

94. Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.

95. Dr Jackson explained that the committee had considered in detail the strengths and weaknesses of the two scales used to measure quality of life in the trials. Whilst they recognised the limitations of the DLQI in not capturing all the symptoms of EPP, they noted that DLQI has been widely validated in other conditions. Scores on the DLQI correlate with both biochemical and clinical measures of the severity of EPP, and are sensitive to the impact of EPP on quality of life. In addition, DLQI scores can be mapped onto the EQ5D to generate utility values. They recognised the strengths of EPP-QOL (it being disease-specific and having been developed with patient input) but felt that it was insufficiently validated as a measure of quality of life, and that the fact that pain was not included lacked face validity. Overall, the committee preferred DLQI for their economic model. However, they took account of the fact that the DLQI may not capture all the benefits of treatment in their decision making (see

paragraph 78 of the FED) and also considered exploratory models based on the EPP-QOL.

96. The appeal panel concluded as follows:

97. It was reasonable for the committee to put less weight on data from uncontrolled studies than randomised controlled trials. The lack of further improvement after 6 months in the Biolcati study was highlighted in the FED as evidence that most benefits can be seen within the time frame of the controlled trials rather than to imply that these data were not important. The conclusion drawn by the committee was that these data did not support the assertion that one reason for the apparently modest effect seen in the clinical trials may have been because it takes a considerable period of time for the learned behaviour of light avoidance to change. The concern expressed by IPPN in this regard (paragraph 92) may have been a simple misunderstanding of the wording of the FED by the IPPN.

98. The panel judged that the committee demonstrated (both in the FED and during the hearing) that they had considered in detail the relative strengths and weaknesses of the DLQI and EPP-QOL and that their decision to prefer the DLQI was not unreasonable. The panel noted that the committee had explicitly considered both results from the EPP-QOL and the limitations of the DLQI in their overall decision-making process. This process was therefore reasonable.

99. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.5: The committee failed to act fairly by denying a Managed Access Agreement (MAA) 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** (This appeal point was named IPPN 2.4 in initial correspondence and during the hearing).

100. Dr Jasmin Barman-Aksözen, for IPPN referred to the reasons given in the FED for an MAA not being pursued. She said she was not able to comment on cost, but that she disagreed with the conclusion in the FED that an MAA would be likely to suffer from the same problems as the trials and therefore fail to resolve uncertainty in the data. In particular, she argued that a longer duration of follow-up during an MAA compared to the randomised trials would allow patients to change their light-avoidance behaviour, helping to capture quality of life benefits. She referred to the PASS (post authorisation safety study) being conducted in Europe and pointed out that this is collecting efficacy data, the first year of which has just been accepted by the EMA for the purpose of extending approval of the product.

101. Dr Robert Sarkany, for BAD, said that they had the impression that the decision not to pursue an MAA had been made with undue haste, without adequate consideration and without BAD having a full opportunity to suggest how uncertainty in the existing evidence could be resolved.

102. Dr Peter Jackson, for NICE, said that because MAAs are burdensome to patients and costly to NHS England they are only recommended where they are likely to be helpful. He argued that there seemed to be agreement on the difficulty of capturing treatment response in EPP and there was no suggestion that an alternative tool was being developed that would allow this to be done better in an MAA than it had been in the trials. In response to a question from the panel, he said that he did not believe that any of the data being collected in the PASS study was likely to resolve the substantial uncertainty which the committee had identified.

103. Dr Jackson said that an even more important consideration was where the ICER was in relation to the threshold. The committee had to ask themselves whether it was possible that data from an MAA could reduce uncertainty sufficiently to bring the ICER to within an acceptable range. They considered the range of ICERs from all models as well as the degree of uncertainty around this and they concluded that this was not plausible.

104. Dr Jackson was asked by the panel whether the appellants were made aware of the nature of the uncertainty in the evidence base. He replied that the FED was clear that the fundamental uncertainty related to whether existing outcome measures are able to capture the full benefit of treatment.

105. Asked by the panel whether the committee engaged with appellants in any discussion about alternative ways of measuring outcome, Dr Jackson said that they had enquired of the company what future steps they were proposing to reduce uncertainty.

106. Sarah Love, for CLINUVEL, said that they had suggested that CLINUVEL and NICE could collaborate to develop a better outcome measure.

107. The appeal panel concluded that although an MAA was ultimately not felt by the committee to be a useful way forward, it was clear that this had been considered and discussed. The panel judged that the FED gave clear reasoning for the decision not to recommend an MAA. The panel thought that both the difficulty in resolving uncertainty and the very large distance between current ICERs and the threshold were reasonable considerations in reaching this decision.

108. The appeal panel therefore dismissed the appeal on this point.

**Appeal by British Porphyria Association**

**Appeal point Ground 2.1: There is a huge gulf between the results of clinical trials that are communicated by NICE as "small" and the benefits that patients in receipt of Afamelanotide repeatedly report as life changing … Despite this recognition, the FED recommendation has been made primarily on the grounds of the ERG economic analysis that was published before this information came to light, which we consider to be unreasonable.**

109. There was some overlap between this appeal point and IPPN appeal point 2.1. The additional comments made at the hearing specifically in relation to BPA 2.1 are set out here, but this should be read in conjunction with the discussion of IPPN 2.1 above.

110. Dr Geoff Sloan, for BPA, emphasised the discrepancy between the notion that the trial showed small benefits and his own experience of the drug as life-changing.

111. Asked by the panel to clarify which information they felt had come too late in the process, John Chamberlayne said that this referred to the patient and clinician testimonies being heard after the ERG economic model was produced.

112. Dr Peter Jackson, for NICE, said that the committee had listened with great care to input from patients and were indeed impressed by their testimony. Dr Jackson explained in detail the committee's view on the strengths and limitations of both the economic modelling and patient/clinician testimony, and how both of these factors were incorporated into this decision making process. This is described in full in paragraphs 78-81 of this letter.

113. The appeal panel concluded that there was evidence both from the FED and the committee's responses during the hearing that they had carefully considered the patient and clinician testimony. The panel judged that the committee had shown detailed consideration of the strengths and limitations of the trial data and information from patients as well as possible reasons for the apparent discrepancy between these. The committee clearly stated the process they had used to incorporate patient and clinician testimonies into their final decision, and this process was judged by the panel to be reasonable.

114. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.2: The economic decision has been made using a flawed model that means the decision is unreasonable in light of the evidence submitted to NICE.**

115. There was some overlap between this appeal point and IPPN appeal points 2.1 and 2.4. The additional points made at the hearing specifically in relation to BPA 2.2 are set out here, but this should be read in conjunction with the discussion of IPPN 2.1 and 2.4 above.

116. John Chamberlayne, for BPA, stated that the economic model had been developed without any input from stakeholders. He argued that the flaws in the model were such that its conclusions could not be considered reliable.

117. Dr Peter Jackson, for NICE, acknowledged that the sensitivity of the DLQI to capturing benefit was a limitation of the model used. However, the alternative model using the EPP-QOL used an indirect method to determine cost effectiveness. The committee had carefully considered different approaches before choosing their preferred model.

118. Mr Francis Pang, for NICE, further described the limitations of the company's proposed model (which used DALYs in place of QALYs and relied on proxies for developing disability weight) but explained that nevertheless this was given due consideration.

119. The appeal panel concluded that the committee had shown careful consideration of the limitations of the economic modelling performed. The appeal panel judged that the limitations of the preferred model were not so severe as to make it unreasonable to use it in decision making. The panel noted that the committee had made efforts to take account of these limitations and incorporate other sources of evidence into their final decision.

120. The appeal panel therefore dismissed the appeal on this point.

**Conclusion and effect of the appeal panel's decision**

121. The appeal panel therefore upholds the appeal on the grounds IPPN 1a.1, CLINUVEL 1b.1, IPPN 1b.1, BAD 2.2, BAD 2.3, IPPN 2.2. The appeal is dismissed on all other grounds.

122. The evaluation is remitted to the evaluation committee who must now take all reasonable steps to address the following issues:

    i) The failure to include an IPPN representative at the second committee meeting (IPPN 1a.1).

    ii) The failure to demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act (CLINUVEL 1b.1 and IPPN 1b.1). The appeal panel considers that this is likely to include express consideration of whether the methodology used in the evaluation discriminates against patients with EPP and if so what reasonable adjustments should be made.

    iii) The appeal panel's conclusion that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide (BAD 2.2 and 2.3, IPPN 2.2).

123. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.

**PRIVILEGED & CONFIDENTIAL**

Dr Peter Jackson
Chairman, Highly Specialised Technologies Committee
National Institute of Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT
Sent via HST@nice.org.uk

CC: Marie Manley, Sidley Austin LLP (mmanley@sidley.com)
Martin Chamberlain QC, Brick Court Chambers (martin.chamberlain@brickcourt.co.uk)
Sarah Love, Brick Court Chambers (sarah.love@brickcourt.co.uk)
Stan McLiesh, CLINUVEL Group (Stan.McLiesh@clinuvel.com)

21 January 2019

**Re: HST 2nd Appraisal following the decision by the NICE Appeal Panel following the hearing of 30 July 2018 – SCENESSE® (afamelanotide 16mg) for the treatment of EPP**

Dear Dr Jackson,

We note that NICE has not responded to all our queries addressed in the letter of 06 November 2018.

In reply to the correspondence received from the National Institute of Health and Care Excellence on 29 October 2018, CLINUVEL kindly adds the following considerations to the previous submissions made to the Highly Specialised Technologies (HST) Committee from 08 March 2016 to 23 April 2018, during the process leading up to the 30 July Appeal Panel hearing, and in various other correspondence to date.

**BACKGROUND MARKETING AUTHORISATION SCENESSE®**

In October 2014 the European Medicines Agency (EMA) explicitly ruled in favour of SCENESSE® (afamelanotide 16mg) as an innovative photoprotective therapy, a controlled-release hormonal therapy in erythropoietic protoporphyria (EPP), a disease which had not been well characterised by medical experts in literature and text books to that point and for which there had not been an available and effective treatment.

Under EC 726/2004 Article 14(8), the Committee for Medicinal Products for Human Use (CHMP) of the EMA stated that under the current state of science no instruments existed to adequately quantify the impact of EPP treatment and the nature of the disorder (orphan) prohibited further exposure of patients in breach of medical ethics, and SCENESSE® was granted approval under *exceptional circumstances*. Further to the marketing authorisation, the EMA (Pharmacovigilance Risk Assessment Committee; PRAC) and CLINUVEL set out to develop a Post-Authorisation Safety Study (PASS), a non-interventional study to follow up patients for a minimum of eight years. In the deliberations of the EMA, a limited number of eligible adult EPP patients in the European Union would receive drug treatment.

**HST APPRAISAL TO DATE**

On 08 March 2016 CLINUVEL submitted to the HST Committee its estimated EPP patient numbers in England. The numbers communicated to the HST were based on a prevalence of 1:140,000 and CLINUVEL's deep knowledge about the EPP community. CLINUVEL communicated a maximum number of 513 EPP patients in England.

On 13 October 2016 it was communicated to CLINUVEL that the HST Committee rejected this number on the basis of an internal assessment of 1,300 patients and therefore rejected CLINUVEL's application for HST assessment, referring SCENESSE® back to a Single Technology Appraisal (STA). After incessant correspondence by CLINUVEL, the HST admitted some five months later that its own assessment of the patient population had been erroneous, despite having in hand the evidence on available patient population in the UK as well as references to the prevalence of disease. The mistake of the HST Committee and its reluctance to respond earlier caused a delay of 16 months prior to the Committee referring the subject back for HST assessment, without further apologies or rectification, but a mere admission that an error had been made.

The Committee eventually referred the subject matter back to a pathway leading to the HST appraisal process, restarting this process from the beginning under a new guidance document and review methodology.

In the correspondence, and as presented during the scoping meeting on 08 March 2016, CLINUVEL clarified that a number of factors would provide ample evidence and assurance for a limited prescription and distribution of SCENESSE® exclusively to specialised university hospitals in the UK, these are:

(i) the burden of clinical compliance with the PASS protocol;

(ii) mandatory enrolment of EPP patients in the European EPP Diseases Registry (EEDR);

(iii) limited number of prescribers available;

(iv) Real World Experience from other European countries; and

(v) previous experience from compassionate use and Special Access Programs.

**MANAGED ACCESS AGREEMENT AND FINANCIAL RISK**

On 12 July 2017 NICE Director Mr Boysen stated on the one hand that leeway could be applied to the appraisal of SCENESSE®, yet, on the other hand – knowing that the quality of life tools and other scientific instruments were not applicable and appropriate to assess the economic benefit of the treatment of SCENESSE® – insisted that CLINUVEL was to submit a QALY model before the HST could engage in a dialogue with CLINUVEL.

On 12 September 2017 NICE submitted financial data on a Budget Impact Test to CLINUVEL. NICE concluded that CLINUVEL was exceeding the budget(s) in some scenarios and therefore would not be meeting the test, despite CLINUVEL's clear and unambiguous data showing that SCENESSE® was not exceeding the threshold of £20 million per annum.

On 06 November 2017, CLINUVEL responded to the Budget Impact Test with modelling demonstrating SCENESSE® would not exceed the £20m threshold in the UK.

On 23 November 2017 in the first HST Committee Meeting in Manchester, NICE suggested in a public meeting that a Managed Access Agreement between all relevant stakeholders (particularly CLINUVEL and the National Health System England), whereby financial risk to the NHS would need to be mitigated or addressed, may be appropriate for this HST appraisal.

In summary of all facts provided and deliberations by CLINUVEL, the financial risk of adopting SCENESSE® by the NHS England is zero for the following reasons:

(i) CLINUVEL has provided an accurate and detailed breakdown of distribution year on year, projected for five years. Since the Company is intimately familiar with logistics and distribution to the European EPP medical community, and therefore knows the national numbers of eligible adult patients per country, it is confident it can reach a financial agreement with NHS England on treatable patients per

annum per centre, without the risk of exceeding budgets or renouncing a commercial agreement made.

(ii) CLINUVEL has projected accurate number of patients treated and product distributed in eight other European countries without exceeding agreed budgets, and in all instances the Company has remained well under the volume threshold agreed during the past three years.

(iii) CLINUVEL is willing to set and agree strict rules on the use of the product and, as reported in the EEDR, is able to provide feedback on effectiveness of the product from rate of discontinuation annually. A financial agreement can be reached in the event of reported lack of effectiveness or discontinuation due to lack of effectiveness (see below for Managed Access Agreement).

(iv) CLINUVEL is willing to evaluate new scientific instruments to be implemented over time to assess the clinical effectiveness of the therapy other than from clinical feedback by expert centres and patients, and from a validated questionnaire, an Inventory of Daily Activities. A validated questionnaire – agreed by expert physicians and patient organisations – is the only measure to quantify how the lives of patients are facilitated by the treatment.

(v) CLINUVEL is willing to evaluate the use of SCENESSE® bi-annually and provide NHS England with access to data on conditions of use and registered directly in the EEDR by the expert centres in England.

**CLINUVEL'S APPROACH TO COMMERCIAL DISTRIBUTION OF SCENESSE®**

From all discussions held with the HST Committee, and from the considerations by the Appeal Panel convened on 30 July 2018, it is sufficiently apparent to all attendees and consultees that SCENESSE® constitutes an exception to other therapies and is therefore a unique case in its health economic assessment.

The Company has approached the product distribution in a transparent manner which differs from the commercial attitude of most peer pharmaceutical companies.

First, in order to allow drug distribution to occur without bias or the Company's intervention, both the clinical demand and willingness to prescribe SCENESSE® dictate the rate of continuation on treatment in all European countries. While it is usual to promote or market pharmaceutical products in the sector, in order to be able to gauge the genuine rate of prescription the Company does not institute a sales force or commercial campaigns. The demand for the drug occurs on an "as is" basis following the clinical assessment by a handful of university centres, and patients themselves, following each treatment. Therefore, the rate of continuation year on year provides an accurate indication of effectiveness, since EPP patients need to seek cyclical treatment every two months. The clinical visits require patients to travel during the night and, in many instances, sleep in the proximity of hospitals at their own expense. EPP patients often take one day off work, forgoing their earnings to be able to receive the implant injection every 60 days. The motivation to continue treatment has proven very high among the treated patients in European countries as seen from real world experience and data. The rate of continuation – as listed in the Company's obligatory Annual Report to the EMA – was 98.5% in 2018 compared to 2017. At the time of print the rate of continuation is 94.5% for those patients seeking treatment at the beginning of 2019.

Second, the Company has been determined to mitigate and annihilate the possibility of off-label use, and self-distributes the product to each European hospital. The product requires special handling through cold-transport at 2-8 degrees. The controlled-distribution precludes off-label use of the product. During three years of past distribution, only one instance of off-label use was permitted to a moribund Congenital Erythropoietic Porphyria (CEP) patient who requested to enjoy one last summer seeking light exposure before giving in to his disease. MHRA permission was obtained to treat through an unlicensed medicines program. There have not been any other cases of off-label indication use in any European country.

Third, through the PASS protocol supervised and controlled by the EMA (PRAC) a non-interventional study is conducted whereby only trained and accredited expert centres, a limited number of university centres throughout the European Union, are allowed to treat EPP patients in a multi-disciplinary team.

Fourth, the use of a European EPP Disease Registry (EEDR) allows for direct control on clinical use of the product, whereby the EMA imposed risk minimisation measures, such as the prevention of off-label use.

**CLINUVEL'S FINAL PROPOSAL 2019**

Following the hearing on 30 July 2018, the Appeal Panel upheld appeals on the grounds IPPN 1a.1, CLINUVEL 1b.1, IPPN 1b.1, BAD 2.2, BAD 2.3, IPPN 2.2. The Appeal Panel determined that the appraisal should be remitted to the appraisal committee who must take all reasonable steps in the decision letter.

Following its investigation, the Appeal Panel ruled that the HST Committee had failed to properly and justly interpret the magnitude of beneficial effects of the pharmaceutical treatment of SCENESSE®. CLINUVEL is willing to

(i) enter a binding Managed Access Agreement with NHS England on the basis of the agreements made – as laid down above in points (i) to (v) – and on the basis of the similar equitable financial conditions agreed with each other European country,

(ii) agree with NHS England the European pricing of SCENESSE® - £12,020 net per injection – to be fixed for 24 months with no further rebates discounts or cashbacks.

(iii) agree on a structured plan to treat EPP patients on the basis of a total of 513 patients in England based on disease prevalence, and most likely 400 eligible adult EPP patients.

(iv) evaluate together with NHS England on a bi-annual basis the EEDR data generated by English patients and distribution data of the product (longitudinal assessment).

(v) enter a volume agreement with NHS England based on the known centres of expertise willing to prescribe the drug in England (currently only two centres), and adhere to a roll-out plan, whereby minimum and maximum volume of drug units can be determined per annum; at a maximum capacity of 50 patients per annum per expert centre; the first year would lead to a maximum of 100 EPP patients to be treated.

(vi) adhere to the patient and treatment projections provided in the Budget Impact Test (see BIT attached, Addendum 1 - Table 1).

(vii) develop a new scientific instrument to be validated in time to assess the patients' ability to overcome their disability and participate in normal life following the treatment ('Inventory of Daily Activities').

(viii) agree stop-start criteria with NHS, expert centres and patients concerning the treatment.

(ix) agree limited resource use under the NHS by reimbursing expert centres for the additional administrative hours expended per patient on the adherence to the PASS protocol, conform and congruent with the agreements made with other European expert centres.

With this far-reaching Managed Access Agreement for SCENESSE®, zero financial risk would be incurred by NHS England while maximum transparency is provided by CLINUVEL. At this juncture, CLINUVEL has made all rational and reasonable attempts to propose and reach an agreement with NICE and NHS England, while an

excessive amount of time has been unnecessarily lost to provide treatment to a limited group of patients who currently have no alternative therapy.

The CLINUVEL proposal has addressed all financial concerns communicated in the FED on 29 March 2018 and addresses the comments made during the Appeal Panel on 30 July 2018.

Following the Appeal Panel's decision, CLINUVEL now has a legitimate expectation that the HST Committee will adopt a different methodology in the appraisal of SCENESSE®, while we are confident that our proposal for a comprehensive Managed Access Agreement has fulfilled all criteria in reducing the financial risk to NHS England by making the drug available to EPP patients, albeit four and half years after receiving European marketing authorisation.

Please contact us so that we may assist the Committee in the fair resolution of any outstanding issues.

We look forward hearing from you at your earliest, in the meantime, CLINUVEL reserves all of its rights.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

Appended: SCENESSE® Budget Impact Assessment England, October 2017

British Porphyria Association

136 Devonshire Rd
Durham City
County Durham
DH1 2BL
Charity No: 1089609
www.porphyria.org.uk
0300 30 200 30

17 January 2019

We, the British Porphyria Association (BPA), are writing to present additional information for your reconsideration of whether afamelanotide should be approved for use in the NHS, following on from the report of the appeal panel.

Many issues were raised during the appeal procedure that require reiteration here as they were not emphasised in the original evaluation. **That several points of appeal were upheld also reinforces our belief that the way the HST process has been applied to the evaluation of afamelanotide has not correctly reflected either the impact of EPP on patient lives or the efficacy of the treatment.**

The following paragraphs summarise the most significant new learning points with regard to three categories of particular interest.

- Nature of the condition
- Clinical effectiveness
- Impact of the technology beyond direct health benefits

**Nature of the condition**

Disappointingly, and despite all of the evidence previously submitted to NICE, at the appeal hearing, Dr Jackson demonstrated a persisting lack of knowledge about the nature of the condition when he explained that the committee did not consider EPP to be a disability because of the absence of visible symptoms (Appeal Hearing report, para 51). Although later highlighted by the appeal panel to clearly meet the definition of disability, the fact that EPP was mentioned in this way at this late stage of investigation demonstrates a clear dismissal or lack of understanding of the severity and reach of the condition.

Throughout the process and in medical circles the lack of visible manifestation for most of the year is what makes EPP so difficult to diagnose. Patients note that the level of severe pain is entirely disproportionate to the physically visible symptoms.

> *Swelling can be similar to a bad sprain, however having suffered from bad sprains and ligament damage, as well as breakages and trauma associated with taking a 60m uncontrolled fall, during which I was knocked unconscious, I can categorically state that the pain of EPP is way beyond and longer lasting than pain that might be associated with trauma. Having experienced the pain, I can only conclude that it might even be akin to that associated with cancers. Invisible yet extreme. There is no wonder why many patients express that they have experienced suicidal thoughts.* [EPP patient]

These aspects of severe and persistent pain were only gradually recognised by NICE through the meetings and it is unfortunate that even at the later stages in the process, the compelling qualitative evidence of patient and clinician testimony is still not being used to its full potential.

Throughout this lengthy process the understanding of EPP has continued to develop, as more patients have voiced aspects that affect them. This is another key reason why patient testimony is so important. Trial participants (likely to be those who see doctors on a regular basis) only make up one category of patients, people who seek and obtain care (rather than the hidden denominator of those that do not seek or cannot access care). It does not take account of those who have given up on or lost contact with doctors due to a lack of medical options for them, or a lack of faith in their ability to help, or even perceived lack of interest from doctors.

Pain and the impact on the mind and body is a key driver in the behaviour of EPP patients (including avoidance tactics). The physiological impact of this pain, along with the chemical effect on haem production, is also key to the extreme impact of fatigue which affects the capability to perform professionally, physically and socially in the days that follow an episode of exposure. We contend that the impact of fatigue (FED 4.1) is not fully reflected in either the EPP-QoL or the model adopted by the ERG.

**Clinical effectiveness**

In initial submissions and, more significantly, throughout the consultation process, it became clear that there is a huge gulf between the results of clinical trials that were communicated by NICE as being “small” (FED p1; 4.7), and the benefits that patients in receipt of Afamelanotide repeatedly report as life changing. This is iterated in (4.9) as reported by a UK patient, but perhaps more significantly by numerous European patients.

The appeal panel acknowledged that the results of the clinical trial were not small [Appeal Hearing, para 71]. In the appeal, Prof Rhodes quoted data that showed that healthy indoor workers spend an average of 22 minutes in the sun between 10am and 3pm [Appeal Hearing, para 64]. She stated that the average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). She argued that this increase thus puts patients with EPP who are on treatment into the normal range for this measure.

She also pointed out that the figure of approximately 10 minutes extra per day of sun exposure represents an average daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest.

Even in the committee’s recognition that 10 minutes extra in the sun is not small, the way the committee and even medical experts present this is still focused on the behavioural change rather than the benefits. We highlight that it is important to consider more deeply ***what it means to patients*** to spend even just 10 minutes more a day in the sun. Why are patients able to make this change? It is because of the diminution of phototoxic reaction and the associated lack of extreme pain, as well as a decreased impact on haem formation. Not only does this permit more 'normal' behaviour, it does so because the lengthy and painful consequences of spending time in the sun are reduced to the point where prolonged exposure can be tolerated without extreme consequence.

**Impact of the technology beyond direct health benefits**

The extended impact on quality of life for family members of those with EPP appears to still be largely disregarded from the appraisal – evidence relating to the far-reaching effects that trying to

protect a family member from the danger of a phototoxic reaction can have, should be taken into account. Please see the moving family testimonies provided in the Appendix, and in earlier documentation [Committee Meeting 1 papers, p264 - 265].

Having considered the FED and comments made by NICE at the recent appeal, the testimony and measurement of impact on the patients' wider life and that of their families remains largely unconsidered. We find no clear evidence of such impacts being incorporated into the ERG and no documented evidence or record of methodology applied by NICE in considering such impacts in the FED.

Afamelanotide can increase the time that an EPP patient can spend outdoors, making the time of exposure similar to other people, which can substantially decrease (maybe even eliminate) the adverse effect on family members and carers. This gives highly beneficial impacts on a family household, not only socially, but educationally, financially and psychologically too, thus increasing their quality of life. To reinforce the wider social impact of EPP and the opportunities that arise from a treatment that can help normalise the behaviour that has become ever more apparent during committee and appeal meetings, we re-append two of the testimonies included on p264 and 265 of the Committee 1 papers and request that NICE act to understand more fully the testimonies presented in subsequent papers and at the appeal.

**Emerging Evidence**

With regard to new evidence, we are aware of the pending submission to the BMJ of a longitudinal study in the clinical efficacy and long-term safety of afamelanotide[1]. The ongoing study has revealed data that addresses a particular issue of concern raised by the committee. The concern raised by the committee was that the uniformly compelling and powerful patient testimonies, 'might not be a complete picture' [Appeal Hearing report, para 78] indicating that only the positive responses might have been selected.

A BPA committee member recently attended the EPNET[2] General Assembly in Rotterdam, where they observed a presentation by Debby Wensink (Erasmus MC, Netherlands), based on data taken from the EMA Post Authorisation Safety Study (PASS) submitted to the EMA annually. **This data showed 98.3% adherence rates** (see Appendix 3). Furthermore, those who decided not to continue with treatment, did so for reasons such as pregnancy or financial constraints of travelling to obtain the drug. This is a very compelling statistic that demonstrates high levels of treatment satisfaction and quantitatively supports the overwhelming benefit already shown by the qualitative patient testimony. This provides support for the fact that the patient testimonies do provide a complete picture.

The weight of these emerging themes; the consistency of patient testimony; the stark contrast between testimony of patients on the treatment and those not on the treatment; are all clear

[1] Expected authors: Debby Wensink, Margreet Wagenmakers, Edith Friesema and Janneke Langendonk. Porphyria Center Rotterdam, Center for Lysosomal and Metabolic Disease, Erasmus MC, Rotterdam, The Netherlands.

[2] EPNET: European Porphyria Network www.porphyria.eu. EPNET consists of 33 EU specialist centres from 21 European and candidate countries that work together to develop an up-to-date consensus-based approach to the management of patients and families with porphyria.

indicators that the impact of EPP on quality of life has not yet been fully incorporated into either the decision, or the models that underpin it.

**Additional points**

We also bring to your attention to the additional points, which seem not to have been factored into the decision.

Overall, patient testimony should carry much greater weight in a structured and measurable way. There is no demonstrable measure recorded or documented that details the extent to which NICE applied patient testimony. Simply 'discussing each factor' [Appeal Hearing report, para 81] feels like an abstract measure with no detailed record and no scientific basis applied.

In particular, it is vital to consider the patient testimonies of international patients, as there is difficulty in obtaining such patient data in the UK. British patients are largely without experience in the benefits of afamelanotide as very few were involved in the trials or know of people on the treatment. Hence, testimonies received from European patients fortunate enough to be able to access the treatment, especially over extended periods of time, have been imperative to obtain such data [Appeal Hearing, para 19]. This point was highlighted by the patient expert at the February committee meeting. Yet this highly relevant and important point, regarding the difference in experience between UK patients and their European peers, was omitted from the FED.

The patient expert also highlighted that testimony provided by European patients not receiving Afamelanotide, or prior to receiving Afamelanotide, is extremely consistent to that of UK patients in relation to how severely EPP impacts upon their life and the quality of life of those around them. Again, this highly valid point appears not to have been reflected in the FED.

**Information submitted to the appeal**

During a committee meeting last year, the patient experts were asked whether or not they would be willing to receive afamelanotide and participate in further studies to evaluate its efficacy. The patient experts responded positively, but given the impromptu nature of the question, did not feel entirely empowered to respond on behalf of all UK EPP patients. To reinforce those individual patient expert answers, and demonstrate the gravity of the impact that a decision not to approve afamelanotide (or consider an MAA) is likely to have on our members, we include some results of a 2018 survey (Appendix 2): 93% of the 100 people surveyed would want to try Scenesse and a further 6% would consider using Scenesse. Given the responses to previous questions this gives a clear indication that there is almost ubiquitous demand for a treatment that reduces the severe impact EPP has on their life. Responses were limited to one per IP address to help prevent duplication and distortion of data.

The survey data (Q4) also demonstrates, in a visual manner, the severe impact that EPP patients feel the condition has on their quality of life in four areas: family life, engaging with friends, work/study and finance, with three out of four categories measuring 8 or more on a scale where 0 is not affected at all and 10 is severely affected.

Additional patient information is also submitted from the patient organisation in the Netherlands[3]. This was referred to in the very first BPA submission and discussed in the ERG report [p122], however was never submitted for the committee's attention. Please now find this attached in Appendix 4.

**Summary**

We believe the points that were upheld at appeal and the weight of emerging evidence indicate that the economic decision was made using a flawed model that means the decision is unreasonable in light of the evidence submitted to NICE.

Indeed, NICE themselves recognise (FED p.1) that "The true benefit of afamelanotide has, however, not been quantified." Despite this recognition, the FED recommendation has been made primarily on the grounds of the ERG economic analysis that was published before this information came to light, which we consider to be unreasonable.

The FED (throughout) indicates that the strength and validity of the argument for improved measures increased as the consultation proceeded. Despite this, the ERG model remains NICE's preferred basis for assessing value for money; a model that has not been updated in light of the evidence submitted during the consultation process; a model that the committee itself recognises as highly uncertain (FED 4.23) "[the committee] concluded that the ERG's exploratory results were also highly uncertain because the benefits of Afamelanotide may not have been fully captured by the DLQI measured in the clinical trials."

Whilst we acknowledge that the committee made some attempt to extrapolate data, we find no documented evidence of this extrapolation or the methodology applied in determining how such calculations were made. Surely such evidence should be front and centre when making economic decisions on people's lives. The BPA contends that an economic decision made on the basis of a highly flawed model is at best unreasonable, definitely inaccurate, and can even be considered as unscientific in light of the evidence submitted during the consultation process. It is therefore logical to conclude that the recommendation is not truly objective.

**MAA**

NICE have stated during this process that testimony from UK patients is preferred, yet recognised that the rare nature of the condition combined with the design of studies means UK patient experience of afamelanotide is extremely limited in comparison to patients on the continent. Throughout the process the BPA has been supportive of the use of an MAA. We have offered to support such a process, to provide patient input into its design. Although we recognise that an MAA is dependent on agreements between Clinuvel and NICE, points raised at appeal raised significant concern as to how serious NICE have been in pursuing such an option, despite the willingness of Clinuvel, clinical experts, patient experts and ourselves to engage. We would like to see the option of an MAA explored further, and we would be very happy to provide patient support in formulating an MAA if this emerges as a suitable way forward.

[3] Jeroen Verheul (2013): *A Life with EPP*. Investigation by the Dutch patient organisation for EPP. Translated and submitted for the EMA approval process.

**Appendix 1: Family testimonies**

**This testimony is from the wife of someone with EPP**

When your children beg you, “Mummy, why can’t daddy come too???”, The story of our life is summed up in one innocent question.

The massive impact the above statement has on family life is un-measureable. Our family unit is strong because we work relentlessly together to overcome the disadvantages that my husband and father to my two children is subject to being an EPP sufferer.

Despite experimenting with lots of creams, clothing, getting out in the light to try and build some sort of resistance, however little, he has still to find anything that can prevent the severe pain and tiredness he frequently has to give in to.

**Advantages of receiving treatment**

**Physical health:** Treatment will allow my husband to vastly improve his ability to participate in outdoors sporting activities that will help getting and keeping him fit, simply having the opportunity to get out for a run or on a bike or even walking the dog. He has never been able to take part in team sports due to the unreliability of him being able to venture outdoors. This, I believe has a very negative psychological effect on him especially as our children are involved in team sports. He regularly cannot support his children at their sports matches and competitions if he is required to be outdoors, these are for our family; cricket, rugby, tennis and lacrosse.

When our garden needs attention, an outdoor physical activity, my husband would be able to do the simple chores such as mowing the lawn and trimming the shrubs at any chosen time of day rather than in the dusk in the late evening. We often have to hire a gardener to complete these jobs.

**Emotional Wellbeing:** Being the wife of a EPP sufferer has been challenging over the years with regard to the level of inclusion that my husband can be involved in family activities. The children and I have to make compromises and difficult choices that often leave my husband feeling guilty, depressed and sometimes suicidal. Being unable to plan ahead and accept invitations to events with friends and family have definitely had a negative impact. Often just the necessity to have to drive to a gathering place or venue can result in frayed tempers and a stressful atmosphere due to the unpredictable and unpreventable physical and psychological effects that my husband will experience.

**Everyday Life:** Of course, he gets into situations where he gets a hit from exposure to sunlight, this is the consequence of trying to battle against the condition he suffers from, to enable him to maintain some form of normality and social acceptance. However, the whole family then feels the effects as well as my husband. We don’t experience his physical pain but can see the physical effects with the skin swellings and his inability to do anything but lie quietly in a darkened room away from the family. Although we certainly share the emotional devastation of his social isolation, feeling responsible for making him ‘come out to play’ and also have to make contingency plans until the time that my husband can once again be well enough to be involved in day to day family life, going to work and meeting his social commitments.

For years we have been forced to take separate holidays, my husband takes his holiday away from his family in the winter season whilst the children and I love to visit sunny Mediterranean climates or go camping on the coast around Britain. Imagine not having those holiday memories to share together, this is a cause of sadness and anxiety for all of the family. Given the chance to have this

treatment would be life-changing for my husband; giving us as a family simple day to day choices that are currently non-existent with his EPP. He may have missed out on much of his children's early years but with the treatment would be able to make a massive difference to their futures.

**What EPP does to Dad. How does it affect me?**

When we are in the garden on a warm, sunny day, dad sometimes feels pain on parts of his body that are exposed to the sun. Then he can't really play with me on the trampoline, in the paddling pool or just in the sun on the grass with a ball. He regularly gets frustrated and takes out his anger on me and mummy but he doesn't mean to. On holiday, when we go somewhere like Greece daddy has to stay at home so he can't come into the pool to play with me or on the beach and in the sea. He loves to go cycling, but has to go early in the morning and ends up in pain so he can't play with me. But it is hard for him in the strong sun and he can swell very easily which leads to me feeling quite lonely on the beach as my mum normally only sun bathes. Then he feels angry with himself and that makes me feel guilty and that it's my fault he has the condition. If he was my only parent, I wouldn't be able to cope very well as I love water and the sun and heat. When I was smaller I didn't understand why daddy couldn't come and play with me and I felt sad when he would not come.

When my friend Charlie and his family go on holiday or a day trip somewhere, they're going to mostly very outdoorsy and sunny places and we regularly try and go with them. They all have so much fun out and about, but although we go outdoors a lot of the time we still have to make sure dad is safe. Daddy is a little bit different to mum, Charlie's mum and dad Jane and Ed and other families as he tries to do as much as he can with me but also has to look after himself.

If my daddy was given a treatment and did not have to worry about EPP any more, my life would be paradise and every day I would treasure each moment carefully. He would be able to do things normally with me such as:

- camping
- go to beaches and lots of different countries
- help me more with my tennis, swimming and other sports
- regular every day outdoors jobs
- go on the trampoline
- go to visit my brother who is living in Australia
- playing on the lawn
- go on boats
- go to exotic places
- HAVE FUN
- Go in the paddling pool
- Come out on bike rides with me and mummy
- And everything else!!!!!

## Appendix 2: BPA Patient Survey May 2018

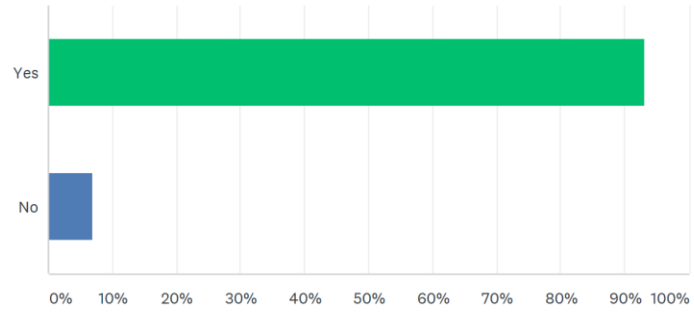
Results from a short SurveyMonkey survey carried out via BPA members in May/June 2018.

Q1

Customize Save As

Do you have a confirmed diagnosis of Erythropoietic Protoporphyria (EPP or XLEPP)?

Answered: 100 Skipped: 20




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Yes | 93.00% | 93 |
| No | 7.00% | 7 |
| TOTAL | | 100 |

Q2

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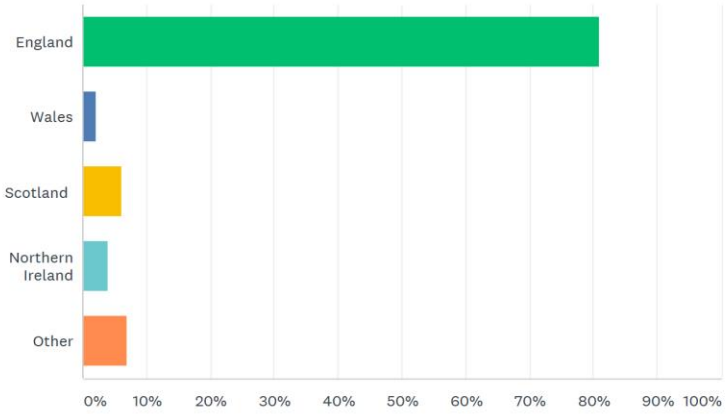
Where do you live?

Answered: 100 Skipped: 20




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| England | 81.00% | 81 |
| Wales | 2.00% | 2 |
| Scotland | 6.00% | 6 |
| Northern Ireland | 4.00% | 4 |
| Other | 7.00% | 7 |
| TOTAL | | 100 |

Q3

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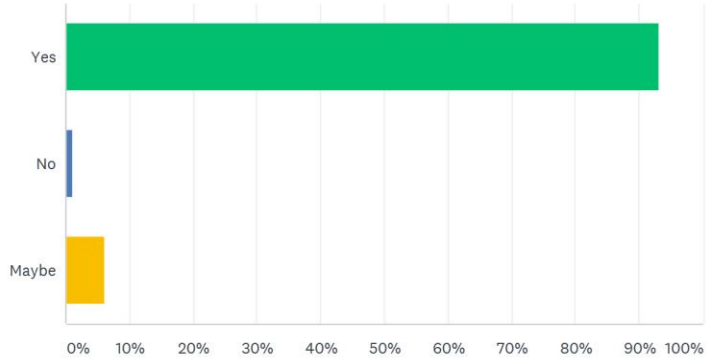
## If Scenesse were to be approved for use on the NHS in the UK, would you try it to see if it worked for you?

Answered: 100 Skipped: 20



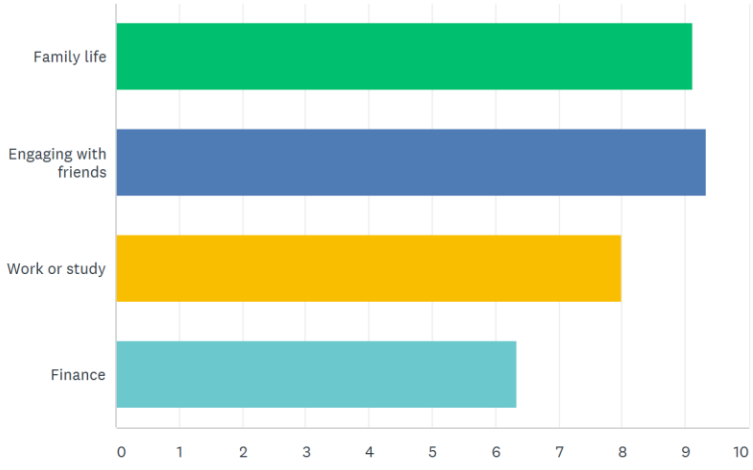

| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Yes | 93.00% | 93 |
| No | 1.00% | 1 |
| Maybe | 6.00% | 6 |
| TOTAL | | 100 |

Q4

Customize Save As

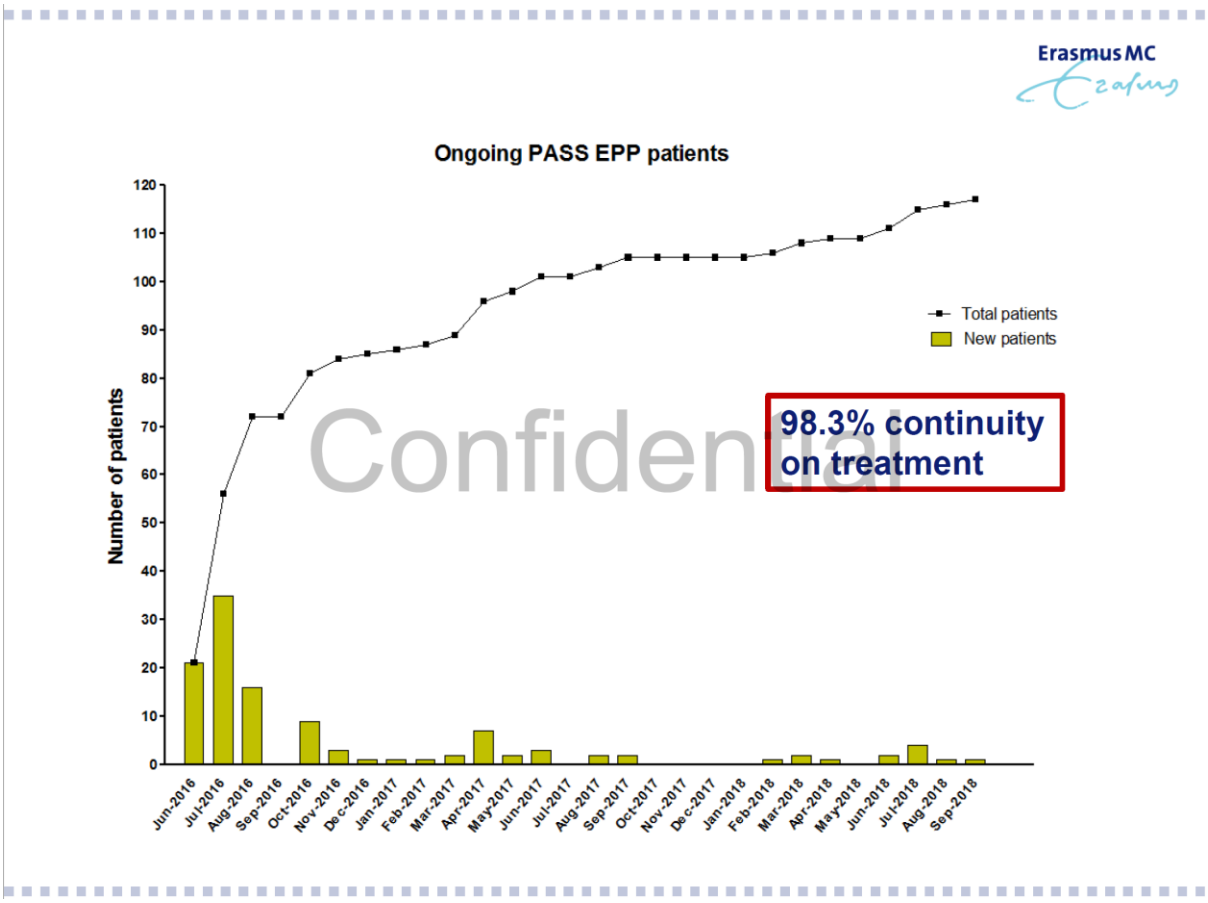
## On a scale of 0 to 10 (where 0 is not affected at all and 10 is extremely affected), how does EPP affect your life in the following categories?

Answered: 99 Skipped: 21



**Appendix 3: Continuity rate of patients being treated with Afamelanotide in the Netherlands**

Statistics kindly provided by Janneke Langendonk and Debby Wensink from Erasmus MC, Netherlands



**Appendix 4: Jeroen Verheul (2013): *A Life with EPP***. Investigation by the Dutch patient organisation for EPP. Translated and submitted for the EMA approval process.

*A group of about 40 patients worked on this paper about EPP. Only their closest relatives and friends know how their lives are influenced by EPP. They felt a great urge to participate in this project and explain their life (A life with EPP) and work (A job with EPP)*

# A life with EPP

## Introduction

It is not possible to simply summarise what EPP means to the 'sufferers' of this condition. Since daylight is present in large quantities at for example the office (due to extended windows) and in public transport, most patients only feel safe in the 'comfort' of their own house. Due to strict regulations for foil in vehicles, that form of protection has partially disappeared too. It is often necessary to apply protective foil to windows, even in homes. Patients suffer from a withdrawn existence mainly out of necessity because they have challenged their limitations with hurtful experiences during their youth. At the same time patients know they have to extend their boundaries to have a normal existence.

The patients suffer worst from April until August when the radiation is at its highest but also when the sun is out longest. Patients are virtually continuously dealing with their limitations and are always trying to plan their days in a way that they are not in danger of exposure. From November to February patients have the best time but still they avoid outdoor activities like ice skating or winter sports holiday.

The physical complaints are sharp pains and can be characterized as the pain one has from stinging nettles with a hairdryer blowing hot air onto it. The pain and burden build up in the course of time and restrain longer and longer. True recovery can only happen after three days of rest in a dark surrounding but one's busy lifestyle does not allow this. The pain level doesn't just drop to zero after a good night's rest. Many patients just keep going and remain hypersensitive during a longer sunny period by virtually every ray of light (also through glass) and even many forms of artificial light. The skin – the radar – keeps giving emergency signals until the weather changes for the worst or there is in fact time to take shelter indoors for a few days. Only then can one say that the pain level is back to zero and a patient will be able to go into the sunlight for anywhere between a few minutes to one hour. If it is partially cloudy outside they may even be exposed for a bit longer but that depends on the light-radiation.



In 40percent of the cases EPP causes unemployment, a considerable larger amount of people calling in sick and it restricts patients in their choice of study and career. Furthermore there is the social and psychological side of the condition. The skin is a sensitive radar which warns a patient at an early stage with painful signals. To avoid isolation and because of obligations towards work, family or social aspects EPP patients will surpass their own boundaries. Social obligations are hardly ever relaxed due to this. Patients feel it on forehand and are held back by the early arising pain and panicky fear they might experience. Without a good social network and understanding from the people around a patient it will lead to more isolation. Even more so for children who suffer from EPP. They have to deal with a lot of pain, anxiety and even panic attacks.

## Children

All EPP patients have at least one childhood memory in common. The burden of the sun: not being able to sleep at night, the itch they experience, the burning agony. Looking for the cool metal of the radiator in the dark. Washcloths to cool with, which turn warm too quickly. The endless hours of not being able to fall into sleep. Staying indoors for shelter 2, 3 days in a row.

And this is just the healing process. Keep in mind the process children undergo before getting to this stage. The pain of the sun on the day in question, but also the fear and anxiety beforehand. The realization you can't escape from the well-intended day-trip in the shade (where there is sun radiation

as well). Sports matches, P.E. or a play date. If one wants to undertake anything, one will be confronted by sunlight. That fear makes matters worse. Like mentioned earlier, the skin functions as a radar. A radar which sends alarm signals on what is coming beforehand. In spite of this children (and grown-ups) keep going because they simply have to go to school, work, shops, sports or the playground with their infants. The sun shines for a long period of time, through windows as well. The light in an ordinary living room is too much with EPP-pain complaints. Being isolated in a dark room is the only remedy. This too is recognised by the patients. Patients claim that sunlight through windows is as harmful as direct sunlight. One does not have to be outdoors to experience the burden of EPP. On that quote, several minutes of sun exposure behind glass e.g. whilst taking public transport can have grave consequences. Therefor patients prefer working on the north side of a building or behind well-functioning sunscreens.

Often children are unable to control their own lives. The limitation, pain and fears caused by EPP form children in the most significant years of their lives. In some cases one can talk about damage ranging from depression to social isolation. Research done by Navarro (1986) and Rufener (1989) have given us founding insight on this matter.

For children in their growth EPP is the worst. During the last patient-day in Utrecht a mother of a nine year old patient emotionally expressed this. In all communication on Scenesse it failed to mention minors. She impressively urged doctors and consultants present to stand together for a prompt realization for children.

**Social aspects**

It is a psychological pitfall not to want to deviate from others, mainly friends. If one wants to connect, one will come along on holiday, also when there is understanding and consideration for the situation. Virtually every time holidays like these will end up in huge painful disappointment and are not really worth repeating. Patients withdraw themselves and calculate whether or not they should turn up at parties. Spending an afternoon on your own in the kitchen is disappointing. Everyone is outside and there you have it; the social norm; one does not want to disconnect from the group and goes beyond their own boundaries. Such a party is hardly ever an event where patients enjoy themselves. Patients are tense when going to the party, mainly because their skin has already been giving warning signals on what is to come. Yet one goes. Even if it is just to please your family. They can't possible become the victim of your limitations? Patients call the effect of EPP on family life severely disruptive. It asks a lot of the partner as well.



**In practise**

As a patient one learns from the many painful experiences from one's youth. One avoids those situations by making conscious decisions about work, sports and social life. When having a family of your own one is forced to adjust to a new rhythm and going outside daily is a part of this. Bringing your child to and from school, sports or play dates. Afternoon sun is unavoidable. Just recently a young single mother (EPP patient) of a two year old alerted us about her burdensome situation. Without a good (social-) network the situation is impossible.

The patient who does go outside under these circumstances needs to wear full protective clothing including gloves. An uncovered hand or stripe of sunlight in the neck or sleeve can cause enough pain to make one turn around and go back inside. The local pain is progressive until it becomes unbearable. A mere sunblock does not protect against the wavelengths of the daylight-spectrum.

Another issue is the holiday; to many a relaxing experience. For patients a fatiguing period. One goes for the family, mainly for the children but the journey and the excursions are a disaster. One sees the surrounding people enjoying the sunlight but the only thought one has is to flee. One patient stated that the children don't tolerate the excuse of work to get out of a holiday anymore.

**Patient's opinion on Scenesse**

Patients who have used Scenesse know that the daily routine can go with less worries. Thus now the father can bring his daughter to the ice hockey match and even stick around to watch it. Something he hadn't been able to do for years!

Furthermore, groceries can be done without pain. A mother doesn't has to feel nervous while seeking shelter in the bike shed at the school of her child because the teacher let the children go a few minutes late. A single mother is less dependent on her social network to help with practical matters, because she can take her child to the playground or children's farm.

Some are scared their vehicle might break down. The foil might keep you save, but what if you have to get out of the car?
A parent doesn't have to tell their child 'no' if it wants to go outside to play together. Instead of having tearful face the child will have a smile on its face because the parent can join in for a change!
And how about the patient using Scenesse who doesn't have to leave the football field the moment the sun comes through. Or the patient who is not afraid of going on a cycling trip with the family, even though the sun might break through?

The medicine doesn't only serve its purpose in the summery periods. Even in winter social isolation can occur because patients can't take part in the normal daily activities due to sunny periods.
It's not just the patient who benefits from Scenesse: the entire family, the social surroundings and the working environment do not have to be in dark spaces anymore because the sun has to be kept out.

The absence from work, school or study will be far less because patients do not have to call in sick. This is due to the fact that complaints during the ordinary daily life will reduce significantly!
Furthermore, patients are far less limited in their choice of profession because the working environment does not have to be adjusted completely. An employee can also go outside easier if work has to be done out of the office.



A social improvement in respect to the social position and the development of the talents of the patient.

A patients needs to plan a lot less and this causes inner peace. On social level EPP patients can develop much better. Even the holidays will become more relaxing. Patients have reported to have been to places which where uncommon to them. They enjoyed being there, places like the school playground. If unexpected discomfort does occur the recovery takes much less time. It is not a cure for EPP but it does give back huge aspects of normal life. For the first time EPP patients have felt free and without worry. One patient felt like he was reborn!

# A job with EPP

## 40 percent of the questioned patients lost their (part-time) job due to EPP.

We have asked patients whether they could keep their job despite of EPP.
The question was: "Have you ever lost a job or been unable to keep a job due to EPP?"
Sadly, 40 percent of the patients answered this question with a yes.
Obviously the worry about the work varies. Different reactions rose according to the sort of employment the patient has. Especially during the current crisis it is worse to lose the job on which you rely for bread winning than losing a holiday job. One patient replied that EPP is currently in his disadvantage during reorganisation. Because of EPP he cannot be active all round and therefore he fears for his job.
Some additional remarks sent in with the answers to the question "Have you ever lost a job or been unable to keep a job due to EPP?"

- *"Yes, often and that frustrates me. I am a hard worker and the fact that I just cannot hold on to a job due to EPP frustrate me immensely. It is likely that I will lose my job in healthcare because it is unavoidable that I have to go outside every now and again. It would help tremendously if I had a medicine which allowed me to get into contact with sunlight, outside, even if it is for just an hour".*

- *"Yes, several times in the past"*

- *"Yes, I have lost two jobs due to EPP"*

- *"When I was 13 years old I delivered leaflets. I had to quite this job in the spring because there were complaints about my delivery work. Currently I am a shelve filler at a supermarket. This is going well because the job is inside and near my house".*



- *"When I was 20 years old I couldn't hold down my holiday job. Tarring drainpipes at de Heidemij in the summer."*

- *"Yes, I prematurely had to give up my holiday job in a department store because I couldn't work for three weeks due to sun-exposure in my spare-time."*

The remarks sent in when the answer to the question was I have <u>never</u> lost a job due to EPP show that it is frequently possible to adjust to the handicap. Apparently these patients were able to conform regularly to their limitations.

- *"No, I have always had jobs indoors"*

- *"No, but is has restricted me in my choice of study and carrier."*

- *"I have done my internship specifically from September to January so that I have outdoor experience for the rest of my carrier. I must say; September was quite a challenge."*

## 91 percent of the patients have adjusted their choice of profession due to EPP.

"Is your choice of profession determined by EPP?" Only a very small percentage of the patients who answered this questionnaire actually have a job in their first choice of trade.
A better question would be how many patients cannot work in their profession of choice. It is clear that patients cannot follow their heart but have to think rationally when it comes to their choice of profession. It means that one can never live up to the ideal. Without dramatizing this, it is very clear that EPP patients are limited in their employment choice.
Some additional remarks sent in with the answer to the question: "Is your choice of profession determined by EPP?"

- *"yes, absolutely"*
- *"Yes, I studied something different to my first choice."*
- *"Sure, I used to be interested in work in developing countries and I wanted to study cultural anthropology. Eventually I ended up in tourism and I pushed all the boundaries, in some extend to the impossible. That hurt a lot, but I did not want to accept that some things had to be left alone. I have done rain dances in many tropical locations, I have prayed for clouds and I have often taken shelter in office work.*
- *'Maybe indirectly, I am doing an IT-study and that is indoors''.*
- *"I feel very limited when it comes to my choice of trade. I have considered doing a sports study but that isn't accomplishable. I think it is quite difficult to decide on which study or profession I will do and I realise I can't decide on anything that involves going outdoors a lot (E.g. sports, adventurous professions, fieldwork). I have noticed it is a difficult decision for many of my friends but I feel far more limited because of EPP. I can't make choices based on emotions.*
- *"Partially, yes (indoor functions instead of execution, although I still combine it as much as possible with outdoor activities)."*
- *"Off course. If you suffer from EPP, you know you are limited in your choice of profession.*
- *"Yes, to a degree. Because of my choice for techniques I was fortunate to be able to do the work indoors."*
- *"Yes, I am a lawyer. I could not possibly choose a profession which forced me to be outside in the summer."*
- *"Yes. I now have my own practise as NMI register mediator (mediation for divorce cases, family affaires, labour, inter- and multi cultural affairs, government, neighbour mediation and vicinity) and Coach. Thus I work indoors."*
- *"Yes enormously! I have always wanted to work with animals but the study consisted of a large amount of courses which had to be done outside. This was not possible. Due to this I had to move towards a different study. Next to this, my dream of living in the countryside and having a farm with live stock and land would stay a dream. Because of EPP I could never realize such a dream. I would like to add that I would have loved to be a part of the recent founded animal police force. And again EPP has restricted me in my wishes"*

- *"Initially not. I chose my study because I have always wanted to work with children. However, it turned out that working with children meant being outside. This is now no longer an option for me as I am an EPP patient and can't be in contact with direct sunlight."*

## 46 percent of patients are claiming health-benefits due to (physical) EPP-complaints.

This is the case for nearly half of the patients. For the other half this is not the case but that needs no explanation. Many of the questioned patients stated that they make sure not to become ill by being careful with themselves in their spare time and by staying indoors.
Patients also answered that they go to work despite of the pain they experience while being ill.
Some additional remarks sent in with the answer to the question "On average, how many days have you called in sick due to EPP over the past five years?"

- *"I have never called in sick because I always take into consideration that I have to work the next day, therefore I stay indoors."*
- *"None. I make sure I don't get physical complaints."*
- *"None, I am a self-employed independent entrepreneur and I have completely adjusted my work to my disability.*
- *"5 weeks"*
- *"On average 5 days per year"*
- *"Certainly one third of a year when it comes to these parts of the day..."*



- *"I cycle back and forth to school daily. The journey takes approximately 40 minutes. Despite of my protective garment I still experience discomfort and complaints. During my school years I have been sick quite often and had to miss lessons due to this. It will amount to approximately 25 days per year.*
- *'' 2 - I don't report in sick often".*
- *"2 days"*
- *"None, I stay indoors as much as possible between March and October. If I do feel discomfort I go to work anyway. My job is indoors and cools due to the air conditioning.*
- *"3 weeks"*
- *"I am retired now. I did call in sick during work more than"*

## 35 percent of patients' employers have made some form of adjustments to the working space for them.

This question is about whether the employers or school bear the costs for the adjustments made to the work environment. This is the case for about one in three of the patients questioned.

Surprisingly a number of patients gave negative answers to this question and their explanation is that their employers do not wish to make adjustments. This is a shocking answer and should lead to further and more detailed subject for discussion.

To continue, it has to be said that a number of the patient are in actual fact working indoors and have sufficient protection if they do not have to work on the sunny side of the building.

Some additional remarks sent in with the answer to the question "whether the employers or school bear the costs for the adjustments made to the work environment".

- *"For the last 10 years I have been taken to school in a taxi (from VMBO (lower vocational education), the MBO (intermediate vocational education), and now HBO (higher vocational education)".*
- *"No, I wish for other less strong and warm lamps, but this is impossible".*
- *"The local council gave my junior school window screens".*
- *"No, often these sorts of things are not taken seriously by the employers, this is in my experience".*
- *"At school I sit in the middle of the classroom, so that I can avoid the sun. I receive extra guidance and support through a budget for long-term ill children till the end of this school year".*



- *"I am allowed to change my work time (office hours), if this is sun technically better",*
- *"I asked for a workspace which is not next to a window or on the west side of the building. This was quickly arranged."*
- *"Yes. When dividing the workspace I requested a space on the shadow side of the room. Here there is virtually no sun at all. When any sun does shine in the laminated curtains are closed. When the sun is a problem the temperature is better here. An additional aspect is that all employees doing the same thing as me have to work in the same area as me too.*
  *Other adjustments have an influence on my own work. While I was the head secretary I frequently had to ask my colleagues if they would go and buy flowers, cards, tourist vouchers, cakes etc. because it was too sunny for me to be able to do this myself.*
  *Lastly I would like to quote the social aspect. Because of EPP I have only been able to attend one teambuilding event in the last 6 years. These activities are organized in the spring and autumn and are usually outdoors.*
- *"Windows screens".*

## 28 percent of the patients have adjusted their home with government funding.

It is apparent that not all patients get funding for the necessary adjustments that have been made. Around 28 percent have been able to claim the costs of the adjustments. Sometimes patients were able to get funding for adjustments which were not given to other patients. This shows a difference in local policy; another thorn in the eye of our patient society. Getting local councils to have the same point of view proves to be very difficult. Many patients have adjusted their home or garden, let alone their choice of house adapted to the disability. We have not questioned this point.
Some additional remarks sent in with the answer to the question "have you had adjustments made to your home which have been funded by your employer, the city council or other sources of funding"

- *"No, I paid for everything myself. I installed dark window screens".*
- *"Screens paid for by the city council, also foil for my car window and an extern roof."*
- *"My parents have paid for all the adjustments themselves"*
- *"I have let some adjustments been made, but paid for it myself."*
- *"The sunscreens added to my house have been paid for by the city council."*
- *"Adjustments to windows but no refunds."*
- *"Shutters in front of the windows which I paid for myself. I do have a parking permit for the disabled"*
- *"Shutters all round my house which I paid for myself."*

## All patients avoid using their bike and taking public transport during the Sunny seasons. Their main form of transport is by car.

This is not a very surprising outcome. The question was: "Do you use the car for trips you could have done by bike f you did not have EPP?" The bicycle is an impossible method of transport during spring, summer and autumn. The car is the best option in these periods. If the car is not an option, patients choose to sit on the balcony of the train as there are fewer windows there.
Some additional remarks sent in with the answer to the question "Do you use the car for trips you could have done by bike f you did not have EPP?"

- *"Yes, otherwise I would not be able to leave the house and I had to cancel my appointments".*
- *"Yes, but I use public transport. I live 5 kilometres from my work. The distance is easily done by bike, but I am forced to take public transport because I then am better protected from the sun. Going by car is not an option because there is no close parking space for me. I don't want to apply for one on medical grounds because I don't wish to be an exception".*
- *"I use public transport to do the groceries at the shops 2 kilometres from here. Something I would normally do by bike.*
- *"Very often in the summer. I am guaranteed to become ill otherwise".*
- *"Yes, this happens a lot in summer.*
- *"Yes, all the time!"*
- *"I am bound to use the yellow-foil-car. I can't take the risk of going by bike. If the sun is not shining when I leave, I have no guaranties it will remain that way. An hour later the sun could be out".*



- *"Yes, my friends live near but it is always uncertain whether I can be exposed outside".*
- *"I live in the city centre and never have to cycle far. Recreational cycling with friend or family is out of the question. I simply can't".*
- *"Very often. Daily in the summer".*
- *"I got my motorcycle drivers license especially because I can cover myself up completely whilst on a motorcycle. I can't do that on a scooter or a moped. It makes me look like an idiot.*

**Submission of the International Porphyria Patient Network (IPPN) on long term effectiveness and new and additional evidence that addresses concerns raised by the HST Committee and/ or the Appeal panel during the Highly Specialised Technologies Evaluation for Afamelanotide for treating erythropoietic protoporphyria [ID927]**

**Short title: IPPN submission of new evidence [ID927]**

Authors: [redacted] [1], [redacted] [2], [redacted] [3], [redacted] [4]

[1] [redacted] International Porphyria Patient Network (IPPN)
[2] [redacted] Officer International Porphyria Patient Network (IPPN)
[3] [redacted] International Porphyria Patient Network (IPPN)
[4] [redacted] International Porphyria Patient Network (IPPN)
Correspondence: [redacted]

## Outline of the submission

On 27 November 2018, IPPN received an e-mail from Helen Knight, Director for the TA, HST and CSP programs at NICE further informing us of the next steps NICE and the HST committee will undertake in order to address the upheld appeal points in the case of afamelanotide:

“The HST committee will meet to discuss this HST evaluation on Wednesday [later corrected to Thursday] 14 March 2019.

In order to support the committee in its reconsiderations, as a participating stakeholder in this technology, we would like to invite your organisation to submit the following:

- New or additional evidence not submitted during the original evaluation, particularly regarding anything that supports long term effectiveness of the treatment.
- Further evidence that addresses the concerns raised by the committee and/or the appeal panel.”

As suggested, we considered in our submission how to demonstrate where some of the benefits of afamelanotide in the 4 categories below may not have been captured in the committee’s previous deliberations:

- Nature of the condition
- Clinical effectiveness
- Impact of the technology beyond direct health benefits
- Value for money

As the ongoing appraisal process in part builds on the decisions made by the Appeal panel, we first outline briefly by way of introduction our understanding of the implications of the Appeal decision.

The Appeal Panel upheld three appeal points raised by the stakeholders:

“The evaluation is remitted to the evaluation committee who must now take all reasonable steps to address the following issues:

i) The failure to include an IPPN representative at the second committee meeting (IPPN 1a.1).
ii) The failure to demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act (CLINUVEL 1b.1 and IPPN 1b.1). The appeal panel considers that this is likely to include express consideration of whether the methodology used in the evaluation discriminates against patients with EPP and if so what reasonable adjustments should be made.
iii) The appeal panel's conclusion that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide (BAD 2.2 and 2.3, IPPN 2.2).”

(Appeal Decision p.20; ¶ 122)

It is worth outlining briefly the implications of the second two issues identified by the Appeal Panel, which in our view have particular implications for the further appraisal process.

Appeal point ii)

“The panel took the view that EPP very clearly meets the definition of a disability under the Equality Act 2010” (Appeal Decision p. 9; ¶ 53).

The British Government defined disability under the Equality Act 2010 as: “You’re disabled under the Equality Act 2010 if you have a physical or mental impairment that has a ‘substantial’ and ‘long-term’ negative effect on your ability to do normal daily activities.” https://www.gov.uk/definition-of-disability-under-equality-act-2010 (Last accessed 13 January 2019)
Therefore,

(1) EPP is a more severe condition with more implications than previously assumed by the Committee. The HST guide “Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes” lists severity of a condition and disability as criteria considered in the cost-effectiveness analysis which should be adjusted accordingly. The severity of the condition is addressed further below.
(2) The Equality Act 2010 requires NICE to make reasonable adjustments, as well as to give due regard to the need to advance equality of opportunity between those with EPP and those without it, including encouraging persons with EPP to participate in public life. In addition, the UN Convention on disability rights, to which the UK is a signatory specifically provides that States must take “appropriate measures to ensure to persons with disabilities access, on an equal basis with others, to the physical environment” (Art. 9). In addition, it provides that reasonable adjustments have to be made to prevent social isolation and segregation from the community (Art. 19).

To meet these legal duties, our view is that NICE cannot do other than permit access to afamelanotide, which enables patients with EPP to lead an almost normal life, which includes accesses to the physical environment and less isolation and segregation from the community.

Appeal point iii):

"[…] it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide (BAD 2.2 and 2.3, IPPN 2.2)."

(1) The benefit is not only perceived, i.e. "believed" (FED p.9) or "valued" (FED p.10) by the patients, but has to be rated as factual.
(2) Because the benefit is not "small", there are no longer "substantial differences" (FED p.10) between the patient`s testimonies and the trial results and the disease specific quality of life measurements – rather, the testimonies reflect the extent of the benefit of the treatment.
(3) The cost-effectiveness evaluation, which takes the extent of the benefit into account, needs to be adjusted and should become more favorable

We hope to support the Committee in its further considerations with the detailed submission on new and additional evidence provided below.

**Disclaimer:**

The authors of this submission state no financial interest in the manufacturer of the product under appraisal.

Comparisons to other HST appraisals under no circumstances are meant to question the validity of the positive decision for funding for the treatments for those other severe and debilitating conditions.

## 1. Nature of the condition

Erythropoietic protoporphyria (EPP) is an ultra-rare condition (1 person in 150.000 affected) with very limited research history and, consequently, many uncertainties. Up to date, 955 peer reviewed scientific articles have been published concerning EPP of which only 22 feature clinical trials (Pubmed, last accessed 2 Jan. 2019). By reading the documents of the HST appraisal and appeal process, it became clear that the Committee has uncertainties about aspects of the nature and severity of the EPP condition with direct consequences on the value assessment of afamelanotide.

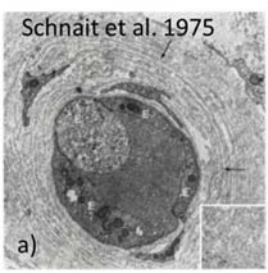
The Committee for example was unsure about the classification of EPP as being a disability because of the assumed absence of visible symptoms in EPP (Appeal Decision p.9; ¶ 51). In addition, EPP is an intoxication-type inborn error of metabolism (Das et al. 2013) and not a dermatological disease as implied by the Evidence Review Group (ERG) which, amongst other things, negatively impacted the economic modeling of the afamelanotide treatment (see section 3 and 4).

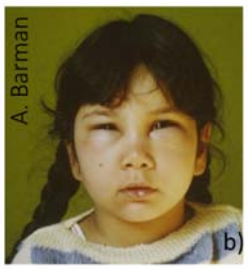
This demonstrates that the Committee was not fully aware of the nature of the EPP condition and, therefore, could not take all factors fully into account when assessing the benefit of the afamelanotide treatment. We address the identified uncertainties by providing the Committee with additional information and evidence not provided before on the nature of the EPP condition, i.e. examples of visible symptoms, behavioral adaptations and the resulting stigmatisation.

### 1.1. Visible symptoms of the EPP condition – physical injuries of the blood vessels

In EPP, visible light interacts with the accumulated protoporphyrin molecules and causes so called “phototoxic reactions”, which are burn-like injuries of the blood vessels (fig.1a; Schnait et al. 1975). Phototoxic reactions lead to a number of severe symptoms, including in an exacerbated phase, immediate burn-like pain in body areas exposed to light – comparable to touching an open flame. While the pain can already be unbearable, alterations on the skin surface however are usually absent or very discrete and might only develop several hours after the light exposure (Lecluse et al. 2008).

If possible, in an early stage of a phototoxic reaction patients withdraw from light exposure to avoid further exacerbation of the EPP symptoms and, therefore, usually do not develop any visible external signs of the phototoxic reaction. However, because of the “invisibility” of the symptoms, patients are often not believed and are sometimes forced to further expose themselves to light, although the pain can already be very severe, which then leads to the rare occasions in which the visible symptoms become very apparent. Due to the physical damage to the endothelial cells surrounding the blood vessels (fig. 1b), the blood fluids leak out into the tissue, which causes swelling of the affected body areas (fig. 2b). Further damage results in blood leaking out into the tissue (fig.1c). In addition, up to second degree burn wounds can develop (fig. 1d), which might even leave scars behind. The provided pictures illustrate the different stages of visible symptoms in EPP:





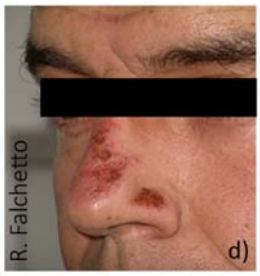


Figure 1: Visible symptoms of EPP: a) Chronic damage to the blood vessels caused by multiple phototoxic reactions in a biopsy from the dorsum of a hand of an EPP patient. Multiple basement membranes, each one resulting from repair process after a preceding phototoxic reaction, surrounding the papillary blood vessels (Schnait et al. 1975). b) Swelling of the tissue after prolonged exposure to visible light, caused by blood fluids leaking into the tissue. c) Massive damage to the blood vessels leads to whole blood leaking into the surrounding tissue. d) Second degree burns and open burn wounds. Visible signs like b)-d) only develop several hours after the acute phototoxic reaction.

### 1.2. Visible adaptations of EPP patients to their condition – protection from light

In order to not have to endure the massive neuropathic pain triggered by phototoxic reactions, which persists for days and does not respond to any known pain medication, EPP patients protect themselves as best as possible from light exposure by physical and behavioral adaptations. As sunscreens and other treatment attempts are not effective in EPP (Minder at al. 2009), the patients use improvised physical light protection as shown in the examples below:


Figure 2: Physical protection against visible light used by EPP patients: Patients use cloth, gloves, hats, umbrellas, masks and other forms of protection when outdoors. As however not all body areas can be sufficiently covered, and light behind window glass and strong artificial light sources can cause phototoxic reactions, the measures are not sufficient to completely protect the patients. In addition, the visible adaptations lead to stigmatisation of the patients, especially since usually visible symptoms of phototoxic reactions are absent.

The pictures provided in figure 1 and 2 demonstrate that EPP are associated with visible symptoms and visible protection measures. The described protection measures are however not sufficient to avoid the symptoms completely, as for example the hands and the face cannot always be covered and the measures cannot be used in indoor settings etc. In addition, they have secondary negative effects as outlined below.

### 1.3. Behavioral adaptation and stigma

Having to wear heavy clothing and other measures for sun protection like umbrellas in bright sunlight exposes patients to stigmatisation by their environment. Moreover, because EPP very rarely presents with visible physical symptoms, the patients are regularly accused of being malingerers and attention seekers who just make up their issues. In order to avoid, on the one hand, the painful phototoxic reactions and, on the other hand, the stigmatisation, from an early age on EPP patients adapt their behavior and restrict their light exposure as much as possible, impacting any social and work-related daytime outdoor activities. In the Committee papers, 16 of the 34 testimonies submitted during the consultation phase directly refer to humiliating experiences due to EPP. Four quotes from the submissions illustrating the behavioral adaptation and stigma associated with the EPP condition are provided below:

Stigma in EPP:

> *"All my life I have been bullied, isolated, misunderstood, shunned, picked on, alone, laughed at, alienated, mistreated and in constant unbearable pain."*
>
> Committee papers p.52; testimony 13

> *"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."*
>
> Committee papers p.56; testimony 18

Quotes demonstrating the behavioral adaptation in EPP:

> *"My life has been completely dictated by EPP with respect to education, career and life style."*
>
> Committee papers p. 58; testimony 22

> *"Isolation has already begun at her young age. We, her parents, dare not imagine what her future will be."*
>
> Committee papers p. 61; testimony 24

The described behavioral adaptations together with the anxiety to be exposed to light and potentially having to endure long-lasting, unbearable pain also affects the way patients react to new treatment options, especially since all other attempts so far have not been effective. The consequences on the afamelanotide trial outcomes are discussed in section 2.

1.4. Severity of the pain – EPP is not just "unpleasant"

During the Appeal Hearing, a Committee member several times described the symptoms of EPP as being "unpleasant". From a patient perspective this wording is concerning because it does not reflect the extent of the suffering experienced by those affected by EPP. Together with the perception of the Committee that EPP would not classify as a disability because of the assumed absence of visible symptoms, it demonstrates an underlying underestimation of the severity of the condition by the Committee during the appraisal process.

Nevertheless, an initial perception of the EPP condition as less serious than it really is closely resembles and reflects the frequent reaction of society to EPP patients and their families. As for the most time physical symptoms are not visible, EPP patients, even if they are already in severe pain, have to permanently justify themselves.

> *"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."*
>
> Committee papers p. 67; testimony 33

The patients during a phototoxic reaction usually stay in a dark and cool place until the symptoms subside, which could take several days. In most cases, they do not visit a physician or an emergency unit - there anyway is no effective pain medication – and therefore even most expert physicians never witnessed a patient in a full phototoxic reaction. We therefore provide the Committee with a short video (30 seconds) of [redacted]

[redacted] mother made the video during an acute phototoxic reaction and we have the permission to share this unique document.

1.5. EPP is a unique, intoxication-type inborn error of metabolism – and not a dermatological condition

We also feel that the unique nature of the EPP condition has not been fully captured by the ERG and, subsequently, the Committee, and want to stress that EPP is not a dermatological condition, but an intoxication-type inborn error of metabolism (Das et al. 2013) which affects the patients already from young age. EPP is characterised by, on the one hand, painful acute phases (the phototoxic reactions) and, on the other hand, by a constantly stigmatising and socially isolating conditioned behavioral adaptation to avoid light and its consequences – a feature not present in any other condition. Stigmatisation is augmented by late diagnosis often delayed for decades (Schneider-Yin et al. 2000; Holme et al. 2006; Wahlin et al. 2006)

1.6. No alternative treatment options

We note that the Committee agreed that no effective treatment options exist for EPP: "The committee concluded that there is no effective treatment for preventing phototoxicity caused by EPP, so there is an unmet need for an effective treatment." (FED p. 6).
Despite this conclusion, we have concerns about the way the ERG described the treatment options in reaching it and so think it is important to correct the record for the purpose of the reconsideration.

The systematic review conducted by Minder et al. (2009) is, to our knowledge, the only publication that systematically compares the scientific evidence of reported treatment options in EPP. Minder and colleagues concluded that "no undisputed and significant efficacy was shown in any of the therapeutic modalities applied in EPP so far" (in 2009). We are particularly concerned that the ERG in its report did not take this publication into account when describing the "treatment options" in EPP (ERG report p.19), although the British Porphyria Association made the ERG aware of it (ERG report p. 126). On the contrary, the presentation of the topic by the ERG creates the impression that, first, effective treatment options exist for EPP and, second, that patients do not pursue them for reasons such as convenience.

| **Treatment options for EPP as presented by the ERG (ERG report p.19)** | **Comment** |
|---|---|
| "Upon discussing treatment options with the ERG's clinical advisors it was noted that beta-carotene compounds (taken orally, on average eight tablets daily) seem to provide some protection for a minority of people. However, it can sometimes be hard to obtain beta-carotene in the UK and it has to be sourced from overseas (e.g. the USA)." | It is not clear why the ERG did not consider the best available evidence on treatment options in EPP, the systematic review by Minder et al. (2009; reference number 49 in the ERGs report), although it was provided by the British Porphyria Association (BPA): "The BPA highlighted a systematic review of treatment options for dermal photosensitivity in EPP, stating that high dose beta-carotene is ineffective.[49]" (ERG report p. 126). |
| "The ERG's clinical advisors also described the use of narrow-band ultraviolet beta (UVB) phototherapy (e.g. 3 x weekly for 4-6 weeks or variations of), which has, according to clinical experience and a few | In addition to the stated marginal effectiveness of the UVB phototherapy, some patients do experience severe phototoxic reactions during the sessions (Minder et al. 2009): The UVB sources |

| | |
|---|---|
| case reports, been shown to marginally increase patients time of exposure to sunlight. Although the ERG's clinical advisors did mention that few patients choose this option due to the practical issues and impact on lifestyle and work routine." | besides emitting UV (which is invisible) also emit strong blue light – the main trigger factor for phototoxic reactions in EPP. This, together with the justified concern about increased risk for skin cancer in case of prolonged usage (as would be necessary for a chronic condition like EPP) are in our experience the reasons why only a minority of patients seek UVB phototherapy. For UVB phototherapy, no prospective, randomised trial data is available demonstrating efficacy (Minder 2009). |
| "The ERG experts state that the use of Dundee cream can also slightly increase the time patients can be exposed to sunlight. However, it tends to be reserved for particular outdoor occasions rather than being used daily. This is because large volumes need to be applied, and it can adhere to clothing. In addition, these creams have an appearance similar to cosmetic make-up and are therefore not always acceptable to some patients (e.g. younger males)." | Sunscreens are of limited effectiveness, most patients do not experience any benefit. For sunscreens, no prospective, randomised trial data is available demonstrating efficacy (Minder 2009). |

From the patient's perspective the main reasons not to use beta-carotene, sunscreen and UVB-treatment is neither "practical issues and impact on lifestyle and work routine" nor "because large volumes need to be applied" nor that "these creams have an appearance similar to cosmetic make-up and are therefore not always acceptable to some patients (e.g. younger males)" as stated by the ERG (ERG report p. 19). The reason not to use these "treatment options" is simply lack of effectiveness, as demonstrated by Minder et al. (2009).

1.7. No "standard of care"

As demonstrated above, protection against light exposure by physical measures and behavioral adaptations are not sufficient to avoid EPP symptoms and, in addition, are associated with negative effects like stigmatisation and social withdrawal. Therefore, there currently is no "standard of care" available for EPP patients in the UK, and the patients are left alone with their condition.

The patient testimonies provided during the consultation phase impressively demonstrate what living with the EPP condition in the UK currently means:

*"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."*

Committee papers p.54; testimony 16

## 2. Clinical effectiveness and impact of the technology beyond direct health benefits – Trial outcomes

Since 2006, afamelanotide has been tested as a treatment for EPP in several clinical trials, collectively including 349 EPP patients. In addition, an eight-year observational study in 115 EPP patients from Italy and Switzerland receiving the afamelanotide treatment during compassionate use and special access programs was conducted. All four randomized controlled trials and the long-term observational study showed significant outcomes regarding the number and severity of phototoxic reactions, time spent in direct sunlight and / or quality of life as measured with a partly validated, disease specific quality of life instrument. (EPAR p. 74 - 75; Langendonk et al. 2015; Biolcati et al. 2015).

During the approval process, the European Medicines Agency (EMA) concluded that because of the rarity and complexity of the EPP condition, i.e. the dependency on external factors and the life-long conditioned behavior of the patients to avoid light, the efficacy of the afamelanotide treatment was not accurately quantifiable in conventional clinical trials (EPAR p.89 - 90). The EMA therefore for the first time in their history involved patients in discussions on benefits and risks of a medicine in a full regulatory meeting with the Committee for Medicinal Products for Human Use (CHMP). The EMA then based their positive recommendation for marketing authorization under exceptional circumstances on the input obtained from patients during the assessment: “The CHMP heard from patients and healthcare professionals involved in an expert group that patients treated with Scenesse [afamelanotide] consistently reported improvements to their quality of life.” (EMA press release, 24 Oct. 2014).

Whilst we acknowledge that NICE is addressing a different question to that asked by the EMA, both entities must consider the extent of the therapeutic effect of afamelanotide on EPP (although the EMA then focusses on balancing this against its risks, whereas NICE has to consider questions of cost). As outlined in our submission, it would be irrational for NICE to require a different kind of proof for effectiveness, especially since the reason put forward by the EMA for basing its positive recommendation for approval on patient input received during the approval proceedings rather than quantitative trial results, was that it is not possible to accurately quantify the benefit of the afamelanotide treatment in EPP because of condition specific characteristics.

During the appraisal for afamelanotide, NICE received 34 written patient statements submitted during the consultation phase, 16 describe first-hand experience with the treatment and provide further insights into the clinical effectiveness and the impact beyond direct health benefits: All 16 testimonies state life-changing effects and that under therapy, patients are able to have an almost normal life. In addition, UK patient representatives and expert physicians during the Committee meetings and the Appeal Hearing contributed first-hand experience with afamelanotide. The International Porphyria Patient Network (IPPN) in addition provides first-hand long-term experience (several Swiss patients receive the treatment since 13 years) on the effectiveness, benefit and the societal value of the treatment (see Appendix C- HST patient expert statement, submitted 4 Jan 2019).

Because of the experiences and conclusion from the EMA approval proceedings the IPPN together with the BPA in the draft scoping documents requested that during the NICE appraisal process patient`s testimonies should be included as an outcome measure (Draft scope and provisional comments table (post referral) p.12, 17 May 2017 (hereafter: Draft scope)). The British Association of Dermatologists (BAD) and the company put forward similar arguments (Draft scope, p.11). Despite the stakeholder’s requests, patient testimonies were not included as an official outcome measure in the final scope (Final scope p.2, 17 May 2017). In the “Action” section of the Draft scope document (p.12), NICE however explains that “the committee can consider a broader range of outcomes during the evaluation” and that “Consultees are encouraged to present evidence of the effectiveness of

the technology, which can come from other sources in addition to the clinical trial data, in their submissions." As the patient testimonies were not assessed as an outcome measure in the appraisal process so far we put forward that for the ongoing process the patient, carers and expert physician`s input should be included as a qualitative outcome measure. Therefore, we below present insights provided by the EPP patients, carers and expert physician's testimonies on the clinical effectiveness and the impact of the technology beyond direct health benefits of the afamelanotide treatment which in our opinion have not been captured in the Committee's previous deliberations because the testimonies were not considered an outcome measure.

Further, we address concerns expressed by the Committee regarding these testimonies, which seem to have prevented the Committee from fully acknowledging the submissions.

2.1. EPP patients are able to assess the clinical effectiveness of the afamelanotide treatment and their testimonies can serve as outcome measure

The European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL) is a group of 15 rare disease experts across seven European countries, including Health Technology Assessment (HTA) practitioners, physicians, patient representatives, academics, politicians and industry representatives. Dr. Sheela Upadhyaya, Committee Member and Associate Director of the HST program at NICE, is one of the 15 experts in the ORPH-VAL working group, which in 2017 published nine principles to help improve the consistency of orphan medicinal product (OMP) pricing and reimbursement (P&R) in Europe and ensure that it reflects the inherent characteristics of rare diseases, the ORPH-VAL recommendations (Annemans et al. 2017).

According to the ORPH-VAL working group, health care professionals, patients and their carers should be involved because they offer "an important insight into the real-world experience of a rare disease." "These stakeholders can help authorities understand what outcomes are relevant in a disease and what level of improvement is clinically meaningful."

In the afamelanotide trials, sun exposure time, and number and severity of phototoxic reactions ("pain") were measured as endpoints (EPAR p.74-75). According to Sullivan (2012) and Vroom (2012) "a clinical meaningful endpoint is an endpoint that directly measures how a patient feels (symptoms), functions (the ability to perform activities in daily life), or survives. Therefore, a primary endpoint should be a direct measure of one of these. A primary endpoint should generally not be a measure of something that is not important to the patient. Who knows better than the patients what is important to them?"

In EPP, a few minutes in sunlight are sufficient to cause massively painful phototoxic reactions:

> *"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."*
>
> Committee papers p. 40; testimony 3

Being able to stay in the light during such situations enables functioning, e.g. to perform activities in daily life, and having to endure less and milder excruciating painful phototoxic reactions is an improvement of the symptoms associated with EPP. Therefore, "more sunlight for less pain" is not a surrogate marker of unknown significance but a clinically meaningful endpoint, which is directly assessable by the EPP patients. The testimonies submitted to NICE illustrate the full extent of the benefit of the afamelanotide treatment:

> "*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."*
>
> Committee papers p. 40; testimony 3, same individual as above

The submissions demonstrate that the effects of the afamelanotide treatment as assessed in the clinical trials are relevant for patients with EPP and their families. The testimonies in addition illustrate "what level of improvement is clinically meaningful" (ORPH-VAL principle 1):

> *"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."*
>
> Committee papers p.39; testimony 1

During the afamelanotide appraisal, the Committee however assumed that "Clinical trial results suggest small benefits with afamelanotide" (FED p.1). The Committee maintained their interpretation, although patient representatives and expert physicians contributed their experience with the treatment at the Committee meetings: "It [the Committee] heard from patient experts and the British Porphyria Association that even small benefits such as being able to spend an extra few minutes in daylight or having fewer phototoxic reactions could have a large impact on people's lives." (FED p.8).
The IPPN and the British Association of Dermatologists (BAD) appealed against the Committee's interpretation of the trial outcome and the Appeal panel "concluded that it was not reasonable for the committee to describe the magnitude of benefits seen in the trial as "small" and thus upheld appeal points BAD 2.2, BAD 2.3 and IPPN 2.2." (Appeal Decision p.15; ¶ 88).

We conclude that the EPP patients, their carers and expert physicians are able to assess the clinical effectiveness of the afamelanotide treatment and can help decision bodies understand what outcomes are relevant and what level of improvement is clinically meaningful. Therefore, the testimonies received during the consultation phase and the inputs from patients at the Committee meetings should be considered and assessed as outcome measures.

2.2. Impact of the technology beyond direct health benefits and on carers and families

While not systematically collected, the impacts of the technology beyond direct health benefits and on carers and families are provided in several written inputs received during the consultation phase. As illustration, we provide one quote:

> *"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."*
>
> Committee papers p. 58; testimony 21

As the direct social environment like parents, partners, children and friends of a patient is affected by the condition in a way that allows them to directly whiteness and assess the benefit of the treatments, their input should be rated as outcome measure for impacts of the technology beyond direct health benefits and on carers and families.

2.3. Are the submissions received by NICE representative?

In general, a valid concern and limiting factor for the reliability of patient testimonies would be a potential selection bias, i.e. that only patients having a good treatment outcome and high treatment satisfaction engage in discussions with and submit testimonies to authorities. However, the experience of expert physicians and patient organisations and the observed high long-term treatment adherence for the afamelanotide therapy indicate that the majority of patients experience the reported life-changing effects:

“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.” (FED p.9)

“The BPA in their submission states that they have not encountered a patient who has not received a significant benefit from afamelanotide.” (ERG report p.127)

“One clinician reported from her experience where 39 out of 40 patients were responding to afamelanotide through increased daily sun light exposure and number of pain free days.” (EPAR p. 88)

“The company and experts stated that an indicator of the effectiveness of afamelanotide was the compliance rate of about 94% despite the cost and time associated with travel for treatment.” (FED p. 10)

We conclude that the descriptions obtained in the 34 testimonies, 16 with experience with the afamelanotide treatment, and the patient and expert physician inputs during the appraisal process are representative.

2.4. Are there “substantial differences” between the trial results and the testimonies?

The Committee was concerned about a perceived “substantial difference” between the trial results and the statements in the submissions received from patients, carers and expert physicians regarding the extent of the benefit: “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 substantial difference between the trial results and the expert testimonies, anecdotal evidence of those present at the meeting, and the consultation comments.” (FED p.22).

We assume that by “substantial differences” the Committee refers to the reported life-changing effects which seem to be in contrast with the perceived small outcomes of the clinical trials. The Appeal Panel however concluded that the trial results shall no longer be assessed as being “small” (Appeal Decision p.12; ¶ 70). It was convinced by the comparison put forward by Prof. Lesley Rhodes about the time normal people spend outdoors which is in the same range as the time EPP patients under treatment were able to spend in direct sunlight without experiencing phototoxic reactions in the trials:

“Professor Rhodes disputed the committee’s view that the clinical trial results suggest “small” benefits with afamelanotide. She stated that the average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). She argued that this increase puts patients with EPP who are on treatment into the normal range for this measure. (She quoted data that showed that healthy indoor workers spend an average of 22 minutes in the sun between 10am and 3pm). She also pointed out that the figure of approximately 10 minutes extra per day of sun exposure represents an average daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest.” (Appeal decision p.11; ¶ 64)

As the trial results are not “small”, consequently, there is also no “substantial difference” between the testimonies and the reported life-changing effects, which are rather a reflection of the therapy’s real benefits.

2.5. Do the testimonies provide the “complete picture”?

The Committee was concerned as to whether the testimonies submitted during the appraisal process would provide the “complete picture” and stated a perceived difference to the scientific literature:

“In response to a question from the panel about whether the patient and clinician testimony was unusually compelling and uniform in this case, Dr Jackson replied that the HST evaluation committee very commonly sees a similar picture of very positive responses with technologies that come before them. When the committee looked at descriptions of EPP in the literature, they felt that while the testimony of the nominated patients and clinicians was very powerful, this might not be a complete picture.” (Appeal Decision p.14; ¶ 78)

To our knowledge, the only publication on real-life and long-term effects of an effective treatment in EPP is the eight-year observational study by Biolcati et al. (2015). The patient testimonies submitted to NICE do reflect the treatment effects described in this publication, e.g. the strong and sustained increase in quality of life and that the benefits of the treatment are relevant and the extent meaningful. In addition, the testimonies also confirm further aspects of the condition, e.g. the social isolation and impacts on family and career choices, the conditioned light avoidance behavior which first has to be overcome to fully test and appreciate the extent of the tolerance to sunlight gained by the treatment.

If the Committee thinks that the descriptions in the submissions from the patients, carers and expert physicians do not represent the complete picture, the Committee should explain which aspects they feel are missing from the testimonies and which literature they refer to.

In addition, the Committee needs to clarify their expectations: Form our perspective it is contradictory to invite submission from patients and expert physicians, who are the individuals with first-hand experience with a condition and the treatment effects, and then invalidate them and their testimonies, because of a perceived difference to unspecified aspects of the condition obtained from undisclosed literature sources.

2.6. Has the conditioned light avoidance behavior influenced the trial results?

During the clinical trials, the behavioural adaptation in EPP patients was one of the reasons why the effectiveness of the afamelanotide treatment was not accurately quantifiable (EPAR p. 89-90). The EMA acknowledged that EPP patients first have to overcome their anxiety and unlearn their conditioned behavior of light avoidance, and approved the afamelanotide treatment under exceptional circumstances because, amongst other reasons, the efficacy is not accurately quantifiable.

The Committee however during the Appeal Hearing questioned the existence of the described effects on the trial results: “Dr Jackson, for NICE, said the committee had considered whether conditioned light avoidance was likely to have resulted in the clinical trials substantially under-estimating the benefit of treatment. They concluded that this was unlikely […].” (Appeal Decision p. 11; ¶ 60). (For further discussion on why the Committee doubted the existence of an effect of the light avoidance behavior on the trial results and further inconsistencies in their assessment of the matter see section 2.7)

We disagree: The unlearning of the behavioral adaptation is best illustrated by a quote from the submissions:

> *"My son (20 years old) has been treated with Scenesse for the last two years, and his life has completely changed for the better! 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."*
>
> Committee papers p. 69; testimony 35

The stated "careful acclimatisation" is partly reflected in the trial results (see figure 3, adopted from EPAR p.71; sun exposure time as measured in the pivotal trial CUV039): During the first 60 days, treatment and placebo group do not perceivably differ in their sun exposure times. However, with the second dose (after day 60), a clear difference is demonstrated between both treatment groups. This picture is best explained by the quote provided above: Patients first need to gain an understanding of the extent of the benefit and need test their new limits in sun exposure that they have under treatment – given the potential massively painful consequences of too much sun exposure an initial reluctance and an adaptation phase is plausible. In addition, as the trials were placebo controlled, patients did not know whether they would experience any effect at all, and since the trials were conducted under real-life circumstances there were significant risks of developing phototoxic reactions, which would have incapacitated trial participants for several days and impacting their ability to function in daily life.

In hindsight, a run-in phase omitting the first 60 days from further analysis would have been an appropriate adjustment for the trial design. This, in addition to other factors not captured during the trials such as the weather conditions and indoor occupation of the individual trial subjects, has affected the trial outcomes and illustrates the challenges in trial design in rare diseases, in which no previous experience with effective treatments options exist.

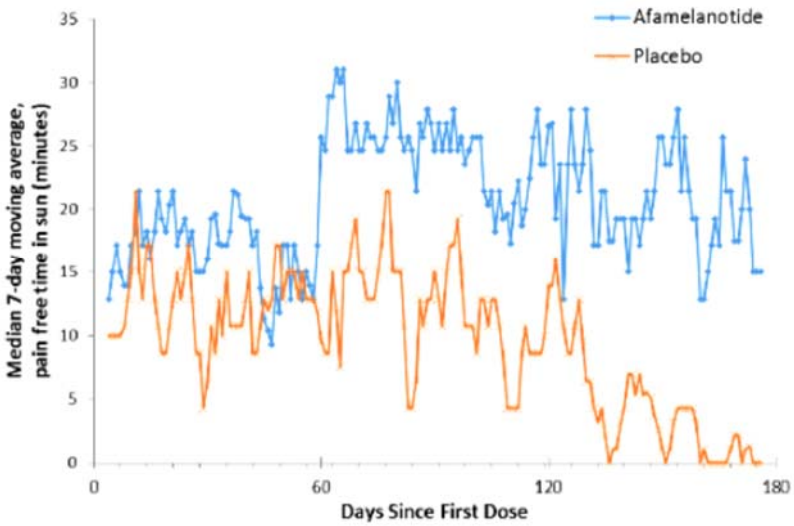



Figure 3: Median of the individual patients' 7 day moving average for pain-free daily exposure to direct sunlight for the CUV039 trial. In the first 60 days of the 180 days study period, no difference in sun exposure times is identifiable between the study groups. After day 60 (2nd dose afamelanotide), the treatment group shows a clear increase in sun exposure times compared to the placebo group. (Figure adopted from EPAR p.71)

Patient testimonies and the trial results measuring time spent in direct sunlight (without phototoxic reactions) strongly indicate that patients with EPP have to first overcome their conditioned light avoidance behaviour and that the trial results have been influenced, amongst other factors, by the patients' behavioural adaptation.

2.7. Impact of the conditioned light avoidance behaviour on quality of life measurements

Interestingly, the Committee on the one hand was concerned that the deeply ingrained light avoidance behaviour increased the uncertainty in the quantification of the benefit to an extent that would not provide sufficient evidence to recommend funding by the NHS or would not even allow for a Managed Access Agreement (MAA):

“The committee was convinced that patients valued the benefits of afamelanotide but remained concerned that no data were available to quantify this impact.” (FED p.10);

“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).

On the other hand, and contrary to the mentioned concerns, during the Appeal Hearing the Committee also fundamentally questioned the effect of the conditioned light avoidance behaviour on trial results:

“Dr Jackson, for NICE, said the committee had considered whether conditioned light avoidance was likely to have resulted in the clinical trials substantially under-estimating the benefit of treatment. They concluded that this was unlikely, because in the observational study by Biolcati et al (2015) there was a substantial improvement in quality of life over the first 6 months of treatment with no additional substantial change thereafter.” (Appeal Decision p.11; ¶ 60)

The sun exposure times measured in CUV039 as shown in figure 3 (see section 2.6) suggest that the patients under treatment needed approximately the first 60 days during the trial to first experience and become confident in the protection by afamelanotide, before they are able to partly overcome their conditioned light avoidance.

The first time point for quality of life measurements (as measured with the disease specific quality of life instrument EPP-QoL) after the determination of the baseline in the referred Biolcati study is on day 180 (see figure 4). During the clinical trials CUV039 (pivotal trial) and CUV029 (European arm of the study), a stepwise increase in quality of life indeed is visible (see figure 5): The biggest increase in quality of life (as measured with the EPP-QoL) is observed between baseline and day 60. After day 60, the quality of life further increases, however the improvement is less pronounced and in both trials levels off at around 80% at day 180.

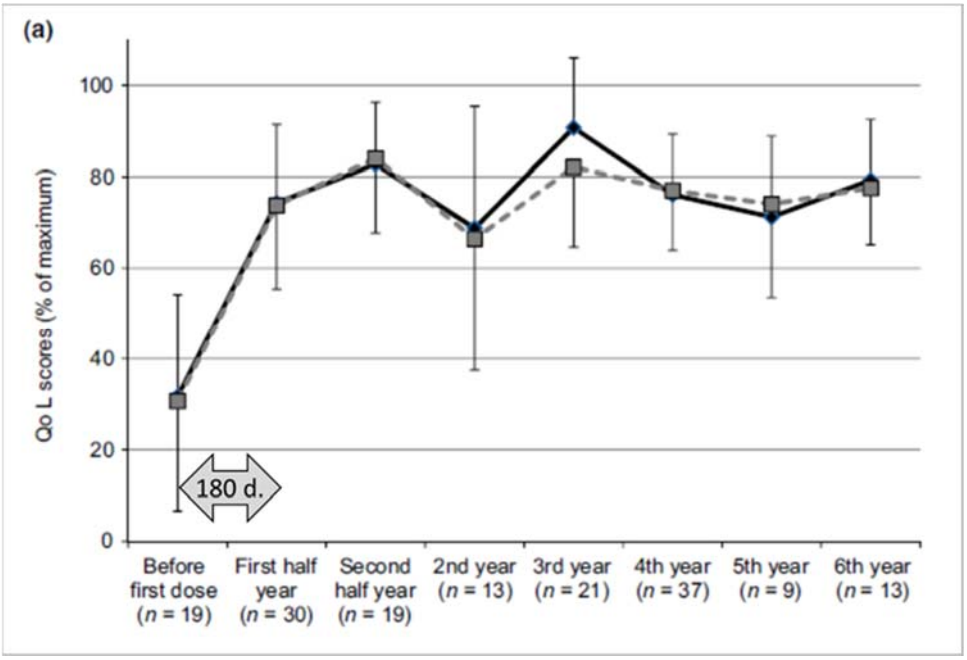



Figure 4: Quality of life as measured with the EPP-QoL in the eight-year observational study by Biolcati et al. (2015). First time point after determination of the baseline (before first dose) is day 180. The stepwise increase in quality of life observed in the clinical trials CUV029 and CUV039 was in the period between baseline and day 180 (figure 4). (Figure adopted from Biolcati et a. 2015 and modified).

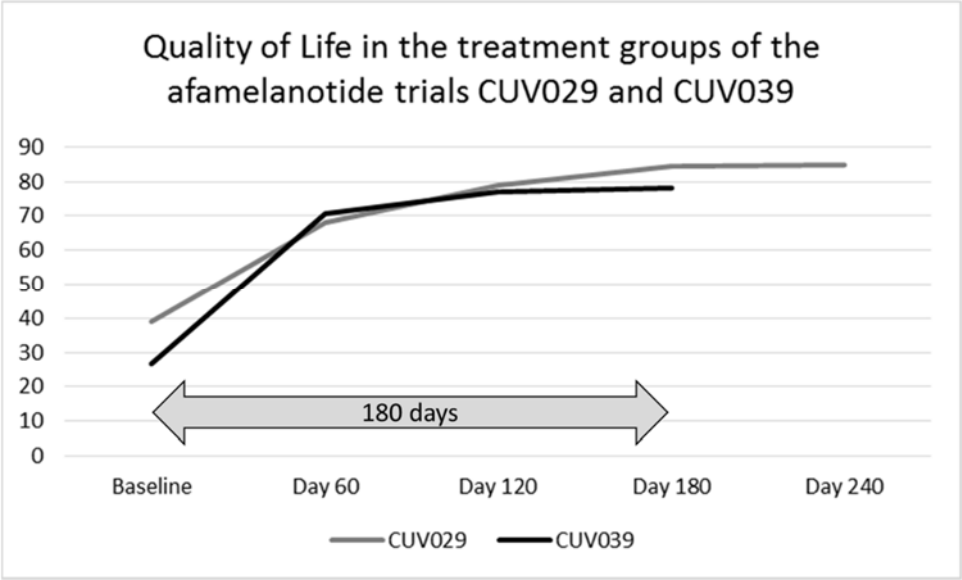



Figure 5: Quality of life as measured with the EPP-QoL in the treatment groups of the afamelanotide trials CUV039 (pivotal trial, duration:180 days) and CUV029 (European arm, duration: 240 days). A period with stepwise increases in quality of life is visible between baseline and day 180. Quality of life seems to level off at around 80 %.

Table 1: EPP-QoL results, excerpt from ERG report p.57

| Treatment | CUV039 | SD | CUV029 | SD |
|---|---|---|---|---|
| Baseline | 26.6 | 19.9 | 39 | 25.8 |
| Day 60 | 70.6 | 24.2 | 68 | 19.1 |
| Day 120 | 76.9 | 22 | 78.8 | 16.2 |
| Day 180 | 78.1 | 24.9 | 84.6 | 12.6 |
| Day 240 | | | 84.8 | 10.7 |

We conclude that the data obtained from the long-term observational study by Biolcati et al. (2015) does not cover the period in which the change in quality of life (further increase) would be visible (figure 4). Therefore, the absence of a further increase in quality of life measurements in the Biolcati study does not indicate that the patients would not need to overcome their conditioned light avoidance behaviour. To further explore how quality of life and the ability to expose to sunlight are connected in EPP, we asked an expert physician from Switzerland on their experience (box 1).

Box 1

Comment of expert physician Prof Elisabeth Minder, MD, who treats EPP patients with afamelanotide since 2006:

QoL und light exposure without pain are independent measurements. QoL is for example influenced by the fact that patients don't need to carry protective measures such as umbrellas, gloves long sleeves and closed shoes during hot and sunny days, which enables them to avoid stigmatization in the public. This effect is perceived comparably fast. Sun light exposure on the other hand is determined to a great extend by the patient's life style, e.g. the patient has chosen a work environment, that does not have a risk of sunlight exposure, his leisure activities he likes and is used to are indoors. Moreover, Swiss patients report that even after years of treatment with afamelanotide, they have consciously to overcome a psychological barrier to expose to light. This is underlined by our experience that it requires years of treatment until patients dare to move to a more rewarding working place that includes higher light exposure than the protected they had before.

E. Minder, January 2019, expert physician Zürich, Switzerland

### 2.8. Would it be unfair to use patient testimonies in the case of afamelanotide? - Patient testimonies in other NICE appraisal proceedings

A Committee member at the Appeal Hearing expressed concerns that using different approaches for the evaluation of afamelanotide would be unfair to those with other rare conditions.

"Jeremy Manuel, for NICE explained that the HST process itself was established in response to potential discrimination faced by sufferers of rare diseases. He felt that the same arguments used with regard to afamelanotide in this appeal point (concerning the complexities of capturing the full benefits of treatment) could potentially be applied to any rare disease. He argued that if a different method had been used in this particular case, it could be unfair to those with other rare conditions." (Appeal Decision p. 9; ¶ 50).

Capturing the full benefits of the afamelanotide treatment by, for example, including the patient testimonies as outcome measures as put forward by IPPN and other stakeholders however would only be unfair in case NICE would not consider patient input in other appraisals.
Staley & Doherty (2016) investigated the use of patient input in NICE appraisal processes and report that "On occasion, the patients' views have had a profound impact on decision-making (see the example of the review of insulin-glargine below) when committee members have drawn conclusions based on the clinical and economic data that do not reflect the reality of the patient experience."

*"We were considering insulin-glargine and the evidence showed that using conventional insulin and insulin-glargine had the same effects on HbA1c [a biomarker for diabetes control] but the glargine cost loads more, but what the committee heard from the patients was that if you have any tendency towards hypoglycaemic events, which can happen with standard insulin, then you literally went to bed every night scared you weren't going to wake up as a consequence of having a hypo. So people wouldn't take their insulin and their base level of HbA1c was much higher. So the committee asked for work to be done to survey patients to see how common this behavioural response was, and what impact the higher HbA1c levels would have on survival. Glargine did not result in hypos so had less behavioural impacts-you could take it and run yourself at the appropriate HbA1c level. With the additional evidence, the committee was convinced that a proportion of patients would respond better that way.* (Committee member 5)". Staley & Doherty (2016)

Diabetes mellitus is not a rare condition, and with over 458.000 peer reviewed publications, approximately 28.000 on clinical trials, a substantial body of evidence exists (Pubmed, last accessed 11 January 2019). Nevertheless, NICE considered patient input when assessing insulin-glargine for the treatment of diabetes mellitus type 1 and 2, to understand patient treatment preferences and behavioural responses.

Also in the HST2 appraisal of elosulfase alfa for the treatment of the ultra-rare condition mucopolysaccharidosis type IVa (MPS IVa), patient input was considered. We quote from the section on "Clinical evidence. Availability, nature and quality of evidence" in the FED of elosulfase alfa:

"The Committee noted that much of the evidence represented anecdotal, patient-reported outcomes. The Committee concluded that some of the true long-term outcomes in people with MPS IVa, such as cardiac and respiratory function and the need for orthopaedic surgery, remained uncertain.
The Committee was aware that the patient experts' opinion was subjective and was at risk of bias because it may represent the experience of only a selected group of patients.
The Committee was aware that the clinical trials measured primarily proxy outcomes, and did not substantiate most of the direct health benefits described by patients. The Committee concluded that data collected within the context of the managed access agreement would help to reconcile the differences between the patient testimonies and clinical trial data when this guidance is reviewed." (FED elosulfase alfa, p.41-42)

In addition, in the HST2 appraisal patient input was considered for the determination of the extent of the benefit:

"A patient expert noted in their submission that the improvement in quality of life associated with elosulfase alfa might be greater than the increase in 6MWT, and noted that even a small improvement in endurance could make a substantial difference to the quality of life of a person with MPS IVa." (FED elosulfase alfa, p.15; ¶ 4.26).

In the HST1 appraisal of Eculizumab for the treatment of the ultra-rare condition atypical haemolytic uraemic syndrome (aHUS), only single-arm, non-randomized trial outcomes were available:

"The key clinical evidence came from 2 published (C08-002A/B and C08-003A/B) and 2 unpublished (interim data from C10-003 and C10-004) prospective studies, and 1 retrospective observational study (C09-001r). No randomised controlled trials were identified. All prospective studies were phase 2, open-label, non-randomised, single-arm studies that included patients with different clinical baseline characteristics."
Guidance for Eculizumab for treating atypical haemolytic uraemic syndrome, https://www.nice.org.uk/guidance/hst1/chapter/4-Evidence-submissions#clinical-evidence (Last accessed 14 Jan 2019)

Also in this case, patient, carers and expert physicians input was considered and Eculizumab was recommended for reimbursement by the HST Committee in charge (appraisal HST1):

“After considering all available evidence, and the opinions of the clinical and patient experts, the Committee agreed that eculizumab represents an important treatment option and effectively decreases thrombotic microangiopathy activity and improves kidney function in most patients with aHUS. The Committee noted that the use of eculizumab would be of significant value to patients with aHUS, but it was aware of its need to consider the extent to which the cost to the NHS of doing so was reasonable.” (FED Eculizumab, p.27)

As patient input was considered in other conditions and the HST program showed flexibility and a sense of proportion when assessing other rare conditions, the consideration of patient input and other reasonable adjustments in the case of the afamelanotide appraisal would not be an unprecedented and unfair act against other rare or common diseases. Rather, the opposite is the case: It is unfair and discriminatory to not take EPP patient input into consideration in the appraisal of afamelanotide.

2.9. New evidence for long-term effectiveness: Treatment adherence rate in the Post-Authorization Safety Study of over 98 %

Treatment adherence is a major concern in all health care systems, causing a significant amount of avoidable complications and costs, also in the UK (Dunbar-Jacob & Mortimer-Stephens 2001; Osterberg & Blaschke 2005; Khunti et al. 2018). The reasons for poor adherence are various but include, amongst other things, lack of (perceived) benefit (Patti et al. 2010). According to Osterberg & Blaschke (2005), missed appointments (“no-shows”) are one of the markers of poor adherence.

For this submission, NICE specifically asked about additional evidence on the long-term effectiveness of the afamelanotide treatment. We think that the exceptionally high adherence rate for the afamelanotide under real-life conditions demonstrates the high treatment satisfaction and should be counted as supporting evidence in the context of the EPP condition.

Already during the eight-year observational study in 115 patients receiving afamelanotide during compassionate use and early access schemes in Italy and Switzerland, a compliance rate of 94 % was noted (FED p.10).
After obtaining marketing authorisation, the Netherlands were the first country which in June 2016 started to regularly treat EPP patients with afamelanotide: Between June 2016 and November 2018, 117 patients started with the treatment at the national porphyria center in Rotterdam. The treatment adherence rate of this cohort is 98.3 % with only a few patients reporting lack of effectiveness as a reason not to continue the treatment (Langendonk and Wensink, personal communication). A detailed list of reasons for discontinuation with the afamelanotide treatment will be published by Langendonk et al. (manuscript in preparation).

The Committee previously “appreciated the compliance rate was high but noted that it was not a quantifiable marker of effectiveness.” (FED p.10). However, the HST can consider a wide range of factors and Barbosa et al. (2012) in a meta-analysis concluded “that greater treatment satisfaction was associated with better compliance and improved persistence.” As “collecting adherence data from subjects is now considered an essential part of clinical trials” (Osterberg & Blaschke 2005), and as the afamelanotide treatment as a condition of approval by the EMA is connected to an obligatory Post-Authorization Safety Study (PASS) to determine safety and efficacy and amongst other outcomes measures treatment adherence, it would be illogical to now not use the data on the adherence rate generated by the PASS.

### 3. Clinical effectiveness- Quality of Life in EPP

The Dermatological Quality of Life Index (DLQI) “was the first dermatology-specific Quality of Life instrument” and developed in 1994 at the University of Cardiff (Finlay et al. 1994). It is a tool validated for many skin disorders and one of the most frequently used quality of life measures in dermatology. Because EPP is associated with painful burns after light exposure and because the lack of a disease specific tool, the DLQI was used in an exploratory way during some of the clinical trials testing afamelanotide for EPP.

However, patients and expert physicians did not feel comfortable using the tool as, according to their assessment, it neither adequately reflected the characteristics of the EPP condition nor captured the treatment effects. Therefore, and because EPP is not a dermatological condition but an intoxication-type inborn error of metabolism and has unique features, the disease specific EPP quality of life instrument named “EPP-QoL” was developed by expert physicians together with Clinuvel. During the development of the EPP-QoL, feedback from EPP patients was collected and the instrument was psychometrically validated by an external company (Biolcati et al. 2015). As the development and validation process was performed while the clinical trials were already ongoing, slightly different versions of the EPP-QoL (18-item, 15-item and 12-item versions) were used in the different clinical trials and for patients receiving afamelanotide in compassionate use and early access schemes.

The quality of life data collected with the EPP-QoL shows a “substantial improvement in quality of life” (as stated by the Committee, Appeal Decision p.11; ¶ 60) which in the observational study in 115 patients receiving afamelanotide during compassionate use and early access schemes was sustained over a period of 6 years (Biolcati et al. 2015). In contrast, the DLQI did not show a significant improvement in quality of life measurements during the clinical trials and was not used thereafter.

Nonetheless, the ERG based their economic model on the DLQI data from the clinical trials, and stated as one of the reasons for their choice that “The DLQI has undergone extensive validation, we believe that it has face validity for use in EPP […]” (ERG report p. 77). The DLQI however has never been validated for EPP. The Committee expressed concerns regarding the ERG`s approach to use the DLQI data, amongst other considerations 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 […]” (FED p.12).

According to the ORPH-VAL recommendations, health care professionals and patients “have the expertise and experience to discuss HRQoL [health-related quality of life], burden of disease and patient preferences [67, 74, 75]. Clinical experts and patients may also help interpret the relevance of trial data, where endpoints might be unusual or not validated in the disease in question.” (Annemans et al. 2017). These ORPH-VAL recommendations have not been met in the ERG evaluation:

During the development of the EPP-QoL, feedback from EPP patients was collected. The patient feedback data collected in the Swiss treatment center between 2010 and 2011 in the Swiss patient cohort demonstrate that EPP patients rate the questions of the EPP-QoL as mainly “appropriate” or “very appropriate”, as elaborated below (Unpublished, 3.1.). Additional questions, e.g. on fatigue, might be considered for inclusion in future versions as the EPP-QoL is further improved in preparation for a full validation.

In addition, we performed a review of the ERG’s “Face validity of content and framing” analysis (ERG report p.94) on the comparability of the DLQI and EPP-QoL tools. Our analysis shows that amongst other issues the ERG was only able to match 5 out of 10 questions of the DLQI with questions from the current version (12-item) of the EPP-QoL. The

comparability of the two tools is further compromised by unspecific questions and the lack of sensitivity of the DLQI for treatment effects in the EPP condition (see 3.2.10).

According to the ERG, “The appropriateness of the DLQI and EPP-QoL questionnaires for EPP is central to the interpretation of the clinical effectiveness and cost-effectiveness evidence.” (ERG report p.94). We therefore put forward that data collected by a tool which knowingly underestimates the benefit of the first effective treatment in an ultra-rare condition is not an appropriate basis to model the cost-effectiveness. As even the Committee expressed their concerns, below we present additional and new evidence on the topic.

3.1. The questions asked in the EPP-QoL are rated as appropriate by the patients

For the development of the EPP-QoL, in the Swiss treatment center expert physicians together with several EPP patients discussed the content and wording of the questions to optimally capture the nature of the condition and the aspects most relevant for the patients. The original EPP-QoL questionnaire had 18 items and an additional global rating of the perceived quality of life on an 11-point Likert-type scale (with 0 being the worst imaginable and 10 being the best imaginable quality of life) for the current time point and, retrospectively, for their adolescence and for their childhood. In addition, in the 18-item version, all patients were asked to rate how appropriate they perceive every questions to capture the symptoms of their EPP condition.The rating was placed adjacent to each specific question. This original version of the EPP-QoL was then further developed and psychometrically validated by an external company (Oxford Outcomes, Biolcati 2015), which also adjusted the scoring algorithm to allow comparability between data obtained by the different versions.

Between 2010 and 2011, 14 Swiss EPP patients received the afamelanotide treatment and were asked to answer the EPP-QoL (18-item version). All patients signed a written informed consent before providing the data and the presented analysis was performed as part of a biobank project and has been approved by the cantonal ethic committee in Zurich (BASEC-No.: 2018-00131). Following, we present the results of the patients’ rating of the appropriateness of the questions for all questions present in the 15-item and 12-item EPP-QoL version (which are the underlying versions for the evaluation by NICE). The wording of the question regarding the appropriateness of each quality of life – question was:

**In order to capture the symptoms of EPP, the questions is[&]:**
**Very appropriate**
**Appropriate**
**Less appropriate**
**Inappropriate**

[&]own translation. Original wording in German: Um die Beschwerden der EPP zu erfassen ist diese Frage: sehr geeignet / geeignet / wenig geeignet / ungeeignet.

Below, we present a summary of the rating for all 15 questions and in addition the rating for each of the questions individually. The wording of the questions was derived from Langendonk et al. (2015), Supplement p.108. Questions with an asterix (*) are only present in the 15-item version of the EPP-QoL, and have been removed from the 12-item version (concerns Q2*; Q3* and Q9*).

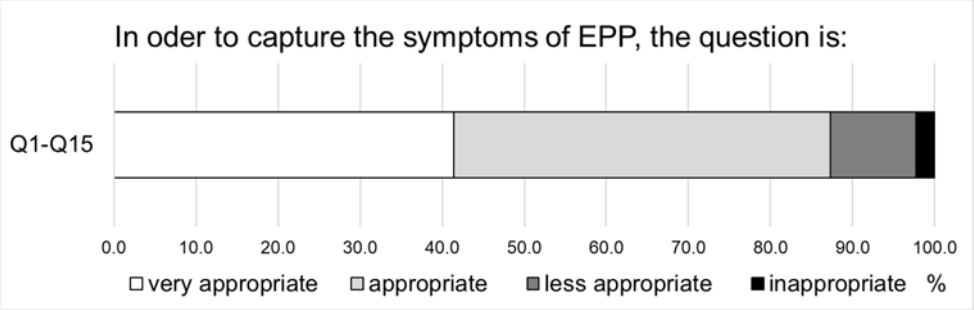
Results

Between 2010 and 2011, in the Swiss treatment center 14 EPP patients (the participants of the CUV010 and CUV017 trials) received the afamelanotide treatment and were asked to answer the EPP-QoL, which contained in addition to the quality of life questions also the rating on the appropriateness of each question. 11 of the 14 patients (73%) provided a rating

of the questions, each person on average assessed 2.9 questionnaires (mean; median 3, range 1 – 6). For each question, on average 31.7 (mean, range 30 – 33) ratings were obtained. Currently, 38 EPP patients in Switzerland receive the treatment, which means that 29 % of the Swiss cohort are covered by the analysis, and we rate the results as representative.

3.1.1. Summary rating on the appropriateness of all questions in the EPP-QoL (15-items):

On average, 87.3 % (mean; median: 90.3 %; range: 67.8 % - 93.7 %) assessments rated the questions as appropriate or very appropriate. The questions were rated as being inappropriate by on average 2.3 % (mean, median: 0 %, range 0 % - 12.5 %) of the answers given.

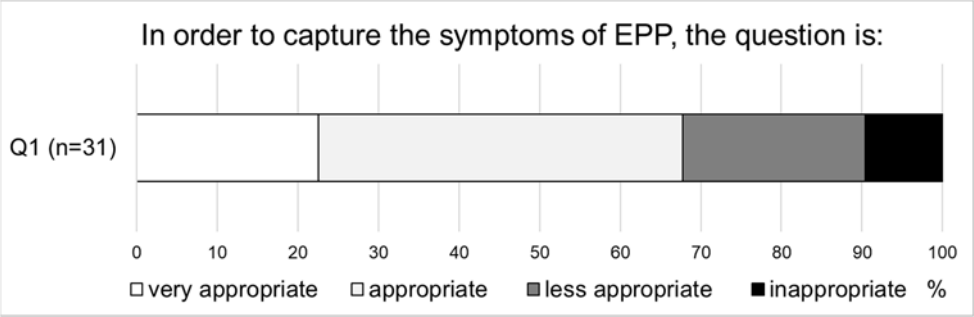



3.1.2. Rating on the appropriateness of single questions in the EPP-QoL (15-items):

Below, we present the ratings for the single questions (Q1-Q15) and highlighted the two questions assessed as being least appropriate and the two questions being assessed as most appropriate.

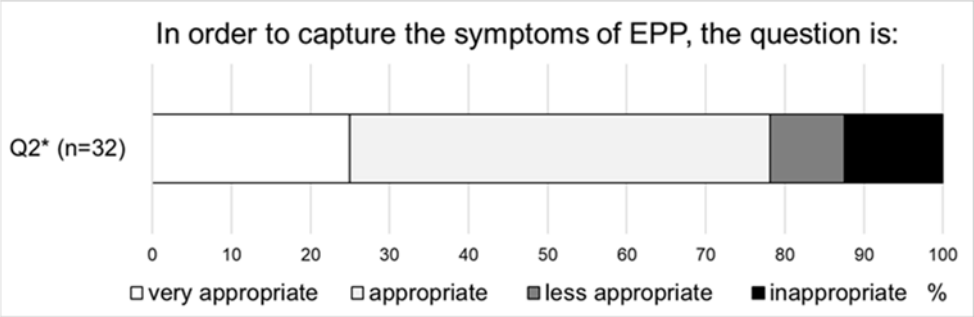
Q1: Over the last two months, how has your well-being been affected by EPP?

With 32.3 % of the answers rating the question as less appropriate or inappropriate (9.7 % of the answers rate the question as being inappropriate) Q1 is the question assessed as the least appropriate by the cohort. Only 22.6 % of the obtained ratings assessed the question as very appropriate.



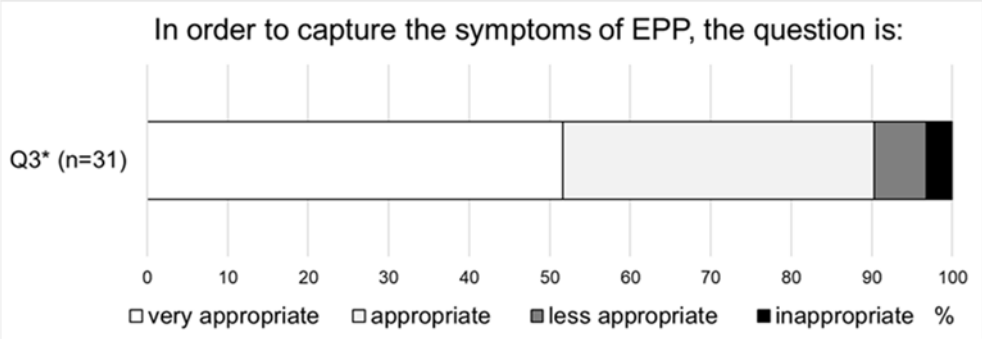

3.1.3. Q2*: Over the last two months, how much has your EPP symptoms influenced your capacity to go to work or school?

With only 78.1 % answers rating the question as very appropriate or appropriate, Q2 has the second worst rating of all questions in the questionnaire. In addition, 12.5 % of all ratings given assess the question on how much EPP symptoms influenced the capacity to go to work or school as inappropriate, which is the highest percentage of negative rating of all questions in the questionnaire.



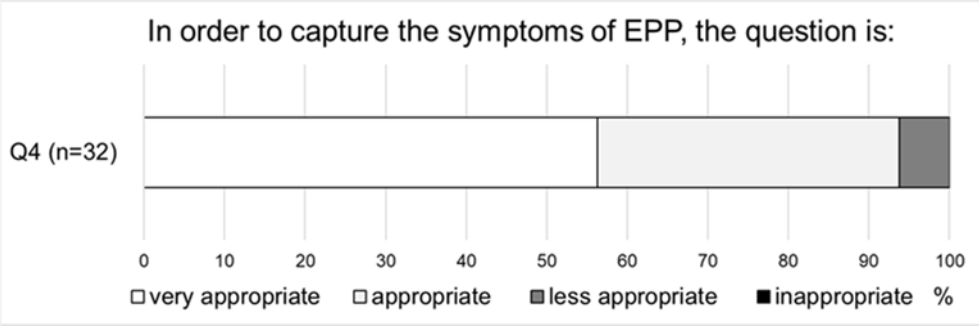

3.1.4. Q3*: Over the last two months, how often did you feel the need to seek out shade?

Seeking shade was rated in 90.3 % of the answers given as an appropriate or very appropriate questions to capture the symptoms of EPP.



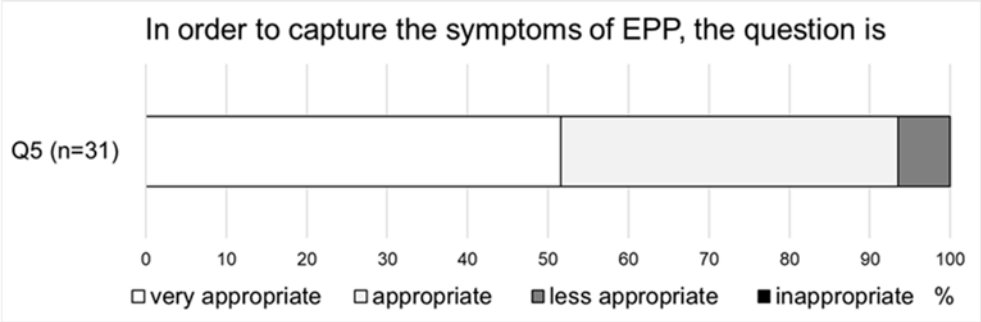

3.1.5. Q4: Over the last two months, how much has EPP influenced the choice of the clothes you wear on a sunny day?

93.8 % of the ratings assessed the question if EPP influenced the choice of the cloth on sunny days as very appropriate or appropriate, and no negative ratings were obtained. Q4 therefore is the best rated question of the EPP-QoL, with 56.3 % of the answers rating Q4 as very appropriate.



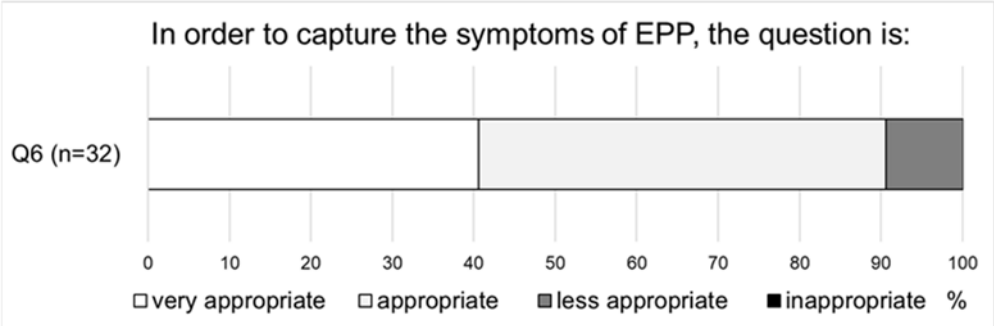

3.1.6. Q5: Over the last two months, how often did you feel you were at risk of developing EPP symptoms?

93.5 % of the ratings assessed the question “Over the last two months, how often did you feel you were at risk of developing EPP symptoms?” as appropriate or very appropriate. No negative ratings were obtained.



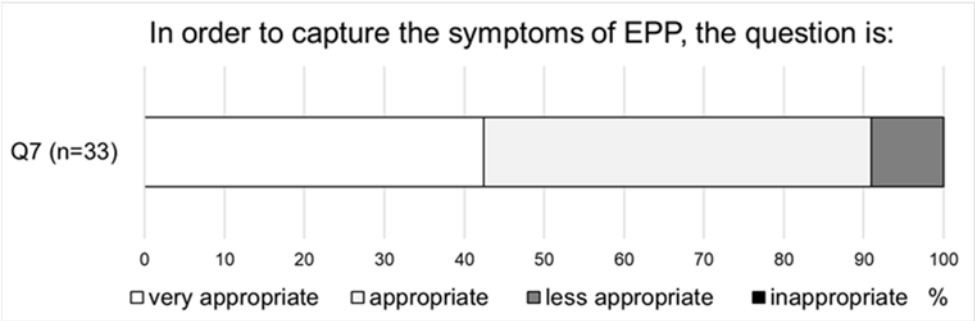

3.1.7. Q6: Over the last two months, how much has EPP affected any social or leisure activities on a sunny day?

90.6 % of the ratings assessed Q6 as very appropriate or appropriate, and 0% as inappropriate.



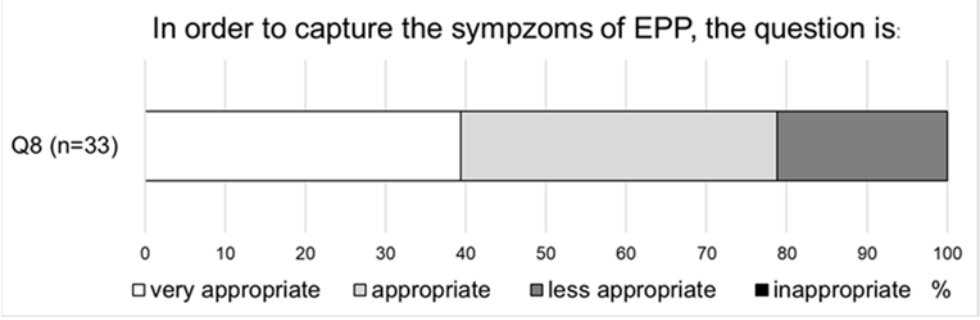

3.1.8. Q7: Over the last two months, how much has EPP influenced your need to plan before leaving your house?

90.9 % of the ratings assess Q7 as very appropriate or appropriate, and 0% as inappropriate.



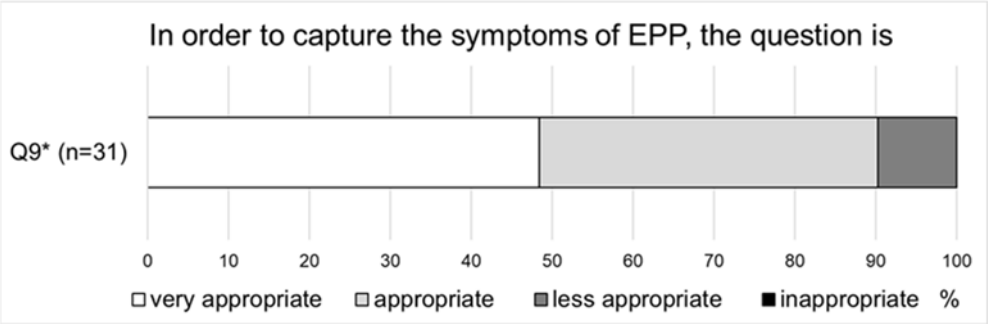

3.1.9. Q8: Over the last two months, has EPP limited your ability to undertake activities in a spontaneous manner?

78.8 % of the ratings assess Q8 as very appropriate or appropriate, and 0% as inappropriate.



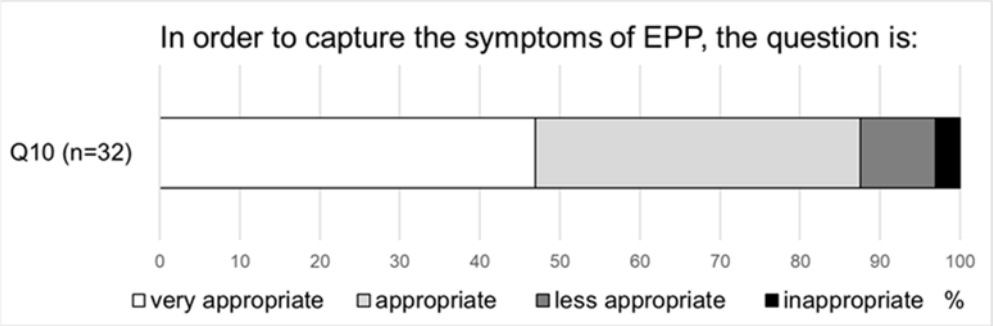
3.1.10. Q9*: Over the last two months, how often have you not worn protective clothing on a sunny day?

90.3 % of the ratings assess Q9 as very appropriate or appropriate, and 0% as inappropriate.



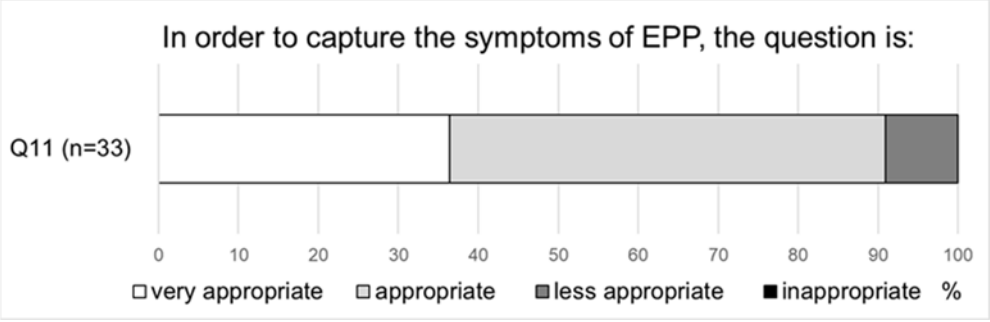

3.1.11. Q10: Over the last two months, how much has EPP interfered with your going shopping or looking after your home (indoors and outdoors) or garden on a sunny day?

87.5 % of the ratings assess Q10 as very appropriate or appropriate, with 3.1 % ratings as inappropriate.



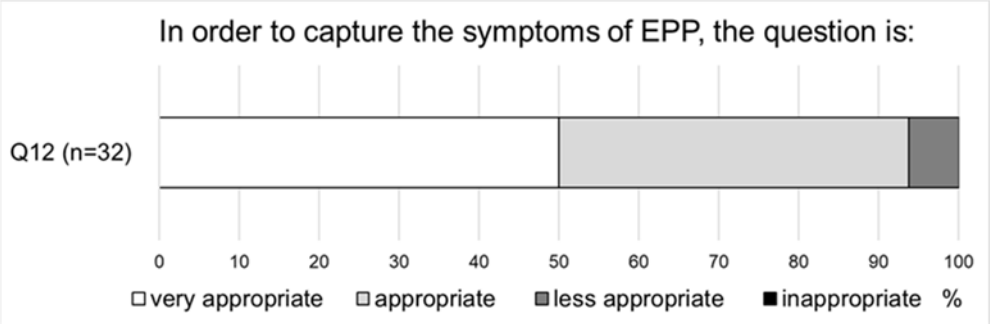

3.1.12. Q11: Over the last two months, how much has EPP prevented you from attending outdoor social activities with family and friends?

90.9 % of the ratings assess Q11 as very appropriate or appropriate, and 0 % as inappropriate.



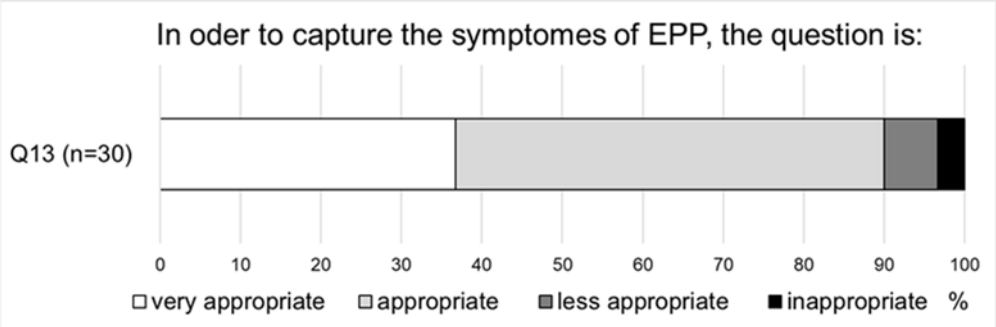

3.1.13. Q12: Over the last two months, how much has EPP limited your amount of outdoor activities?

93.8 % of the ratings assess Q12 as very appropriate or appropriate, and 0 % as inappropriate. Q12 therefore is the second best rated question of the questionnaire.



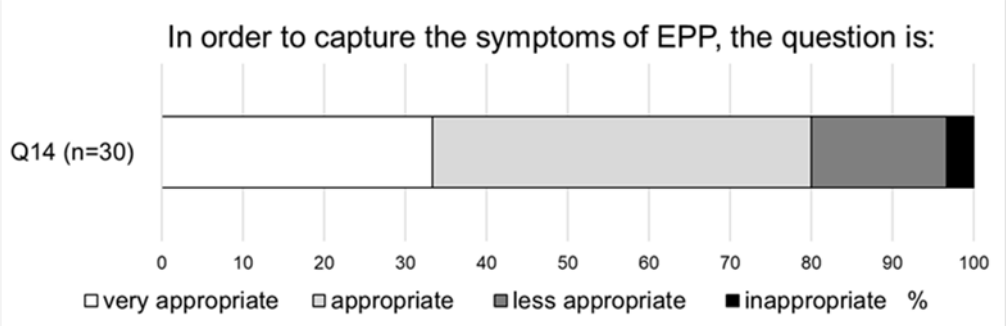

3.1.14. Q13: Over the last two months, how often did you experience typical EPP skin complaints?

90 % of the ratings assess Q13 as very appropriate or appropriate, with 3.3 % ratings as inappropriate.



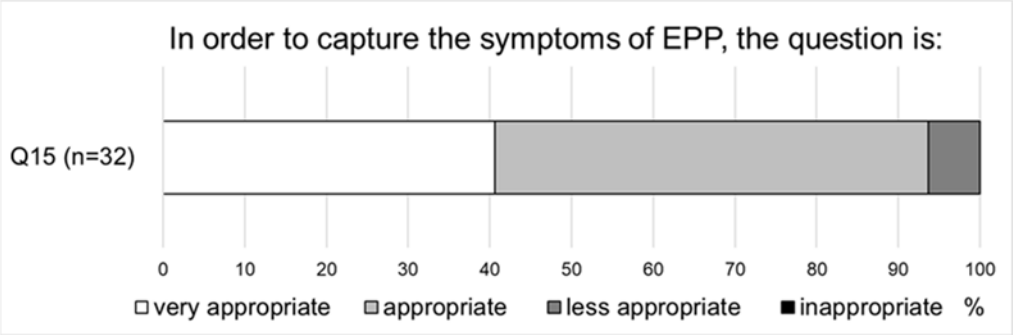

3.1.15. Q14: Over the last two months, how much has your quality of life improved?

80 % of the ratings assess Q14 as very appropriate or appropriate, with 3.3 % ratings as inappropriate.




3.1.16. Q15: Over the last two months, how much has EPP influenced your method of transportation or seating preference during transportation?

93.7 % of the ratings assess Q15 as very appropriate or appropriate, and 0 % as inappropriate.




Discussion:

Summary rating of Q1-Q15

On average, all questions together (Q1-Q15) obtained a rating of being 87.3 % appropriate or very appropriate (mean; median: 90.3 %; range: 67.8 % - 93.7 %). The questions were rated as being inappropriate only by on average 2.3 % of the answers (mean, median: 0 %, range 0 % - 12.5 %).
We in addition analysed the rating of the self-perceived quality of life as assessed by the 11-point Likert-type scale (with 0 being the worst imaginable and 10 being the best imaginable quality of life) for the current time point, which was part of the 18-item EPP-QoL with the outcome of the quality of life measurements (as assessed with the EPP-QoL questions). A Pearson`s r of 0.647 ($p < 0,0001$; Analyse-it v4.51 for Excel) was achieved, which suggests that the self-perceived quality of life in EPP patients is captured to a high degree by the questions in the EPP-QoL.

These results demonstrate that at large EPP patients rate the questions of the EPP-QoL as covering aspects important for their EPP condition. In addition, the detailed analysis of each question provides an overview which of the questions were rated more or less appropriate. Some of the ratings of individual questions are discussed in detail below.

Q1: Over the last two months, how has your well-being been affected by EPP?

With only 67.8 % of the answers rating the question “Over the last two months, how has your well-being been affected by EPP?” as appropriate or very appropriate, Q1 is the question assessed as the least appropriate of the EPP-QoL (15-item version). In addition, 9.7 % of the ratings assessed the question as inappropriate. In the ERG report is noted, that “Unlike the DLQI, the EPP-QoL includes a direct question on well-being” (p. 95), but no further discussion or conclusion is provided.

Q2*: Over the last two months, how much has your EPP symptoms influenced your capacity to go to work or school?

With only 78.1 % answers rating the question as appropriate or very appropriate, Q2* has the second worst rating of all questions in the EPP-QoL (15-item version). In addition, 12.5 % of all ratings given assess the question on how much the EPP symptoms influenced the capacity to go to work or school as inappropriate, which is the highest percentage of negative rating of all questions in the questionnaire. The ERG expressed concerns because “the EPP-QoL (12-item version) excludes questions on feelings and ability to work or study, which are important aspects of life” (ERG report p.95). However, EPP patients themselves did rate that the question is of limited appropriateness in the context of EPP. This may be due to the fact that EPP patients develop coping strategies for compensating their incapability in order to remain able to go to school or work, and subordinate this aim all other aspects of life, such as they limit or suppress their leisure, social and family activities (personal communications). For further discussion see 3.2.

Q3-Q7, Q9:

All questions obtained ratings above 90 % (90.3 % – 93.8 %) as being appropriate or very appropriate, and only Q3 (Over the last two months, how often did you feel the need to seek out shade?) has 3.2 % ratings as being inappropriate.

Q10-Q12 on “outdoor activities”:

The ERG criticized that “The EPP-QoL also emphasises the ability to perform outdoor activities on sunny days, but does not measure the relative importance of these activities to the individual.” (ERG report p.95). Q10, Q11 and Q12 in the EPP-QoL specifically ask about outdoor activities, and our analysis provides evidence that the patients rate this aspect as very important: All three questions were rated by at least 87.5 % of the assessments given as very appropriate or appropriate, and Q12 is even the second best rated question of the EPP-QoL (Q12: Over the last two months, how much has EPP limited your amount of outdoor activities?): 93.8 % of the answers rated Q12 as appropriate or very appropriate. The importance of outdoor activities on sunny days, respectively not being able to perform said outdoor activities can be also depicted from the patient testimonies (see section 2).

Q14: Over the last two months, how much has your quality of life improved?

80 % of the obtained ratings assessed Q14 as appropriate or very appropriate, and 3.3 % of the ratings assessed the question as being inappropriate.
The ERG stated that it was “concerned about the framing of the quality of life question (Q14), which does not allow for the possibility of deterioration” and point out that this represents a potential source for bias (ERP report p. 95). We agree with this critic but point out that the overall impact of the improper wording only affects 1/12 of the results at maximum (12-item version) or 1/15 of the results in the 15-item version.
We examined the German version of the EPP-QoL, which is the one used for the presented analysis. In contrast to the English version, the wording in the German version is neutral, asking not for an “improvement” of the quality of life, but for a “change” in quality of life. Therefore, the possible answers are balanced in regard of improvement or deterioration: “Over the last two months, how much has your quality of life changed: Very much/much/not much/not at all.” (Original wording in German: “Wie stark hat sich in den letzten beiden Monaten Ihre Lebensqualität bezogen auf die EPP verändert?” Sehr stark/ Stark/ Wenig/ Überhaupt nicht).
As the German version of the question was not affected by the improper wording, the presented assessment of the appropriateness is not affected by the wording. In addition, the studies using the German version of the EPP-QoL, which includes the Swiss cohort in the eight-year observational study (Biolcati et al. 2015), is not affected.

Conclusion:

12 of the 15 questions of the EPP-QoL were assessed as being appropriate or very appropriate in ≥ 80 % of the ratings given, and 10 questions even were assessed as being in ≥ 90 % appropriate or very appropriate. While there is room for improvement, and a full validation of the EPP-QoL should be carried out, the questions in the tool already reflect to a very high degree aspects rated as relevant and appropriate to capture the characteristics of the condition by the EPP patient cohort. In addition, as the rating was conducted in patients receiving the treatment, the high ratings also reflect that patients assess the EPP-QoL tool as appropriate to capture treatment effects in EPP.

3.2. The DLQI is inappropriate to measure treatment effects in EPP – review of the ERGs comparison of the DLQI with the EPP-QoL

The ERG claims that because: “The DLQI has undergone extensive validation, we believe that it has face validity for use in EPP and that it has been shown to reflect marked impairment in quality of life for people with EPP [17].” (ERG report p. 77).

However, only because the DLQI “has been shown to reflect marked impairment in quality of life for people with EPP”, it is not automatically a suitable instrument to also measure treatment effects – during the time Holme et al. (2006) performed the cited measurement using the DLQI in a cohort of British EPP sufferers (reference 17 in the ERG report), no effective treatment was available for EPP and no conclusion on the ability to measure treatment effects using the DLQI can be drawn from that study.

The ERG presents “a summary comparison of the content of the DLQI and EPP-QoL”, named “Face validity of contend and framing”. (ERG report p. 94). We reviewed the ERGs analysis on the comparability of the questions in the DLQI (DLQI Q1-Q10) and the EPP-QoL (EPP-QoL Q1-Q15) and present the results for category of questions below. We first discuss the effects of the limited sampling period and the absence of weather specifications (named “concepts”) in the DLQI and later present the analysis for the categories of questions in the order they are presented in the ERG report (table 27, p.97):

3.2.1. Concepts: Absence of weather specification and effect of the sampling period

The sampling period of the DLQI comprises the last week (7 days), while the EPP-QoL has a sampling period of the last two months and in addition specifies that the sampling time only consists of the sunny days and / or the time spent outdoors during those two months.

Table 27, ERG report p. 97: Excerpt on “concepts”

**Table 27 Comparison of questions from DLQI and EPP-QoL**

| Concepts[a] | DLQI questions[b]<br>Over the last week, how much has skin affected... | EPP-QoL questions[c]<br>Over the last two months, how much has EPP affected... |
|---|---|---|

Absent weather specifications

The specification in the EPP-QoL that the sampling period only contains sunny days / time spent outdoors is crucial because the phototoxic reaction in EPP only develop after exposure to light, the main trigger factor is sunlight. Not selecting for sunny days strongly reduces the sensitivity and specificity of the tool: The absence of EPP symptoms could be either caused by the high effectiveness of a treatment - or completely unrelated to the treatment, like for example due to bad weather condition or indoor occupation. This identified limitation concerns all questions in the DLQI.

Sampling period of one week

The sampling period in the DLQI is seven days, however, as the weather conditions are volatile and several other factors might limit the time spent outdoors (for example having a flue, high workload etc.), only including the last seven days of the two-month treatment period is not a representative sample but introduces a substantial sampling error and reduces the sensitivity to detect and quantify treatment effects.

The ERG in its report questioned the reliability of the two-month recall period and assumes a recall bias: “Another important difference between the two questionnaires is the recall period - one week in the DLQI and two months in the EPP-QoL. Again, it is unclear which is more

appropriate, as a longer recall period reduces the risk of missing periods of time when EPP may have had less of an effect on patients' lives, but it does also increase the risk of recall bias." (ERG report p. 95-96). However, the fully validated quality of life questionnaire MetabQoL 1.0 for pediatric patients with intoxication-type inborn errors of metabolism does have a recall period of 12 months (Zeltner et al. 2016). Therefore, while the potential for a recall bias for longer sampling periods (e.g. 2 months) has to be discussed, even considerably longer recall periods (12 months) did not prevent a disease specific quality of life instrument to become fully validated in diseases with similarity to EPP.

For EPP, shorter sampling times are associated with a substantial sampling error by for example volatile weather conditions. The less suitable sampling period and the missing specifications for the relevant weather conditions are limitations concerning all questions in the DLQI and adversely affect both the sensitivity to detect treatment effects and their quantification.

3.2.2. Symptoms: Limited overlap between symptoms in the DLQI and the unique EPP symptoms

ERG report p. 97: Table 27, excerpt on "symptoms"

| | | |
|---|---|---|
| Symptoms | Q1. Itchy, sore, painful or stinging | Q5. Frequency at risk of developing EPP symptoms<br>Q13. Frequency of typical EPP skin complaints<br>~~Q3. Frequency of need to seek out shade~~ [d] |

While "painful, itchy and stinging" could be used to describe the symptoms in EPP, the skin usually does not become "sore" because of the phototoxic reactions. The description "typical EPP symptoms" is more specific and in addition discriminates between EPP symptoms and other skin conditions which the patient might suffer from in addition. Moreover, the question asking for the "risk of developing EPP symptoms" includes not overt manifestations, but the necessity for avoidance strategies that, as we discussed above, impairs the patient's condition to function normally as a subject in the society.

3.2.3. Feelings: No corresponding question

ERG report p. 97: Table 27, excerpt on "feelings"

| | | |
|---|---|---|
| Feelings | Q2. Embarrassed or self conscious | |

"Feelings" like distress or anxiety (ERG report p.69) could indeed be considered as an additional outcome measure, however we stress that when included into a quality of life instrument, also the specific circumstances need to be captured adequately. In addition, in our experience EPP patients conceal their embarrassment by their condition and we have the following explanation: (1) they have frequently experienced to be accused of malingering, (2) they previously have experienced most extreme pain conditions (VAS10/10), so that they suppress the memory of it like observed in persons affected by Post traumatic stress disorder, (3) if they try to protect themselves from light, they are exposed to stigmatization, (4) the diagnosis is often delayed for more than a decade, which together with the above mentioned points (1) and (2) causes the patients to conceal and suppress the feelings of embarrassment.

3.2.4. Daily activities

ERG report p. 97: Table 27, excerpt on “daily activities”

| | | |
|---|---|---|
| Daily activities | Q3. Going shopping, looking after home or garden<br>Q4. Clothes you wear | Q10. Going shopping, looking after home or garden on sunny day<br>Q4. Choice of clothes on sunny day<br>~~Q9. Frequency not wearing protective clothing on sunny day~~ [d]<br>Q15. Transportation method or seating preference |

Relevance of the questions is dependent on the weather conditions

For the questions DLQI Q3 and DLQI Q4 on shopping, looking after home or garden and choice of clothes the same limitations apply as discussed above: Without specification that only the sunny days are relevant, the questions become meaningless in the context of EPP.

EPP-QoL Q15: Transportation method or seating preference are one of the most important factors for EPP patients

For the question Q15 in the EPP-QoL on “transportation method or seating preferences”, no matching questions exists in the DLQI. This question however is an excellent example for the uniqueness of the EPP condition: In skin conditions transportation and seating preference is not a relevant concern and therefore such a question is not included in the DLQI. This is in stark contrast to EPP, a condition in which managing the way from one destination to another (home to school or work, traveling to a conference etc.) is one of the biggest concerns, as those are the moments when EPP patient have the least control over their environment but the most risk to be exposed to sunlight. EPP patients take measures like choosing their flat in vicinity to their workplace, checking out the safest way to a destination in advance for example by google earth research or they travel during night only, many make sure to only sit on the window seat during a flight in order to control the shutter and to never sleep during travels as the vehicle might take a turn and expose the patient to sunlight while sleeping. As not all aspects always can be planed ahead or in accordance with the needs of the EPP patient - for example when traveling in groups or when all seats in the transportation vehicle are occupied - traveling and transportation are some of the biggest stress factors for an EPP patient.

The importance of the aspects asked in EPP-QoL Q15 are reflected in the very high rating on the appropriateness of the question (see analysis 3.1.16): 93.7 % of the ratings assessed EPP-QoL Q15 as very appropriate or appropriate, and 0 % as inappropriate. By using the DLQI only, this important feature is not reflected in the quality of life outcomes.

3.2.5. Social and leisure activities

ERG report p. 97: Table 27, excerpt on “social and leisure activities”

| | | |
|---|---|---|
| Social and leisure activities | Q5. Social or leisure activitites<br>Q6. Sport | Q6. Social or leisure activities on sunny day<br>Q11. Outdoor social activities with family and friends<br>Q12. Amount of outdoor activities<br>Q7. Need to plan before leaving house<br>Q8. Ability to undertake activities in spontaneous manner |

Treatment effects are not captured without a specification on outdoor activities and / or sunny weather conditions

EPP is a chronic condition and the patients are at a constant risk to develop painful phototoxic reactions when exposed to light. Therefore, whenever possible, EPP patients plan their social, leisure or sport activities accordingly. By not specifying that only social and leisure activities and sports outdoors and / or on sunny days should be reported, the treatment effect is missed by the DLQI: “However, patient and EPP experts have confirmed that the increase in outdoor light exposure possible with Scenesse was enabling to alter patients’ quality of life and translated in the uptake of outdoor lifestyle.” (EPAR p.104).

The relevance of the “outdoor” aspect can be also depicted by the rating of the appropriateness of the EPP-QoL questions provided in 3.1. The question EPP-QoL Q12: “Over the last two months, how much has EPP limited your amount of outdoor activities?” is the second best rated question of the EPP-QoL with 93.8 % of the answers rating the question as appropriate or very appropriate.

The EPP specific requirement to plan ahead is not reflected in the DLQI

In addition, EPP is connected with a substantial amount of planning efforts to reduce uncertainties and stress (see also discussion on EPP-QoL Q15 above). No questions related to the need to plan ahead before an outdoor activity for example by checking the weather forecast can be found in the DLQI.

3.2.6. Work and study: No corresponding question (12-item version)

ERG report p. 97: Table 27, excerpt on “work and study”

| | | |
|---|---|---|
| Work and study | Q7. Prevented or problem with work or study | ~~Q2. Capacity to go to work or school~~ [d] |

All aspects of daily life are optimized by the EPP patients in order to not become incapacitated for work and other important duties

The ERG was specifically concerned that the question EPP-QoL Q2* on ability to work or study has been excluded for the 12-item version of the EPP-QoL: “But the EPP-QoL (12-item version) excludes questions on feelings and ability to work or study, which are important aspects of life.” (ERG report p. 95). However, when the patients in the Swiss cohort assessed the appropriateness of this question, it was rated as the second worst question with 22 % of the results of the survey stating that the question is less appropriate (9.4 %) or even inappropriate (12.5 %, see point 3.1.3). The 12.5 % of the answers rating the question as inappropriate is the highest amount of ratings as inappropriate of all questions in the EPP-QoL.

While the capacity to go to work or school might be restricted during an ongoing phototoxic reaction, the question for most of the time is not applicable for adult EPP patients: Most adult EPP patients have adapted their lifestyle according to their chronic condition and optimized their daily life to avoid light – and therefore symptoms – as best as possible. EPP patients would not be able to keep a job in case it would pose the patient at risk for frequent phototoxic reactions. Like persons bound to a wheelchair, most EPP patients have chosen a work compatible with their disability. In addition, EPP patients take precautionary measures to not be exposed to sunlight and therefore being incapacitated for work. This is also reflected in the low frequency of phototoxic reactions during the randomized controlled trials. This question therefore does not give a good estimation on quality of life in EPP, especially not if the sampling period only consists of one week like in the DLQI.

3.2.7. Personal relationships: No corresponding questions

ERG report p. 97: Table 27, excerpt on “personal relationships”

| | | |
|---|---|---|
| Personal relationships | Q8. Problem with partner, close friends or relatives<br>Q9. Sexual difficulties | |

This questions are only marginally applicable to the EPP condition: As EPP is a chronic, life-long condition partners, family members and close friends are usually adapted to the EPP condition as well.

3.2.8. Treatment: No corresponding question

ERG report p. 97: Table 27, excerpt on “treatment”

| | | |
|---|---|---|
| Treatment | Q10. Treatment problems, e.g. making home messy or taking time | |

This question is not applicable for the afamelanotide treatment, as it is a two-monthly slow release formulation with no additional complications. It could be applicable to other treatment options but for the current situation does not give a relevant outcome (noise).

3.2.9. Overall

ERG report p. 97: Table 27, excerpt on “overall”

| | | |
|---|---|---|
| Overall | | Q1. Well-being<br>Q14. Quality of life |

The EPP-QoL is the first attempt to specifically measure quality of life in EPP, and the patients were asked to provide self-perceived quality of life scores in addition to answering questions about specific aspects of EPP. Question Q14 on self-assessed quality of life was rated as being 80 % appropriate or very appropriate, which is one of the lower ratings.

As discussed in 3.1.2., question EPP-QoL Q1 (well-being) was rated as the least appropriate question in the EPP-QoL with 32.3 % assessments rating the question as less appropriate or inappropriate.

3.2.10. Summary comparison of the EPP-QoL and the DLQI. Quantitative assessment – review of the “Face validity of contend and framing”-analysis

Based on the review of the ERGs analysis on the comparability of the DLQI and the EPP-QoL named “Face validity of contend and framing” (ERG report p. 94), we tried to quantify the overall impacts on sensitivity and specificity in case the DLQI is used instead of the disease specific instrument EPP-QoL.

| EPP-QoL | DLQI | Impact | Comment |
|---|---|---|---|
| Sampling period 8 weeks (8 out of 8 weeks between the treatments) | Sampling time 1 week (1 out of 8 weeks between the treatments) | 87.5 % loss in sensitivity when using the DLQI | Due to the conditioned light avoidance and the dependence on external factors (light exposure, weather conditions etc.), phototoxic reactions are occasional events and the probability to miss them is |

| | | | |
|---|---|---|---|
| | | | higher, the shorter the sampling time |
| Sampling only on sunny days/ during outdoor activities | No distinction of the weather conditions or in regard to indoor/ outdoor activities | Approx. 20 % loss in sensitivity in the DLQI, 7 out of 10 (70 %) of the questions in the DLQI affected (underlying assumption that 1 in 5 days the weather is not sunny). In addition, the missing distinction between indoor and outdoor activities renders the questions unspecific. | The sampling period is further compromised by volatile weather conditions. This also introduces a substantial sampling error (for example if the weather was cloudy during the week used for baseline determination, all subsequent measurements will be affected by this one week) |
| 12 (15) questions | From the 10 questions in the DLQI, only 5 could be matched by the ERG to questions in the EPP-QoL with related content | 50 % noise in the DLQI: 5 out of 10 (50 %) questions in the DLQI do not have a roughly matched partner question in the EPP-QoL (in the ERGs own comparison; 12-item version) and are of unknown / less significance for the EPP patients (see discussion of those questions above: DLQI Q2,Q7,Q8,Q9,Q10) | Questions in the DLQI without an equivalent in the EPP-QoL are of unknown significance for the EPP patients, and some of the questions (DLQI Q10 on problems with the treatment) are not applicable. Only disease experts should base a comparison on “face-validity”, as disease specific aspects are not known to non-specialists, see question on “work”, DLQI Q7(but even disease experts would need to validate their assumptions).<br>From a statistical point of view, the noise induced by the questions not related to the EPP condition reduces or abolishes statistical significance. |
| Disease specific and relevant aspects present (need to plan ahead: EPP-QoL Q7 and Q8, transportation and seating preference: EPP-QoL Q15) | No corresponding questions | 20 % - 25 % relevant outcomes missed in the DLQI: 3 out of 15 questions (15-item version) or 3 out of 12 questions (12-item version) in the EPP-QoL do not have a corresponding partner question in the DLQI, but cover aspects highly relevant for the patients (like see analysis 3.1.) | Aspects important in EPP are not represented in the DLQI, which makes the DLQI less sensitive and specific for EPP |

Conclusion:

With our review of the “Face validity of contend and framing”-analysis (ERG report p. 94) we showed that the DLQI and the EPP-QoL are not interchangeable, as assumed by the ERG. In the comparison provided by the ERG only 5 of the 10 questions of the DLQI do have a counterpart from the EPP-QoL, which means that 50 % of the DLQI questions give unspecific readouts of unknown significance (“noise”). In addition, disease specific aspects rated as relevant by the patients like seating preferences, transportation method and the need to plan ahead are not covered by the DLQI. On top of that, the sampling period of the DLQI questions only covers the last seven days, and does not differentiate if those days were sunny (relevant) or not (not relevant), which introduces a substantial sampling error. Only disease experts should base a comparison on “face-validity”, as diseases specific aspects are not known to non-specialists (see question on “work”, DLQI question Q7), but even disease experts would need to validate their assumptions.

We therefore strongly disagree with the assumption of the ERG that the DLQI data sufficiently reflects treatment effects in EPP and can be used for economic modelling of the benefits. While the EPP-QoL needs further development and a full validation, the DLQI clearly cannot be rated as an appropriate tool in EPP. Moreover, the DLQI data should not be used because it would be illogical to use a Patient Reported Outcome Measure which is not accepted by the patients.

3.3. Further concerns and uncertainties

Further concerns and uncertainties expressed by the Committee and /or the Appeal Panel and benefits of afamelanotide which may not have been captured in the committee’s previous deliberations in relation to quality of life in EPP are discussed below:

3.3.1. The EPP-QoL is only partly validated – but the DLQI is not validated for EPP at all

The Committee expressed concerns that the EPP-QoL tool is not yet fully validated: “The committee concluded that it would take the EPP-QoL into account in its decision-making but that, without full and appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide.” (FED p.12)

However, the DLQI has not been validated for EPP at all. EPP is a unique, intoxication-type inborn error of metabolism and not a dermatological condition. The EPP-QoL not only was developed together with disease experts and feedback from patients was obtained, it also is psychometrically validated by an external company (Biolcati et al. 2015). The validation of a quality of life instrument is a multi-step approach which has to be undertaken for each condition separately.
EMA’s “Guideline on Clinical Trials in Small Populations” (p.6) states “if quality of life is measured, it should always be assessed using scales validated for the particular indication being treated”. It is also recognised in the guideline “that sometimes there are too few patients for validation exercises as well as separate treatment evaluation”.

While we support that the EPP-QoL should be further developed and fully validated, the same concerns expressed by the Committee apply to the DLQI: Without full and appropriate validation, there is substantial uncertainty about how the DLQI could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide.

In addition, the HST has experience in the evaluation of disease specific quality of life questionnaires which are not fully validated, for example in the appraisal HST2 of elosulfase alfa for mucopolysaccharidosis type IVa (MPS IVa):

“QoL was measured using the MPS HAQ [MPS Health Assessment Questionnaire] in MOR-004, which is a disease-specific instrument developed to measure disability in patients with MPS over 8 years of age. It should be completed by the parent/care giver for children less than 14 years of age. There is no validated tool to evaluate QoL in MPS IVA.” (ERG report elosulfase alfa p.29).

Elosulfase alfa was recommended for reimbursement by the NHS within a Managed Access Agreement.

3.3.2. Clinical significance of the changes observed by the EPP-QoL and the DLQI

Holme et al. (2006) measured an impairment in quality of life in patients with EPP in the UK by using the DLQI. Based on these results, the ERG argues that the DLQI would be also an appropriate tool to capture treatment effects in EPP. However, only because the DLQI “has been shown to reflect marked impairment in quality of life for people with EPP” (ERG report p. 77), it is not automatically a suitable instrument to also measure treatment effects – during the time Holme and colleagues performed the cited measurement using the DLQI in a cohort of British EPP sufferers, no effective treatment was available for EPP and no conclusion on the ability to measure treatment effects using the DLQI can be drawn from that study.

The ERGs reasoning in the case of the DLQI is in stark contrast to their evaluation of the EPP-QoL, in which the ERG criticises for example that “The clinical significance of the changes in EPP-QoL results was unclear as minimal important differences have not been established.” (ERG report p.11).

As also no clinical significant changes have been established for the DLQI in the context of EPP, the ERG clearly applies different measures in their assessment of the two tools. Again, we support that the EPP-QoL has to be fully validated, however we are concerned by the inconsistencies in the evaluation of the tools by the ERG.

3.3.3. Minimal important differences are disease specific

The ERG further refers to significant changes in the quality of life scores obtained using the DLQI estimated for other conditions: “The ERG notes that for general inflammatory skin conditions (e.g. psoriasis, eczema) a change in DLQI score of at least four points is considered clinically important [23]. The largest change observed for afamelanotide was around eight points which is double the recognised minimal clinically important difference for general skin conditions.” (ERG report p. 61)

However, every (skin) condition has it`s individual minimal important differences, for example Shikiar and colleagues established the minimal important difference for chronic idiopathic urticaria between 2.24 points and 3.10 points using DLQI measurements. (Shikiar et al. 2005). This demonstrates that minimal important differences established for a particular skin condition cannot just be applied to other conditions.

Moreover, the ERG even implies that for EPP, higher scores for the minimal important difference should be applied: “It could be that a larger change in score on the DLQI is required to be clinically important (i.e. because the DLQI isn’t necessarily sensitive enough for this condition), though the magnitude of this change cannot be quantified at present.” (Committee papers December 2017, p. 54; slide: DLQI - ERG comments). We want to highlight the inherent unfairness of the suggested approach: The ERG basically argues that higher achievements have to be demonstrated in the case of EPP by a tool knowingly less suitable to also capture them.

3.3.4. Increase in the quality of life in the placebo group by using the EPP-QoL – why did the ERG not report that the same effect was present in the DLQI?

The Committee stated that is was concerned with the EPP-QoL data because an increase in quality of life was observed in the placebo group, too: “Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.” (Appeal Decision p.16; ¶ 94).

However, also in the DLQI, an increase in quality of life was observed in the placebo group: “DLQI scores between the study groups were comparable at baseline at the mid-point in the scale at around 10.4 to 10.7 out of 30 (scores of 6-10 indicate a moderate effect on a patient’s life and scores of 11-20 indicate a very large effect on a patient's life [22]). Scores declined over time in both groups to a nadir of 2.4 to 3.1 for afamelanotide and placebo respectively at day 180 (a score of between 2 to 5 indicates a small effect on a patient’s life [22]). The decline in scores was larger in the afamelanotide group, though differences between the groups in the change from baseline were not statistically significant.” (ERG report p. 60-61).

The EPP-QoL results were statistically significant in both trials:
CUV029: “The differences between the groups were statistically significant at days 120, 180, and 240.” (ERG report p.56)
CUV039: “Differences between the groups in the change from baseline were statistically significant at day 60, day 120, and day 180.” (ERG report p. 58)
In addition, the duration of the quality of life measurements in the long-term observational study was 6 years, and during this time the increase in the measured quality of life was sustained (Biolcati et al. 2015), which indicates a “real effect”.

As the effect on quality of life in the placebo group is observed in both tools, it is not an argument to prefer the DLQI over the EPP-QoL. Again, we are concerned that the mentioned effect in the placebo group was only pointed out for the EPP-QoL and not for the DLQI, which together with the other observed inconsistencies in the evaluation of the tools to measure quality of life in EPP (3.3.1.- 3.3.3) suggests an objectionable bias in the assessment.

## 4. Value for Money

The underlying calculations for quality adjusted life years (QALYs) and incremental cost-effectiveness ratio thresholds (ICERs) and the cost-effectiveness model used by NICE as a basis for their decisions are not accessible to us.
However, NICE published the criteria which inform their cost-effectiveness assessment in their "Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes". We provided new evidence which addresses concerns of the Committee and the Appeal Panel which hopefully clarifies aspects which not have been captured in the committee's previous deliberations. This new evidence on the nature of the condition, the clinical effectiveness and the impact of the technology beyond direct health benefits should to our understanding also modify several of the underlying assumptions which inform the criteria for the cost-effectiveness calculations, amongst others:

- The EPP condition is more severe than previously assumed by the Committee
- The effects measured in the clinical trials are not "small"
- Quality of life as measured with the DLQI is inappropriate to demonstrate the benefits of the afamelanotide treatment
- The testimonies received during the appraisal are reliable, representative and can be used for decision making (as the EMA did)
- It would not be unfair to make reasonable adjustments in the case of the appraisal of afamelanotide, because the HST considered other forms of evidence in other appraisals before (as shown in details for appraisal HST2)

We hope that with the new evidence provided and the findings of the Appeal Hearing the Committee will consider to recommend afamelanotide for reimbursement by the NHS. Following, we address further concerns expressed by the Committee regarding the feasibility of a Managed Access Agreement (MAA) and the cost-effectiveness of afamelanotide.

### 4.1. National value assessments of the afamelanotide treatment

The ORPH-VAL principle 9 recommends, that in order to avoid duplication of efforts and enable faster access to orphan drugs, national value assessments should be coordinated (Annemanns et al. 2017). In the case of afamelanotide, the current pricing was determined during the appraisal process in Germany in 2017 by an independent arbitration board, which on the one hand aimed to achieve cost-effectiveness for the German health care system and on the other hand balanced the interests of the payors against a reasonable return on investment for the manufacturer (https://www.g-ba.de/informationen/nutzenbewertung/217/.; Last accessed 17 Jan 2019). To our knowledge, the pricing asked for afamelanotide by the company in the UK is similar to the price in other countries where afamelanotide is available to EPP patients (Germany, the Netherlands, Italy, Austria and Switzerland).

In addition, we could identify information on pricing and budget impact in other HST appraisals performed and published by NICE so far, and find that afamelanotide has the lowest annual treatment costs per person: For afamelanotide the annual costs per person are between 36.060 GBP (three doses applied) to 48.080 GBP (4 doses applied) and can be as low as 12.020 – 24.040 GBP / year in a minority of patients who only require 1 to 2 doses as seen in the Swiss patient cohort. Most treatments which received a positive recommendation in the HST appraisals so far have annual costs per person approximately between 200.000 to 400.000 GBP (as published by NICE).
With 400- 500 EPP patients in the UK (EPP has a prevalence of 1:150.000) the overall budget impact is also lower than that for the other treatments so far recommended for reimbursement by the HST Committees. (**Side note: The comparison under no circumstances is meant to question the validity of the positive decision for funding for the treatments for those other severe and debilitating conditions**.)

In Ireland, a recent bill aims to reform the reimbursement process for orphan drugs by exempting them from health technology appraisals with heavy emphasis on ICER thresholds and QALYs. The bill also wants to introduce other criteria for considering whether to reimburse such drugs, including budget impact and the availability of the drug elsewhere in Europe. In addition, Scotland just passed new legislation to improve early patient access to 'ultra-orphan' drugs by introducing a system for provisionally funding such medicines while more evidence is gathered on their effectiveness. Ireland and Scotland thereby introduced highly commendable initiatives, recognising the challenges related to orphan drugs.

4.2. Feasibility of a Managed Access Agreement

The Committee during the appraisal process at NICE in agreement with the assessment of the EMA "…noted the possibility that deeply ingrained light avoidance behaviour may have influenced the trial results." (FED p.22). "The committee accepted that data collection in the context of a MAA [Managed Access Agreement] 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) and therefore did not recommend afamelanotide for use in the NHS in England within a MAA. (FED p.23)

However, the NICE Social Value Judgments - Principles for the development of NICE guidance Second edition, section 6.5 and 6.6 (see box 2) states that uncertainty in effectiveness of a treatment caused by behaviour is not a sufficient reason to deny access to a treatment, even if this behaviour impacts on the effectiveness of an intervention and routine quality of life assessments:

**Box 2:**

**Social Value Judgments - Principles for the development of NICE guidance; Second edition: Section 6: Avoiding discrimination and promoting equality:**

"6.5 Conditions associated with stigma
Some conditions, for example, sexually transmitted diseases and drug dependency, are associated with stigma. NICE does not consider that stigma itself is a reason for altering its normal approach to assessing cost effectiveness. However, NICE is aware that stigma may affect people's behaviour in a way that changes the effectiveness of an intervention and that the relief of stigma may not always be captured by routine quality of life assessments. Therefore, NICE expects its advisory bodies to take these considerations into account."

"6.6 Behaviour-dependent conditions
The Citizens Council advised that NICE should not take into consideration whether or not a particular condition was self-induced. It was often impossible, in an individual, to decide whether the condition was dependent on their own behaviour or not; and receiving NHS care should not depend on whether people 'deserved' it or not."

Social Value Judgments - Principles for the development of NICE guidance; Second edition: Section 6: Avoiding discrimination and promoting equality; p.24

In EPP, the conditioned light avoidance behaviour changes the effectiveness of interventions and, consequently, the effects of the afamelanotide treatment were not accurately quantifiable in the clinical trials. By making the afamelanotide treatment available to sufferers in the UK, it can be expected that the majority of these patients would also first need to unlearn their conditioned light avoidance behaviour, and would not immediately enjoy the full extent of the benefit. Nevertheless, it has been shown that most EPP patients manage to unlearn their behavioural adaptation (see section 2 and 3). In the case of EPP, it would be irrational to deny access to an effective treatment, only because its quantification is coupled

with uncertainties caused by necessary behavioural adaptations. This consequentially is also recognized in the NICE guidelines on Social Value Judgments.

In addition, the ORPH-VAL principle 5 recommends that “to accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time”. The working group in their publication further states that “Systematically collecting data from registries as well as implementing managed access schemes (where possible) could help mitigate the uncertainties and fill data gaps.” (Annemanns et al. 2017)

The EMA assessed that quantification of efficacy endpoints in the post approval phase are reasonable and feasible in EPP and as a condition of marketing authorization requires a Post-Authorisation Safety Study (PASS) which also includes efficacy endpoints: “The CHMP has recommended approval for Scenesse [afamelanotide] on the condition that the applicant puts in place a robust risk management plan that ensures close surveillance of the safety and efficacy of the medicine. As part of this plan, the company will establish a registry of patients to collect safety and efficacy data.” (Press release EMA/638997/2014; 24 October 2014).

Therefore, as the EMA already collects efficacy data from patients receiving the afamelanotide treatment in Europe it would be unreasonable and irrational for NICE to assume that this is not possible because of the uncertainties connected to evidence generation in EPP.

**Conclusion**

We demonstrated with new evidence and the outcomes of the Appeal hearing that:

a) The EPP condition is more severe than previously captured by the Committee and indeed qualifies as a disability (Appeal Decision p.9; ¶ 53)
b) The effectiveness, although not accurately quantifiable in randomised controlled trials, shall no longer be assessed as “small” (Appeal Decision p.12; ¶ 70) and the full extent of the benefit can be assessed when taking into account patient input as outcome measure
c) The DLQI is an inappropriate tool to capture the benefits of the afamelanotide treatment (section 3) and that
d) The possibility for an MAA should not be denied because of uncertainties caused by disease specific behavioural adaptations which interfere with an accurate determination of the efficacy (section 4.2.), which would also be illogical.

In addition, we are highly concerned by the observed lack of consistency in the evaluation provided by the ERG: In our submission, we report examples in which the ERG applied different assessment standards when they evaluated results by their preferred or alternative tools, ignored the best available evidence and presented analyses which do not stand up to close scrutiny.
As the ERG report informs the Committee on key aspects for their appraisal, we think that a critical evaluation of the ERG report and adaption of the conclusions presented is central for a fair and equitable appraisal process.

Lasty, we urge the Committee and the NHS to enable access to this life-changing treatment: EPP patients suffer second-degree burns in their blood vessels after very short exposure times to sunlight and strong artificial light sources. If during a barbeque someone accidentally suffered second-degree burns on the face and hands, they would be rushed to an emergency unit of a hospital, and everything possible would be done to alleviate the pain and treat the consequences of the burns. Until recently, EPP specialists could not offer their patients anything to either treat or prevent the massively painful phototoxic reactions. Now, with afamelanotide an innovative therapy exists which finally enables EPP suffers to live an almost normal life.

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**British Association of Dermatologists**
**Response to NICE Highly Specialised Technology Appraisal**
**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

On behalf of the British Association of Dermatologists, thank you for inviting us to the NICE meeting in order to address the upheld appeal points in the case of afamelanotide.

1) **Upheld Appeal Ground 1a.1: The committee failed to act fairly by demonstrating consistent discrimination against IPPN as a stakeholder group**
   We look forward to IPPN taking a full part in this NICE meeting. We strongly agree with the Appeal Panel that, given the extensive use, and much greater experience, of afamelanotide in treating EPP patients in other countries outside England (including Italy, Switzerland and several other countries), their long-term experience of treatment with afamelanotide in a real-world setting, their experience and their testimony is crucial to this process. With IPPN represented, NICE will have the opportunity to be provided with additional information about patients' experience from long-term treatment with afamelanotide.

2) **Upheld Appeal Ground 1b.1. (IPPN)**
   **Appeal Ground 1b.1: The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward**
   **And upheld Appeal Ground 1b.1 (CLINUVEL (UK) Ltd): NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities**
   Although these upheld appeal points were presented by IPPN and Clinuvel, the BAD strongly agrees with the Appeal Panel's decision and we have specific criticisms of NICE's qualitative evidence analysis methodology. It is critical that NICE has not followed its own procedure in terms of how it considers evidence in cases, like this, where the disease is rare and where the existing quality of life issues measures do not fully capture the quality of life issues in the disease. Specifically, NICE has been found by the Appeal Panel to have ignored its own 'Interim Process and Methods of the HST Programme' guidance, paragraph 41:

   *"The Evaluation Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Evaluation Committee to consider all of the evidence presented to it, including RCTs, observational studies and 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. In evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions."*

   This is a critical point in this case where the ICER has been used alone in determining the NICE Panel's decision, in a situation where ICER was clearly inadequate and where NICE's own guidance required them to take the qualitative evidence into account in making their decision. In this case, the qualitative evidence from patient (and also physician) testimony was of a striking and dramatically effective therapeutic effect. It is critical that NICE's re-evaluation of afamelanotide, in light of the Appeal Panel's decision, must take a proper account of the qualitative evidence. Formal Qualitative analysis, by methodology including Framework Analysis, is a well-established core set of methodologies in the Social Sciences and in Health Psychology. NICE has previously made no attempt to formally analyse the extensive qualitative interview evidence with which they were presented. NICE has never

indicated that they have sought out any Qualitative Analysis expertise at all, from a Health Psychologist or other relevant expert. NICE was unable to answer the question posed during the Appeal Hearing by Dr Sarkany as to what methodology they had used to objectively assess the qualitative evidence. NICE was also unable to answer the question as to how the analysis of this evidence was incorporated into the NICE Panel's decision. In fact, senior members of the NICE panel and NICE organisation, during the previous meetings, made it clear on several occasions that their decision was made entirely on the basis of the ICER calculation. In the light of the Appeal Panel's decision against NICE on this point, the BAD requests that 1) NICE agree to use a recognised Qualitative Analysis methodology with the expertise of Qualitative Analysis Experts to formally analyse the qualitative evidence presented to them by patients and physicians in the previous hearings, and that these Experts can request further qualitative evidence as required 2) NICE specify, create and use in this case a transparent methodology which enables formally analysed qualitative submitted evidence to be formally incorporated into the process by which the decision is made. This will enable NICE to comply with paragraph 41 of their own guidance.

3) **Upheld Appeal point Ground 2.2: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide (This appeal point was named BAD 2.1 in initial correspondence and during the hearing)**
**And Appeal point Ground 2.3: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide (This appeal point was named BAD 2.5 in initial correspondence and during the hearing)**
**And upheld Appeal point Ground 2.2: The evidence provided shows that the benefit is significant and not small, as assessed by the committee (This appeal point was named IPPN 2.1 in initial correspondence and during the hearing)**
The BAD notes that the Appeal Panel upheld our Appeal on this crucial issue. Specifically, the BAD disputes the committee's view that the clinical trial results suggest "small" benefits with afamelanotide. The average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). This is meaningful as it increases the average time spent by patients with EPP who are on treatment to the expected level for this measure. Data presented by Professor Rhodes has shown that healthy indoor workers spend an average of only 22 minutes outdoors between 10 am and 3 pm on summer weekdays.[1] Several publications also show that time spent outdoors throughout the day (6 am to 8 pm) by the average person is of the order of minutes, not hours, i.e. minutes are of consequence: minutes matter. Moreover, it should be noted that time spent in direct sun may be less that time spent outdoors. The figure of approximately 10 minutes extra per day of sun exposure represents an average daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest. We note the testimony of James Rawnsley, for IPPN, at the Appeal Hearing, who explained that for a patient with EPP, a small absolute change in the number of minutes in the sun could be life-changing. He commented that when he took part in the trial he was able to spend a whole day outside in the sun without any reaction, but that sometimes the feedback in his trial diary about how much time he had actually spent in the sun appeared less positive because of poor weather or his own work commitments. Other patients have made similar observations to us, and to the NICE Committee in the previous meetings. The observational study by Biolcati *et al*. (2015) may have been uncontrolled, but it still found

[1] Webb AR et al. The role of sunlight exposure in determining the vitamin D status of the UK white adult population. Br J Dermatol 2010; 163: 1050-5.

improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first 6 months of treatment.

We will let the Appeal Panel's highly critical judgement of NICE on this point speak for itself, when the Appeal Panel judged this issue of NICE describing the benefits of afamelanotide in EPP patients as 'small'. The Appeal Panel said:

*"Whilst the panel noted Dr Jackson's comment that the term "small benefits" was intended to refer to the randomised trial results rather than the overall benefit of treatment, it also noted that this term was used repeatedly both in the FED and during the hearing. The panel was persuaded by Professor Rhodes' argument that whether an increase of 10 minutes represents a small or a large change can only be interpreted with regard to the normal range for this measure. The panel noted that FED paragraph 4.7 cites differences in the amount of time spent in daylight and decreases in phototoxic reactions that would not necessarily sound small to someone reading the document. The panel judged that describing these differences as small lacks face validity….. Overall, the panel concluded that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide."*

The BAD notes that evaluation of points (2) the qualitative evidence and (3) the size of the benefit would be assisted by participation in the forthcoming NICE meeting of a clinical expert with broad and long-term experience of prescribing afamelanotide for EPP patients, i.e. in a real-world setting, particularly Professor Elisabeth Minder, Zurich, senior author of Biolcati *et al.* (2015) (Elisabeth.Minder@triemli.zurich.ch). Professor Minder would be willing to attend the meeting. This is important and entirely consistent with participation of the international patient group (IPPN) in point (1) above.

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

**Appendix D - professional organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

**About you**

**Your name:** [redacted]

**Name of your organisation: Salford Royal NHS Foundation Trust**
**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:**

I have no links to declare

**Appendix D - professional organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

1. **New or additional evidence not submitted during the original evaluation, particularly regarding anything that supports long term effectiveness of the treatment.**

   - There are no further published trials of clinical effectiveness of Afamelanotide in EPP apart from those considered in the original evaluation
   - The ongoing European Post Authorisation Safety Study (PASS) seems likely to be the only emerging source of additional data in the near future.
   - On 18th March 2018, Clinuvel published a company announcement on its website, giving some "headline" information following analysis of 13 months of data from the PASS study.
   - On 27th October 2018, Dr Debby Wensink (Erasmus Medical Centre, Rotterdam) gave an oral presentation at the General Assembly and Scientific Meeting of the European Porphyria Network, held in Rotterdam. This was an update on their clinical experience of use of Afamelanotide since 2016.
   - The above sources report extremely high rates of long term compliance with afamelanotide treatment (>98%), confirming and strengthening a finding of the observational study Biolcati et al 2015: Br J Dermatol 72:1601

2. **Further evidence that addresses the concerns raised by the committee and/or the appeal panel.**

   **You might also wish to consider how to demonstrate in your submission where some of the benefits of afamelanotide in the 4 categories below may not have been captured in the committee's previous deliberations:**

   I refer in my comments below to paragraphs in the NICE Appeal Hearing document: "Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927] Decision of the panel"

- **Nature of the condition**

**Para 19-26**: It seems entirely appropriate that given the rarity of EPP, information and testimony from the international patients' representative group (IPPN) should be considered alongside that from the British Porphyria Association.

Including this wider pool of patients' testimony will enable a more reliable picture to be gained of the nature of the condition, the resultant disability and its impact on patients' lives.

**Para 43-55:** EPP meets the definition of a disability under the Equality Act 2010. I was surprised to read in the Appeal hearing documentation that this had been a matter of debate.

As a clinician, I regularly provide explanatory letters to support patient requests to schools or employers to implement changes to the learning/working environment, rotas etc. I advise young patients going away to University to register with their student Disability Advisory and Support Services to ensure that they can be offered "reasonable adjustments" and appropriate support to enable them to meet the requirements of their course. In clinical practice, it is obvious that EPP results in disability.

**Appendix D - professional organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

The equality questions posed by NICE in the original scoping exercise were as follows

*"Please let us know if you think that this evaluation:*
*• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
*• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
*• could lead to recommendations that have any adverse impact on people with a particular disability or disabilities"*

I note that most stakeholders (including me) responded to these questions by identifying sub-groups of the EPP population who might be disadvantaged relative to other EPP patients (eg children, who would not be eligible).

EPP as a cohort sharing the protected characteristic of disability was therefore not highlighted in these answers.

- **Clinical effectiveness**

Appeal ground 2.2 and 2.3:

The appeal panel upheld that it is unreasonable to conclude that clinical trial results suggest "small benefits". This is an extremely important finding.

Professor Rhodes argued in the Appeal Hearing (paragraph 64) that the average absolute benefit gained through afamelanotide treatment (approximately 10 minutes per day of additional time in the sun) puts EPP patients into the normal range for healthy indoor workers.

- **Impact of the technology beyond direct health benefits**

If a person with a disability receives a treatment that enables them to function comparably with a person without that disability, this is a substantial overall benefit. Such a difference may, for example, enable a person with EPP to gain employment they could not otherwise contemplate.

- **Value for money**

I am unable to comment on technical aspects of the cost-effectiveness models under debate.

**Further comments**

- It has been accepted that the available trials show that Afamelanotide is clinically effective and the appeal panel upheld that the benefit was significant and not "small".
- A key area of uncertainty is the magnitude of the clinical effectiveness and how to establish this rigorously. The testimony from patients who have experienced the treatment and expert evidence in the appeal point to the trial results having under-estimated the overall impact and benefit of the treatment.

- Given the above findings, it is a great pity that a Managed Access Agreement (MAA) seems not to be possible at this time (para 27-40). This relatively new mechanism, as I understand it, has been introduced specifically to deal with analogous uncertain situations in the NHS.
- If EPP patients could access Afamelanotide via a suitable MAA, further data would be generated to address the uncertainties identified. English EPP patients would be monitored in accordance with the PASS protocol, thus contributing to the validity of the larger international post-marketing evaluation of afamelanotide, which is ultimately to the benefit of all EPP patients.
- The Evaluation Committee view (outlined in para 102 and 103) that it is implausible that further data gathered during a MAA could resolve uncertainty and result in an acceptable ICER, closes a possible route to progress. It is to be hoped that this is not the case and that further negotiation between Clinuvel and NHS England can take place.
- It otherwise feels implausible that a treatment shown to be clinically effective, perhaps highly beneficial overall, cannot otherwise be offered on the NHS to patients with this rare, lifelong, disabling condition.

NICE National Institute for Health and Care Excellence

## Highly Specialised Technology Evaluation - Patient expert statement

# Afamelanotide for treating erythropoietic protoporphyria [ID927]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1.Your name | **Dr. Jasmin Barman-Aksözen** |
| 2. Are you (please tick all that apply): | ☒ a patient with the condition?<br>☐ a carer of a patient with the condition?<br>☒ a patient organisation employee or volunteer? |

| | |
|---|---|
| | ☒ other (please specify): Molecular biologist with PhD in EPP research and since 5 years responsible for the diagnostic for all forms of porphyrias in the Swiss reference centre |
| 3. Name of your nominating organisation | International Porphyria Patient Network (IPPN) |
| 4. Did your nominating organisation submit a submission? | ☒ yes, they did<br>☐ no, they didn't<br>☐ I don't know |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |

| | |
|---|---|
| 6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☐ yes<br>I contributed to the submission of our organisation as a scientist and expert in the field of porphyrias, however want to also provide my personal experiences with the condition below. |
| 7. How did you gather the information included in your statement? (please tick all that apply) | ☒ I have personal experience of the condition<br>☒ I have personal experience of the technology being appraised<br>☒ I have other relevant personal experience. Please specify what other experience:<br>EPP was the research topic for my PhD in molecular biology at the Swiss porphyria competence centre in Zurich at the municipal hospital Triemli. Since five years, I am Head of the Clinical Chemistry laboratory at the Triemli hospital and in charge of the porphyria diagnostics. I am co-author of 13 peer reviewed articles on porphyrias and actively involved in ongoing national and international research projects concerning all forms of porphyrias.<br>☒ I am drawing on others' experiences. Please specify how this information was gathered:<br>As the Vice-President of the IPPN, the Scientific Advisor of the Swiss Society of Porphyria and former Scientific Advisor of the German EPP patient organisation I am in contact with around 400 EPP patients worldwide, many of them having experience with the afamelanotide treatment and other remedies to try to address the disease. |
| **Living with the condition** | |
| 8. Did you have any difficulty or delays in receiving a | Despite considerable efforts to obtain a correct diagnosis by my parents and later also myself, I diagnosed myself with EPP after reading a Wikipedia description of the condition not until during my master's thesis. After contacting specialist physicians, I received helpful information and since the early access scheme for |

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| diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family? | afamelanotide started in Switzerland in 2012 also the appropriate therapy. From my own unsuccessful literature search I know that textbook descriptions of EPP are often misleading and incorrect. |
| 9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to | I grew up with the knowledge that "rain is wet and sun is pain". Spring and summer were hell on earth, because every ray of sunlight immediately induced massively painful burns, the so called "phototoxic reaction", in all parts of the body which were exposed to light. The feeling can only be described as being burnt alive. The pain is so intense, that every second in the sunlight has to be avoided as best as possible – but I had to go to school and take part in outdoor sports events etc. The problem was that the burns in the beginning of the reaction did not lead to visible alterations on the skin, and therefore teachers and physicians did not believe me although sometimes I already was in severe pain and only wanted to immediately get out of this terrible sunlight.<br><br>When I was forced to stay in the sunlight, often for several hours, the exposed body parts – mainly hands and the face because one cannot cover them consistently - developed visible signs: The day after the exposure they became swollen and deeply red, because the blood vessels were burnt and damaged, and the blood leaked out into the tissue. In this condition, words are not sufficient to describe the pain. No pain medication helped, my own body heat was unbearable, the body heat of my parents who wanted to comfort me was unbearable to a degree that I had to push them away from me, and I could not sleep for several nights. I remember that at the age of six or seven I started to consider suicide, because I figured that there is no place for me to exist in a world in which even physicians did not believe me, and people forced me into extremely painful situations again and again. Often, there was no hope left in me.<br><br>My parents did understand that and protected me. They tried – without a confirmed diagnosis – to explain the situation to school teachers and all the expert physicians we visited in order to obtain an answer. My parents were labelled as being hysterical and I was sent to a psychotherapist. This is when we stopped seeing physicians for my EPP symptoms altogether. After that, we only tried to somehow adjust my life around the condition more consequently: I did not join my friends for outdoor activities but stayed at home |

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| school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings? | alone with some excuse, I ignored the strangers making fun of me when in bright sunlight I used an umbrella as protection and I stopped telling anybody when I was in distress or pain, because nobody would believe me anyway.<br><br>At university, I was deeply intrigued about the new prospects of genetically modified plants, and I trained to become a plant scientist. However, although modifying plants basically is lab work, I was required to take outdoor excursions in order to complete my training. I tried to participate with all the protective measures possible but could not stay outdoors for long enough. That forced me to give up this career path, and I lost two years at the university because not only I had to lay the foundations for a new subject but I also was depressed that again those unexplained symptoms interfered with my life choices.<br><br>At the end of my biology studies, I however found a Wikipedia article authored by another EPP patient. She described the symptoms with an accuracy I had not encountered before and this was the day I obtained my diagnosis. I convinced the dermatologists at my university hospital to confirm my “Dr. Google” diagnosis in a specialist lab in Germany and thereafter was invited to give a talk at a conference on porphyrias. This resulted in a research position at the reference centre for EPP and related diseases in Zurich, Switzerland where I successfully conducted research on gene expression and iron metabolism in EPP.<br><br>In 2012, the early access scheme for afamelanotide started in Switzerland and I could access the treatment for the first time. Since then, I have completed my PhD, became Head of the clinical chemistry laboratory, started teaching at the university of Zurich, been invited to Keystone and other important international science meetings, have co-founded the International Porphyria Patient Network and had so many other magnificent moments. My life did not only turn to the better and more normal, but became exceptional. I now can use my full potential, I am no longer restricted to the dark spaces, but feel confident to be in the spotlight.<br><br>I can and I will not accept that EPP patients are not taken seriously any longer and that treatments which enable them to live an almost normal life, to even enjoy sunlight, will be withheld based on unreasonable grounds. |

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| **Current treatment of the condition in the NHS** | |
| 10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough? | Currently, there is only one approved treatment for EPP with proven efficacy and safety, afamelanotide. Under treatment with afamelanotide, I am able to live an almost normal life with considerably less pain (reduced number and severity of phototoxic reactions) and can expose myself for several hours to direct and strong lights.<br>I unsuccessfully tried several remedies including beta-carotene, a variety of sunscreens (some with pigments) and UV-B therapy. Many of the treatment attempts I tried for years like beta-carotene and sunscreens, and I did not care that they made me look strange (orange hue) or were inconvenient to apply, I stopped because they did not help me at all. |
| 11. Is there an unmet need for patients with this condition? | EPP is a severely painful and underestimated ultra-rare condition which urgently needs to be treated. |
| **Advantages of the technology (treatment)** | |
| 12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also | I have access to the afamelanotide treatment since 2012, and since then have a normal life:<br>Under treatment, I can be outdoors in the sunlight for hours as opposed to only a few minutes without treatment. Phototoxic reactions might also be triggered under treatment when staying outdoors for a very long time, however they are much less severe than without the treatment and they resolve the next day. In the beginning I was cautious, because I did not yet know if the treatment would both work for me, and if so, what my new limits, the new tolerance would be. Therefore, I extended my exposure to sunlight successively, every day daring a few more minutes – until one day I stayed outdoors with my husband the entire day. This was the moment I knew that a new life had begun for me, but also for my husband, my parents and friends – everybody who had to forgo outdoor activities and plans because of my condition.<br>Previously, on sunny days, I often felt anxious and I also had fears about my future. I felt as a burden to my family and friends, and often found excuses to not join an outdoor activity to not hinder their plans. This all has normalised now, I am a full member of society, have a job and career options, can travel to conferences even if they are in the summer. |

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| include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life. | |
| 13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment? | The treatment is a slow release implant formulation which provides almost complete protection against phototoxic reactions for about 8 weeks. The implant is applied with a thick needle to the fat tissue just above the hip. Besides the unproblematic medical procedure, there is the data collection for the ongoing Post-Authorisation Safety (and Efficacy) Study implemented by the EMA as a condition of approval. This takes some time, too.<br>Since I work at the Swiss reference centre I do not have to travel, however I know Swiss patients travelling 2-3 h one way for an appointment. Others even fly in from Germany or the USA. |
| **Disadvantages of the technology (treatment)** | |
| 14. What do patients or carers think are the disadvantages of the technology?<br>Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they | Disadvantages of the technology (slow release implant formulation) are the fixed dosage in terms of fixed concentration and treatment intervals. Adaptable doses would be preferable, especially also for the treatment of children, the most severely affected group of EPP patients.<br>The few mild side effects like a slight nausea after the injection (which was also present in the placebo group during the trials) and one to two days of a little bit fatigue are in my opinion clearly outweighed by the considerable benefits the treatment provides. |

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| long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially? | |
| **Patient population** | |
| 15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why. | Patients more daring to expose themselves to sunlight and strong artificial light under treatment experience a bigger benefit or might benefit faster.<br>I am aware of two patients in Switzerland, two patients in Germany and one in Austria who did not experience a sufficient treatment effect and stopped with the treatment, however the reasons are not entirely clear. These non-responders are significantly outnumbered by approximately 180 patients I am in contact with who experience a massive benefit which they describe as life-changing.<br>Currently, children cannot benefit from the afamelanotide treatment because there is not yet a marketing approval for paediatric use. However, to my knowledge, trials are in preparation. |
| **Equality** | |
| 16. Are there any potential equality issues that should be taken into account when | EPP is connected to behavioural adaptations, e.g. avoidance of all daytime outdoor activities including social and work-related activities and a massive stigmatisation due to the necessity for protection against visible light, e.g. thick long clothes, hats, umbrellas etc. in bright sunshine and even indoors (light coming through window glass, light from energy saving bulbs). Due to the massive pain of the |

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| considering this condition and the treatment? | phototoxic reactions which cause secondary burns in the blood vessels, the patients have to protect themselves from all forms of light exposure. However, because the symptoms mostly remain invisible and/or patients completely cover up, usually the environment does not believe the necessity of the behavioural adaptions and bully and harass the patients, which leads to further social withdrawal, lower self-esteem, less supportive networks and so on.<br>The behavioural adaptations very likely also led to issues during the clinical trials, as the patients first had to unlearn their light avoidance and had to dare to expose themselves to sunlight during the trials (time in sunlight was the main outcome measured for the studies). |
| **Other issues** | |
| 17. Are there any other issues that you would like the committee to consider? | As EPP is an ultra-rare condition with a limited research history (less than 1000 peer reviewed publications) many uncertainties might remain for the appraisal process. We urge NICE to keep in mind the “ultra-orphan” nature and the great unmet need of the EPP condition but also the consistency in the more that 35 testimonies submitted during the appraisal process and consultation phase by EPP patients, carers and / or experts who describe the treatment effects of afamelanotide as truly life changing. |
| **Key messages** | |
| 18. In up to 5 bullet points, please summarise the key messages of your statement:<br>• EPP is an inborn error of metabolism associated with severely painful reactions to the visible light range.<br>• EPP is connected with a massive behavioural adaptation which stigmatises the patients and leads to social withdrawal and isolation.<br>• No effective treatment option exists for EPP besides the approved afamelanotide therapy.<br>• The afamelanotide treatment enables the patients to live an almost normal life and makes them full members of society.<br>• As an ultra-rare condition with limited research history and, accordingly, still many uncertainties, we appeal to NICE to listen to the patients voice. | |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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# CONFIDENTIAL UNTIL PUBLISHED

## Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

## Afamelanotide for treating erythropoietic protoporphyria

## ADDENDUM 2 (post appeal)

## CONFIDENTIAL


**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

**Authors** Joanne Lord, Professorial Fellow in Health Economics
Jonathan Shepherd, Principal Research Fellow

**Correspondence to** Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute, Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac



**Date completed** **15 February 2019**

# 1. Introduction

Following the NICE Appeal Panel decision of 9 October 2018, the company submitted a proposal for a Managed Access Agreement (MAA) to NICE (Clinuvel letter of 21/1/19). This letter included a copy of a revised Budget Impact Assessment (BIA) document, dated October 2017 and previously submitted to NICE in a letter dated 6/11/17. As the Evidence Review Group (ERG) assigned to this evaluation, NICE have asked us to comment on the revised BIA and proposed MAA.

In this document, we summarise and comment on the assumptions and calculations in the company's budget impact assessments:

- The original BIA from the Company Submission (CS) and economic model
- The company's revised BIA of October 2017

We developed an Excel model to check the company's original and revised BIA calculations and enable further sensitivity analysis if required. These were adapted from the 'BIM' and 'Costs and Resources' sheets of the company's economic model, and replicate their calculations.

We also summarise the provisions of the company's proposed MAA and comment on how they relate to the assumptions in the company's budget impact calculations.

# 2. Original Budget Impact Assessment (August 2017)

The company estimated the budget impact for the NHS in England to be [redacted] in the first year of uptake and [redacted] for each of the subsequent 4 years (CS section 13).

The company state that these estimates reflect a '*maximum* budget impact to NHS England', based on the following assumptions:

- [redacted] EPP patients 'eligible for treatment in England'
- [redacted] of eligible patients treated in year 1 and [redacted] from years 2 to 5
- [redacted] implants per treated patient per year
- An acquisition cost of [redacted] per implant

Assumptions about the costs of administration were not explicit in the CS, but we note that an additional cost of [redacted] per patient per year was included on top of the drug acquisition cost (see calculations in Table 1 below).

Based on the cost and resource use calculations in the company's economic model, we infer that this administration cost comprises:

- [redacted] for dermatological screening (1 extra visit at £170 plus laboratory tests)
- [redacted] for [redacted] implant injection visits (£203.75 per visit)
- [redacted] for a final visit after the last implant of the year

**Table 1 Estimated budget impact from company submission**

| | Uptake [a] | Patients treated [b] | Implants used [c] | Acquisition cost [d] | Administration cost [e] | Budget impact NHS England [f] |
|---|---|---|---|---|---|---|
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Percentage of eligible patient population. Company submission section 13.2

b Calculated by multiplying % uptake by the company's assumed eligible population ([redacted])

c Calculated by multiplying the number of patients treated by [redacted] implants per patient per year

d Calculated by multiplying the number of implants by the cost per implant ([redacted])

e Calculated by subtracting the drug acquisition cost from the total budget impact.

f Company submission section 13.7

In the ERG report, we noted the inconsistency between the assumed number of implants and the number of implant injection visits in the company's calculations (ERG report section 5.1). With [redacted] per patient per year, the estimated budget impact rises slightly to [redacted] in year 1 and [redacted] in years 2 to 5 (CS Table 36).

We also presented sensitivity analysis to illustrate the impact of varying assumptions about the number of patients eligible for treatment (from 300 to 600 each year) and the mean number of implants per patient, per year (2 or 3) (ERG report Table 37).

## 3. Revised Budget Impact Assessment (October 2017)

The company presented revised estimates of budget impact in Appendix 1 of their report dated October 2017.

The calculations differed from those in the original company submission in four respects:

- The number of people eligible for treatment was reduced by excluding children under the age of 18 ([redacted]), to reflect the marketing authorisation.
- The numbers of patients treated per year were reduced, based on assumptions about constraints on current and projected service capacity in England. The company identified 2 current expert centres for EPP treatment and 6 other centres with expertise in rare metabolic disorders who could provide afamelanotide with training, and [redacted]. The company defined three scenarios of treatment numbers over the five-year period (see Table 2 and Table 3 below).
- The mean number of implants per patient varied from [redacted] per year in the 'most probable' scenario, up to [redacted] in the 'maximum' scenario. This is the key driver of cost per patient; hence, the assumption of fewer implants gives a lower predicted budget impact.
- Additional administration costs were fixed at [redacted] per patient per year in all scenarios. This matches the cost reported in CS Table D6, but the assumptions underlying this estimate were not specified.

The company's revised budget impact predictions are lower than those reported in the CS under all scenarios.

We note an apparent error in application of the administration cost in the company's revised budget impact calculations: the additional cost of [redacted] per patient per annum was actually only added once per year for the whole population, and not multiplied by the number of patients treated. We correct this error in Table 3. This causes a small increase in the revised budget impact estimates across all scenarios.

**Table 2 Company scenarios in revised budget impact assessment**

| | Most probable | Possible | Maximum |
|---|---|---|---|
| Number of centres | [redacted] | [redacted] | [redacted] |
| Patients treated per centre per year | [redacted] | [redacted] | [redacted] |
| Mean implants per patient per year | [redacted] | [redacted] | [redacted] |

***Source:*** Table 1 Clinuvel Budget Impact Assessment for England, October 2017

**Table 3 Company's revised budget impact assessment (with ERG correction)**

| | Uptake [a] | Patients treated [a] | Implants used [a] | Acquisition cost [a] | Administration cost [b] | Budget impact NHS England [c] |
|---|---|---|---|---|---|---|
| **Most probable scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Possible scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Maximum scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 [d] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Table 1 Clinuvel Budget Impact Assessment for England, October 2017

b ERG correction: [redacted] per patient treated

c ERG correction: acquisition cost + administration cost

d Company states that scenario is impossible in year 5, as patients treated exceeds estimated prevalence

## 4. ERG critique of revised BIA

**Number of people eligible for treatment**

The company's revised estimate of the number of patients in England who would be eligible for treatment is reasonable. The restriction to people aged 18 years and older reflects the marketing authorisation and the calculation is accurate based on the Elder et al. prevalence of 9.2 per million and population of 43,752,473 adults in England (ONS mid-year 2017).[1] [2]

We note that there is uncertainty over the Elder et al. prevalence estimate: reported 95% confidence interval 7.7 to 11.6 per million, which translates to between 337 and 508 adults diagnosed with EPP in England. There are also other uncertainties that are difficult to quantify. Elder et al. found variations in incidence between countries: with a higher incidence in the UK than in most other countries. Their prevalence estimates are also higher than reported numbers of cases in retrospective studies: e.g. only 389 cases of all ages were identified in the UK by Holme et al (2006).[3] Elder et al. argue that this disparity may be due their own assumption of constant incidence, whereas rates of diagnosis had actually been increasing.

Uncertainty over prevalence does not cast doubt on the company's revised budget impact estimates, because these are driven by the capacity constraints. However, it does suggest that the upper limit of treatment capacity ([redacted] treated patients in year 5 in the company's maximum scenario) might not be 'impossible'.

**Number of patients to be treated**

The company's revised method of estimating treatment numbers based on capacity is an improvement, as it reflects information about real-world constraints. Whether the assumed number of treatment centres and the limits on how many patients each centre could treat are realistic is a matter of judgement for NHS England and clinical experts. But we consider that the company has explored a fair range of scenarios from [redacted] patients treated in year 1 up to between [redacted] in year 5.

**Mean number of implants per patient**

There is uncertainty over the mean number of implants that patients will receive per year. In their cost-effectiveness analysis, the company assumed a mean of [redacted] per year, based on experience with expanded access and commercial distribution in other countries (CS Table D5). The evaluation committee uncertainty over whether this number is generalisable to

England, and concluded that they should take into account that people may have up to 4 implants per year (FED 4.18).

**Administration costs**

There is a lack of clarity over what costs the NHS will incur in addition to the drug acquisition cost. The company assumes a fixed additional annual cost of [redacted] per patient in their revised budget impact calculations. This is equal to the estimated annual cost for members of the placebo group in the company's economic model: which comprises one dematological screen, one photoprovocation test, one set of laboratory tests and prescription of calcium and vitamin D (see Table 4 below).

The company's economic model assumes that patients treated with afamelantotide will require one extra dermatological screen and one extra set of laboratory tests each year, in addition to specialist outpatient visits for implant injections and an extra final visit of the year. We summarise the total additional administration cost for each treated patient in Table 5 below. If these total administration costs are included, there is a small increase in the estimated budget impact (up to [redacted] in year 5 under the company's maximum scenario).

**Table 4 Resource use and unit cost assumptions from the economic model**

| Resources | Unit cost | Afamelantotide | Placebo |
|---|---|---|---|
| Implant injection | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| Photoprovocation test | [redacted] | [redacted] | [redacted] |
| Calcium + Vit D | [redacted] | [redacted] | [redacted] |

Source: Extracted by ERG from "Costs and Resources" sheet in company economic model

**Table 5 Additional administration costs per patient treated with afamelanotide**

| Resources | Most probable [redacted] implants | Possible [redacted] implants | Maximum [redacted] implants |
|---|---|---|---|
| Implant injections | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| **Total administration cost** | [redacted] | [redacted] | [redacted] |
| **Drug** | | | |

Source: Calculated by ERG from assumptions in "Costs and Resources" sheet in company economic model

## 5. Proposed MAA (January 2019)

| Proposed Managed Access Agreement | ERG comments |
|---|---|
| i) [redacted] | |
| ii) [redacted] | [redacted] |
| iii) [redacted] | Prevalence estimates support an estimate of [redacted] adults with diagnosed EPP in England (95% confidence interval 337 to 508).[1 2] There is additional uncertainty around these figures due to methodological issues. |
| iv) [redacted] | |
| v) [redacted] | [redacted] |
| vi) [redacted] | [redacted] |
| vii) [redacted] | |
| viii) [redacted] | |

| | | |
|---|---|---|
| ix) | [redacted] | [redacted] |

**References**


1. Elder G, Harper P, Badminton M, et al. The incidence of inherited porphyrias in Europe. *Journal of inherited metabolic disease* 2013;36(5):849-57. doi: 10.1007/s10545-012-9544-4 [published Online First: 2012/11/02]
2. Office for National Statistics (ONS). Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2017, 2018.
3. Holme S, Anstey A, Finlay A, et al. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. *Br J Dermatol* 2006;155:574-81.

# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## Pro-forma Response

## ERG report

## Afamelanotide for treating erythropoietic protoporphyria [ID927]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm**, **Friday 1 March 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

## Issue 1 Confidentiality marking

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 4, bullet 2: This information has never been made public, and is proposed for redaction by NICE below | [redacted] | Information is confidential | This information was included in the Scenesse Budget Impact Assessment (October 2017). The entire document is marked as confidential, thus we have marked it as CIC. |
| Page 8, row 3, prevalence estimate: Redacted elsewhere in this document; presented above as [redacted] | "Prevalence estimates support an estimate of [redacted] adults" | Correction of error; information is confidential | Error corrected. Data is marked as CIC in recognition of its confidential status. |

# CONFIDENTIAL UNTIL PUBLISHED

## Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

## Afamelanotide for treating erythropoietic protoporphyria

## ADDENDUM 2 (post appeal)

## CONFIDENTIAL

## ERRATUM


**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

**Authors** Joanne Lord, Professorial Fellow in Health Economics
Jonathan Shepherd, Principal Research Fellow

**Correspondence to** Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute, Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac



**Date completed** **15 February 2019**

# 1. Introduction

Following the NICE Appeal Panel decision of 9 October 2018, the company submitted a proposal for a Managed Access Agreement (MAA) to NICE (Clinuvel letter of 21/1/19). This letter included a copy of a revised Budget Impact Assessment (BIA) document, dated October 2017 and previously submitted to NICE in a letter dated 6/11/17. As the Evidence Review Group (ERG) assigned to this evaluation, NICE have asked us to comment on the revised BIA and proposed MAA.

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- The company's revised BIA of October 2017

We developed an Excel model to check the company's original and revised BIA calculations and enable further sensitivity analysis if required. These were adapted from the 'BIM' and 'Costs and Resources' sheets of the company's economic model, and replicate their calculations.

We also summarise the provisions of the company's proposed MAA and comment on how they relate to the assumptions in the company's budget impact calculations.

# 2. Original Budget Impact Assessment (August 2017)

The company estimated the budget impact for the NHS in England to be [redacted] in the first year of uptake and [redacted] for each of the subsequent 4 years (CS section 13).

The company state that these estimates reflect a '*maximum* budget impact to NHS England', based on the following assumptions:

- [redacted] EPP patients 'eligible for treatment in England'
- [redacted] of eligible patients treated in year 1 and [redacted] from years 2 to 5
- [redacted] implants per treated patient per year
- An acquisition cost of [redacted] per implant

Assumptions about the costs of administration were not explicit in the CS, but we note that an additional cost of [redacted] per patient per year was included on top of the drug acquisition cost (see calculations in Table 1 below).

Based on the cost and resource use calculations in the company's economic model, we infer that this administration cost comprises:

- [redacted] for dermatological screening (1 extra visit at £170 plus laboratory tests)
- [redacted] for [redacted] implant injection visits (£203.75 per visit)
- [redacted] for a final visit after the last implant of the year

**Table 1 Estimated budget impact from company submission**

| | Uptake [a] | Patients treated [b] | Implants used [c] | Acquisition cost [d] | Administration cost [e] | Budget impact NHS England [f] |
|---|---|---|---|---|---|---|
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Percentage of eligible patient population. Company submission section 13.2

b Calculated by multiplying % uptake by the company's assumed eligible population ([redacted])

c Calculated by multiplying the number of patients treated by [redacted] implants per patient per year

d Calculated by multiplying the number of implants by the cost per implant ([redacted])

e Calculated by subtracting the drug acquisition cost from the total budget impact.

f Company submission section 13.7

In the ERG report, we noted the inconsistency between the assumed number of implants and the number of implant injection visits in the company's calculations (ERG report section 5.1). With [redacted] per patient per year, the estimated budget impact rises slightly to [redacted] in year 1 and [redacted] in years 2 to 5 (CS Table 36).

We also presented sensitivity analysis to illustrate the impact of varying assumptions about the number of patients eligible for treatment (from 300 to 600 each year) and the mean number of implants per patient, per year (2 or 3) (ERG report Table 37).

## 3. Revised Budget Impact Assessment (October 2017)

The company presented revised estimates of budget impact in Appendix 1 of their report dated October 2017.

The calculations differed from those in the original company submission in four respects:

- The number of people eligible for treatment was reduced by excluding children under the age of 18 ([redacted]), to reflect the marketing authorisation.
- The numbers of patients treated per year were reduced, based on assumptions about constraints on current and projected service capacity in England. The company identified 2 current expert centres for EPP treatment and 6 other centres with expertise in rare metabolic disorders who could provide afamelanotide with training, and [redacted]. The company defined three scenarios of treatment numbers over the five-year period (see Table 2 and Table 3 below).
- The mean number of implants per patient varied from [redacted] per year in the 'most probable' scenario, up to [redacted] in the 'maximum' scenario. This is the key driver of cost per patient; hence, the assumption of fewer implants gives a lower predicted budget impact.
- Additional administration costs were fixed at [redacted] per patient per year in all scenarios. This matches the cost reported in CS Table D6, but the assumptions underlying this estimate were not specified.

The company's revised budget impact predictions are lower than those reported in the CS under all scenarios.

We note an apparent error in application of the administration cost in the company's revised budget impact calculations: the additional cost of [redacted] per patient per annum was actually only added once per year for the whole population, and not multiplied by the number of patients treated. We correct this error in Table 3. This causes a small increase in the revised budget impact estimates across all scenarios.

**Table 2 Company scenarios in revised budget impact assessment**

| | Most probable | Possible | Maximum |
|---|---|---|---|
| Number of centres | [redacted] | [redacted] | [redacted] |
| Patients treated per centre per year | [redacted] | [redacted] | [redacted] |
| Mean implants per patient per year | [redacted] | [redacted] | [redacted] |

***Source:*** Table 1 Clinuvel Budget Impact Assessment for England, October 2017

**Table 3 Company's revised budget impact assessment (with ERG correction)**

| | Uptake [a] | Patients treated [a] | Implants used [a] | Acquisition cost [a] | Administration cost [b] | Budget impact NHS England [c] |
|---|---|---|---|---|---|---|
| **Most probable scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Possible scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Maximum scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 [d] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Table 1 Clinuvel Budget Impact Assessment for England, October 2017

b ERG correction: [redacted] per patient treated

c ERG correction: acquisition cost + administration cost

d Company states that scenario is impossible in year 5, as patients treated exceeds estimated prevalence

## 4. ERG critique of revised BIA

**Number of people eligible for treatment**

The company's revised estimate of the number of patients in England who would be eligible for treatment is reasonable. The restriction to people aged 18 years and older reflects the marketing authorisation and the calculation is accurate based on the Elder et al. prevalence of 9.2 per million and population of 43,752,473 adults in England (ONS mid-year 2017).[1] [2]

We note that there is uncertainty over the Elder et al. prevalence estimate: reported 95% confidence interval 7.7 to 11.6 per million, which translates to between 337 and 508 adults diagnosed with EPP in England. There are also other uncertainties that are difficult to quantify. Elder et al. found variations in incidence between countries: with a higher incidence in the UK than in most other countries. Their prevalence estimates are also higher than reported numbers of cases in retrospective studies: e.g. only 389 cases of all ages were identified in the UK by Holme et al (2006).[3] Elder et al. argue that this disparity may be due their own assumption of constant incidence, whereas rates of diagnosis had actually been increasing.

Uncertainty over prevalence does not cast doubt on the company's revised budget impact estimates, because these are driven by the capacity constraints. However, it does suggest that the upper limit of treatment capacity ([redacted] treated patients in year 5 in the company's maximum scenario) might not be 'impossible'.

**Number of patients to be treated**

The company's revised method of estimating treatment numbers based on capacity is an improvement, as it reflects information about real-world constraints. Whether the assumed number of treatment centres and the limits on how many patients each centre could treat are realistic is a matter of judgement for NHS England and clinical experts. But we consider that the company has explored a fair range of scenarios from [redacted] patients treated in year 1 up to between [redacted] in year 5.

**Mean number of implants per patient**

There is uncertainty over the mean number of implants that patients will receive per year. In their cost-effectiveness analysis, the company assumed a mean of [redacted] per year, based on experience with expanded access and commercial distribution in other countries (CS Table D5). The evaluation committee uncertainty over whether this number is generalisable to

England, and concluded that they should take into account that people may have up to 4 implants per year (FED 4.18).

**Administration costs**

There is a lack of clarity over what costs the NHS will incur in addition to the drug acquisition cost. The company assumes a fixed additional annual cost of [redacted] per patient in their revised budget impact calculations. This is equal to the estimated annual cost for members of the placebo group in the company's economic model: which comprises one dematological screen, one photoprovocation test, one set of laboratory tests and prescription of calcium and vitamin D (see Table 4 below).

The company's economic model assumes that patients treated with afamelantotide will require one extra dermatological screen and one extra set of laboratory tests each year, in addition to specialist outpatient visits for implant injections and an extra final visit of the year. We summarise the total additional administration cost for each treated patient in Table 5 below. If these total administration costs are included, there is a small increase in the estimated budget impact (up to [redacted] in year 5 under the company's maximum scenario).

**Table 4 Resource use and unit cost assumptions from the economic model**

| Resources | Unit cost | Afamelantotide | Placebo |
|---|---|---|---|
| Implant injection | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| Photoprovocation test | [redacted] | [redacted] | [redacted] |
| Calcium + Vit D | [redacted] | [redacted] | [redacted] |

Source: Extracted by ERG from "Costs and Resources" sheet in company economic model

**Table 5 Additional administration costs per patient treated with afamelanotide**

| Resources | Most probable [redacted] implants | Possible [redacted] implants | Maximum [redacted] implants |
|---|---|---|---|
| Implant injections | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| **Total administration cost** | [redacted] | [redacted] | [redacted] |
| **Drug** | | | |

Source: Calculated by ERG from assumptions in "Costs and Resources" sheet in company economic model

## 5. Proposed MAA (January 2019)

| Proposed Managed Access Agreement | ERG comments |
|---|---|
| i) [redacted] | |
| ii) [redacted] | [redacted] |
| iii) [redacted] | Prevalence estimates support an estimate of [redacted] adults with diagnosed EPP in England (95% confidence interval 337 to 508).[1 2] There is additional uncertainty around these figures due to methodological issues. |
| iv) [redacted] | |
| v) [redacted] | [redacted] |
| vi) [redacted] | [redacted] |
| vii) [redacted] | |
| viii) [redacted] | |

| | | |
|---|---|---|
| ix) | [redacted] | [redacted] |

**References**


1. Elder G, Harper P, Badminton M, et al. The incidence of inherited porphyrias in Europe. *Journal of inherited metabolic disease* 2013;36(5):849-57. doi: 10.1007/s10545-012-9544-4 [published Online First: 2012/11/02]
2. Office for National Statistics (ONS). Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2017, 2018.
3. Holme S, Anstey A, Finlay A, et al. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. *Br J Dermatol* 2006;155:574-81.

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Dr Peter Jackson, Chairman, Highly Specialised Technologies Committee
Ms Sheela Upadhyaya, Associate Director Highly Specialised Technologies
National Institute of Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT
Sent via HST@nice.org.uk

CC: Marie Manley, Sidley Austin LLP (mmanley@sidley.com)
Martin Chamberlain QC, Brick Court Chambers (martin.chamberlain@brickcourt.co.uk)
Sarah Love, Brick Court Chambers (sarah.love@brickcourt.co.uk)

08 March 2019

**Re: SCENESSE® for the treatment of erythropoietic protoporphyria [EPP]**

Dear Dr Jackson, Ms Upadhyaya,

We have duly noted the ERG report dated 15 February 2019.

ERG provided commentary to NICE around uncertain outcomes. We address the commentary and identify certain inaccuracies for the purpose of eliminating doubt in our discussion and your assessment.

The ERG failed to recognise in its report that the product is made available only to trained and accredited academic expert centres in the European Union, which would also be applicable to the UK. Further, the ERG failed to acknowledge that the distribution of SCENESSE® takes place through a closed supply chain, and that the pharmaceutical product is not made available to any other prescribers, general pharmacies or other wholesale channels. The 'closed distribution' provides each European nation with a guarantee on limited prescription of the product, and therefore poses a limited burden and no financial risk to the respective European healthcare systems.

**Budget Impact Assessment [BIA]**
CLINUVEL has consistently disclosed to the HST Committee the number of EPP patients in England who would be eligible for treatment with SCENESSE®. Since CLINUVEL has specialist knowledge of the patient population, the number of eligible adult patients is estimated to be 404. The maximum recommended dose is four implants per annum, with the discretion for expert physicians to prescribe up to six per calendar year. However, the ERG incorrectly uses a range of 300 to 600 eligible EPP patients in its sensitivity analysis. Since there could only be a maximum conceivable 404 eligible EPP patients eligible, the number of 600 is inappropriate, incorrect and misleading. This figure should not be factored into any further analysis or discussion.

Three scenarios have been provided by CLINUVEL and the ERG, a) most probable, b) possible, and c) maximum. In none of these scenarios would CLINUVEL exceed the maximum annual budget under the NHS of £20 million.

Under the most probable scenario the impact on the NHS budget would range from £3.3M to £6.4M, in a possible scenario from £7.8M to £14M, and in a maximum scenario £12.M to £19.4M per annum.

The sensitivity of BIA lies in the number of centres prepared to provide clinical care, while the HST has been all too aware of the limited number of university centres in the country willing to provide the multidisciplinary care required for EPP patients, and hence the limited willingness from academic clinical experts to prescribe the drug. Further compounding the BIA model, the HST has been equally aware that British university centres have proven reluctant to register more than 50 EPP patients for clinical care due to the administrative time expended under the PASS protocol. Therefore, it will be challenging for CLINUVEL to commit eight academic expert centres by year 4 and 5 to provide treatment, though we will undertake the best efforts to make the treatment available to all EPP patients.

**PASS Expenditures and associated administration cost**
The European Porphyria Network demanded from the Company in 2014 – upon receiving marketing authorisation and post-marketing commitments – unconditional financial support for up to 12.5 hours per patient per annum to enable treatment under the EMA's imposed PASS protocol. This reflects the time required to facilitate treatment under the PASS. In full transparency and in the principle of fairness CLINUVEL had agreed to reimburse each European EPP expert centre under the PASS protocol – through a Clinical Trial Agreement – a net amount of €1,400 maximum per annum per patient for the additional administrative time spent on each EPP patient, and for entering data onto the European EPP Disease Registry. As stated and part of CLINUVEL's international policies and governance, CLINUVEL does not provide discounts, rebates or other payments to hospitals, physicians, intermediaries or third parties, nor does it promote or advertise the sale of the product.

**Price of SCENESSE®**
CLINUVEL has lowered the price of SCENESSE® on two occasions in the course of the availability of treatment since 2014, from €21,971 to €16,842 and in 2017 from €16,842 to the current €14,100.95, 64% of the original price of the treatment. As of 19 April 2019, the price will be adjusted by CPI (1.6%) to €14,327 for all countries, including Switzerland. In the coming two years there will be an increase according to CPI, before CLINUVEL increases its drug price in 2021. The remainder of the ERG commentary on pricing is correct.

**Proposed Managed Access Agreement [MAA]**
CLINUVEL fully understands that each European country is working within the budgets to each treatment allocation, and the Company would commit to:

(i) the European pricing of SCENESSE® - £12,020 net per injection – to be fixed for 24 months except for annual CPI adjustments - with no further rebates discounts or cashbacks under any scheme. A price increase is foreseen to conform to market rates and the increase in cost of goods in 2021.

(ii) treat all eligible adult EPP patients in England by 2022 to 2024, depending on the centres willing to participate and prescribe the product. The number of 404 EPP patients is correct and serves as the basis for this MAA and Budget Impact Assessment.

(iii) NHS obtaining annual reports from the disease registry (EEDR) relating to British patients on treatment, whereby an evaluation would be made with the Company after 24 months.

(iv) a maximum midpoint between the most probable (a) and possible scenario (b) of £10.2 million maximum implant expenditures per annum for the first two years (24 months from start in 2019 to 2021) with a total of £20.4 M, after which a formal evaluation would be made but with the intention to continue the supply of treatment.
Since CLINUVEL has intimately known the patient populations it focuses on, and since it has never exceeded these volume agreements in any other European country, it is confident it will be able to meet and stay within the proposed threshold for England. It would agree to reimburse 35% of each

individual implant cost upon exceeding the overall threshold; ex aequo tam if the Company underbids the threshold by more than 10% (less than £9 million product expenditures per annum under the NHS), the NHS would publicly acknowledge the accuracy of the Company's commitment under the agreed MAA, in view of the delays NICE has incurred and errors made during the review process at the detriment of EPP patients.

(v) reimbursement of 50% of the last administered product's net costs to the NHS in the event the treatment has proven ineffective.
Inefficacy of treatment is defined as an independent written assessment and declaration by the expert physician, together with the patient's declaration, that the patient wishes to indefinitely cease treatment with SCENESSE® due to the lack of improvement or effectiveness during daily life. An interruption of treatment due to inability to travel, work commitments or pregnancy does not constitute lack of efficacy.

(vi) further develop and fund the "Inventory of Daily Activities" to enable assessment of impact of treatment.

(vii) continue the financial support to the British EPP expert centres trained and accredited by CLINUVEL for the administrative resources used under the PASS protocol.

In the ERG report a comment is made on prioritising EPP patients. CLINUVEL will not accept the responsibility of preselecting EPP patients since all patients annually and periodically are affected by phototoxicity and anaphylactoid reactions, and the Company does not see making these decisions included in its remit. This decision to treat is exclusively made by the treating physicians in consultation with their patients.

CLINUVEL has exhausted its efforts to demonstrate that zero financial risk would be posed by SCENESSE® for the treatment of EPP, congruent with other European countries, and therefore we have fulfilled the essential criteria. In light of the undisputed benefit of the treatment and all proposed cost minimisation measures, CLINUVEL anticipates that NICE will work the Company to ensure patient access to this life-changing treatment.

I look forward to discussing the proposed MAA with the HST Committee. We reserve all our rights.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

NICE National Institute for Health and Care Excellence

# Highly Specialised Technology Evaluation

# Afamelanotide for treating erythropoietic protoporphyria [ID927]

# Evaluation Report

NICE National Institute for Health and Care Excellence

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

**Contents:**



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

**Commented [JE1]:** No confidentiality marking - request a marked version from company? Or confirmation it contains no AIC or CIC

**Commented [JE2]:** Should the images in this submission also be redacted?

**Commented [JE3]:** No confidentiality marking - request a marked version from company? Or confirmation it contains no AIC or CIC

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final evaluation document

# Afamelanotide for treating erythropoietic protoporphyria

## 1 Recommendations

1.1 Afamelanotide is not recommended, within its marketing authorisation, for preventing phototoxicity in adults with erythropoietic protoporphyria (EPP).

1.2 This recommendation is not intended to affect treatment with afamelanotide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### Why the committee made these recommendations

EPP is a condition in which exposure to light causes painful and debilitating reactions in the body. Because there is no treatment, people try to avoid light. This limits their ability to do normal daily activities, and leads to feelings of social isolation, anxiety and poor quality of life.

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.

The cost-effectiveness estimates for afamelanotide are all very much higher than the range normally considered acceptable for highly



Issue date: May 2018

specialised technologies. This is despite taking into account the impact the condition and technology have on quality of life, 'disability', and likely non-health-related benefits such as improving employment and study options, and the fact that afamelanotide is an innovative treatment.

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.

# 2 The condition

2.1 Erythropoietic protoporphyria (EPP) is a genetic disorder. It is caused by impaired activity of the enzyme, ferrochelatase. The condition results in excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma and red blood cells. EPP is a cutaneous porphyria, and the major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and some types of artificial light. The skin may become painful, swollen, itchy and red, and skin erosions can also occur. A phototoxic reaction typically lasts between 2 days and 3 days. However, it can last 10 or more days, with severe pain and loss of sleep. These symptoms, along with anxiety and social isolation because of sunlight avoidance, can have a profound impact on quality of life. Over time, light exposure can cause thickening of the skin on the knuckles and scarring on the face. A small proportion of people with EPP may have important complications related to liver and gallbladder function.

# 3 The technology

3.1 Afamelanotide (Scenesse, Clinuvel) activates the synthesis of eumelanin mediated by the MC1R receptor. Eumelanin contributes to photoprotection by: strongly absorbing UV and visible light (acting as a filter); antioxidant activity; and inactivating the superoxide anion and increasing the availability of superoxide dismutase to reduce oxidative stress. Afamelanotide has a UK marketing authorisation under

'exceptional circumstances' for 'the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)'. It is administered as a subcutaneous dissolving implant. One implant is administered every 2 months before expected and during increased sunlight exposure, for example, from spring to early autumn. Three implants are recommended annually, depending on the length of protection needed, and the maximum recommended dose is 4 per year. Treatment with afamelanotide would be life-long. The marketing authorisation stipulates that afamelanotide should only be prescribed by specialist clinicians in recognised porphyria centres, and that it should only be given by a clinician trained and accredited by the marketing authorisation holder to insert the implants.

3.2 The most common side effects with afamelanotide seen in clinical trials were nausea and headache, and discolouration, pain and redness at the implant site. These were generally mild and affected about 1 in 5 of people. Afamelanotide is contraindicated for people with reduced liver or kidney function. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 Afamelanotide has not been launched in the UK, but the company has stated that the cost of an implant will be £12,020 (excluding VAT).

# 4 Consideration of the evidence

The evaluation committee (see section 6) 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). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

## *Nature of the condition*

### Burden of disease

4.1 The committee heard from patient experts that phototoxic reactions can be triggered by even a few minutes of exposure to light, particularly when light is at its most intense on sunny days in the summer, and the reaction itself can last for days. The patient experts described the pain during a reaction as intense, intolerable and not relieved by pain medication. Furthermore, the pain is neuropathic, meaning that even a light touch to the skin during a reaction exacerbates the pain. Patient experts also reported an all-encompassing tiredness associated with a phototoxic reaction. Sometimes, the phototoxic reactions are accompanied by redness and swelling but often there are no external signs. The committee acknowledged that phototoxic reactions can be associated with intense pain and extreme tiredness that lasts for days.

4.2 People with erythropoietic protoporphyria (EPP) report the symptoms of phototoxic reactions as being debilitating, preventing them from being able to do day-to-day activities. They also say that, without anything to treat the pain or the phototoxicity, their only option is to wait for the phototoxic reaction to stop and their bodies to heal. The patient experts explained that, because phototoxic reactions are unbearable, they will do anything it takes to prevent them. In the absence of any treatment that prevents phototoxicity, this involves avoiding light. The patient experts reported that they constantly assess the light conditions and measures they need to take to minimise the risk of a phototoxic reaction. This, and the fear of a phototoxic reaction, are major and constant causes of anxiety. People with EPP report that they often turn down invitations to activities or events, which leads to feelings of social isolation and compromises family life because they cannot take part in outdoor activities or go on holidays. A patient expert explained that his children cannot understand why he cannot join in, which leads to guilt and depression. The patient experts stated that they have had to adapt their

careers to manage the measures they need to take to avoid light. The British Porphyria Association stated that its members reported choosing jobs that are indoors with minimal travel and even night jobs to minimise light exposure. A study from Holme et al. (2006) reported that most people with EPP were in employment or education but that 47% (n=66/127) of those in work felt their choice of profession had been influenced by their condition. Education choices are similarly affected. The British Porphyria Association stated that, for some families, the children may take on caring for a parent with EPP or other responsibilities that the parent cannot do because of their EPP. It also noted that EPP can place a financial burden on families because of loss of earnings and the expense of measures to protect against sun exposure. The committee heard from a clinical expert that EPP either causes debilitating pain if people with the condition try to live a normal life, or anxiety and isolation if they try to avoid the pain by staying indoors. Testimonies received during consultation emphasised the extent of the burden of the condition, including the physical pain from light exposure, and the severe anxiety and social isolation from having to avoid light. The committee was clear that EPP can have a far reaching impact on the lives of patients and their families, resulting in poor quality of life.

### Current treatments

4.3 The committee heard that there is no effective treatment for the underlying cause of EPP, to protect against phototoxicity or to relieve pain caused by it. 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 and associated adverse effects (such as an increased risk of death from lung cancer and cardiovascular disease with beta carotene, and an increased risk of developing skin cancer with narrow band UVB). Light avoidance and covering the skin are the only options available to people with EPP. A clinical expert noted that light blocking creams like Dundee cream do not provide complete blocking of light and are also not ideal because they are

noticeable on the skin. The committee concluded that there is no effective treatment for preventing phototoxicity caused by EPP, so there is an unmet need for an effective treatment.

### Diagnosis

4.4 The committee noted that, like many rare conditions, people with EPP have experienced delays in getting a diagnosis. The British Porphyria Association stated that the median age of diagnosis is 22 years, although for most people the age of onset of EPP is at birth or soon after; 1 reason is that awareness and knowledge of the condition is very low, both among the public and in general medical practice (outside of specialist porphyria centres). People with EPP have reported that other people not understanding their experience, when it is not accompanied by external signs of phototoxicity, has led them to feeling isolated and it means they have often had the condition without support for years. The committee concluded that delay in the diagnosis of EPP is a problem, and could result in people with the condition developing automatic behaviour over time to avoid light and so phototoxic reactions.

### Variation in symptoms

4.5 The committee discussed the variation in symptom severity in people with EPP. A clinical expert stated that most people (around 70) under his care have 'classical' EPP. These people could have between 2 minutes and 40 minutes of sun exposure before experiencing a phototoxic reaction. However, the pain severity and duration of a phototoxic reaction are similar among these people. The clinical expert noted that he had treated around 16 people with mild EPP, who could be in very strong sunshine for several hours without a phototoxic reaction. Both clinical experts stated that people with mild EPP may not need, or choose, to have afamelanotide. The company stated that it is not possible to measure the severity of EPP. The committee acknowledged that there is some variation in how long people with EPP can be exposed to sunlight without

a reaction. It concluded that any variation in patient experience of the condition was unclear because of a lack of data.

## *Impact of the new technology*

### Clinical benefits and uncertainties

4.6 The committee discussed the evidence available for afamelanotide, noting that there were 4 randomised placebo-controlled trials (CUV017: 100 patients and 12-month duration; CUV029: 76 patients and 9-month duration; CUV030: 77 patients and 6-month duration; CUV039: 94 patients and 6-month duration ). The committee noted that, although the trials were designed so that the patients would not know what they were having, some patients may have known they were having afamelanotide because it caused their skin to tan. The committee understood that CUV039 was the pivotal trial and this was carried out in the US. It noted that the other trials had included people from the UK and other European countries. It also noted the view of the clinical experts that the trials were generalisable to clinical practice in England. The committee was disappointed and concerned to note that the company submission did not include complete trial details, such as full baseline data. It meant that the ERG was unable to independently assess the methods and reliability of the clinical-effectiveness assessment of afamelanotide in the clinical trials. The committee understood that the ERG had, where possible, extracted data from publications available to supplement the information available in the company submission. The ERG pointed out 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. The company highlighted that it had been through a long and complex regulatory process and, based on input from patient and clinical experts, afamelanotide had been granted a marketing authorisation under exceptional circumstances. This was because the EMA recognised that the comprehensive data on the efficacy and safety required for a regular marketing authorisation could

not be generated but that the benefit-risk balance based on the evidence available was favourable. The company stated that the evaluation committee should not reopen the conclusions made by the EMA's Committee for Medicinal Products for Human Use about the efficacy of afamelanotide. 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. 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 population health gains 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.

4.7 The committee noted that the clinical trial results indicated a relatively small but statistically significant increase with afamelanotide compared with placebo in the median amount of time a person could spend in daylight (between 10:00 and 15:00) without pain (CUV029: 5.63 hours with afamelanotide and 0.75 hours with placebo, p=0.006; CUV039: 69.4 hours and 40.8 hours respectively, p=0.044), and a decrease in the median number and severity of phototoxic reactions (CUV029: 77 reactions with afamelanotide and 146 with placebo, p=0.04). The data on severity are not reported because the company has deemed them to be commercial in confidence. It heard from patient experts and the British Porphyria Association that even small benefits such as being able to spend an extra few minutes in daylight or having fewer phototoxic reactions could have a large impact on people's lives. For example, a few minutes may allow a person with EPP to get into a shop or travel to work. A patient expert also explained that a few minutes in full daylight would typically equate to many more minutes, and even hours, in dappled light (shade). This would mean people with EPP would be in a much stronger

position to manage their lives without being debilitated by the disease. The comments received following consultation strongly echoed these statements. Additionally, the committee understood that the company considered conditioned light avoidance behaviour was a likely reason the trial outcomes showed relatively small benefits with afamelanotide. The committee was aware that, in the trials, patients were asked to voluntarily expose themselves to light and the duration of light exposure was measured. It agreed that conditioned light avoidance could have impacted on the trial results, but it was unclear to what extent. The committee heard from a patient expert who had had afamelanotide that it had taken time to unlearn this behaviour and increase the amount of time spent in light. It understood that, with time, it was possible that conditioned light behaviour could be unlearnt, but it was unclear how long this would take and whether it would vary from person to person. A clinical expert stated that the length of the clinical trials may have been too short for patients to have changed this ingrained behaviour. 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. The committee concluded that the trials had shown relatively small benefits with afamelanotide, and that clinical and patient experts believed the effects would be greater than those seen in the trials.

4.8 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. A clinical expert stated that the increase in the first 6 months was important, and speculated that the climate in Switzerland and Italy may have contributed towards the

stabilisation in scores beyond 6 months. The committee was aware that, in the trial, there was also an improvement in quality-of-life scores in the placebo arm; the company explained that this was likely because EPP is a neglected disorder and the opportunity to enrol in a trial would have provided patients hope for the first time. The committee considered that these results were in contrast to the discussions around the impact of conditioned light avoidance. The committee concluded that afamelanotide was likely to improve quality of life but the true size of any improvement was uncertain.

4.9 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. The committee was convinced that patients valued the benefits of afamelanotide but remained concerned that no data were available to quantify this impact. It heard from the company that the issue was of a lack of scientific tools to capture the true impact of the disease and so the benefit of afamelanotide, rather than a lack of data. The company and experts stated that an indicator of the effectiveness of afamelanotide was the compliance rate of about 94% despite the cost and time associated with travel for treatment. The committee appreciated the compliance rate was high but noted that it was not a quantifiable marker of effectiveness. It concluded that, although there was a substantial difference between patient and clinical expert testimonies and trial

outcomes and although it believed afamelanotide did offer a clinical benefit, the size of the benefit remained uncertain.

### Quality of life

4.10 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 from clinical experts that these measures were not appropriate for capturing the quality of life of people with EPP. The committee further noted that the company had developed a condition-specific quality-of-life questionnaire called the EPP-QoL, but that this had not been fully validated. The committee noted that, to be appropriately validated, it should be suitable to support labelling claims granted by the EMA and the US Food and Drug Administration. Furthermore, the EPP-QoL had been modified while the trials were ongoing and data were being collected, and some questions were removed. The company stated that it had consulted with EPP experts to develop the EPP-QoL, but was unable to provide the committee with a response to whether it had used standard methods for developing and validating this tool. The committee was particularly concerned that a question relating to capacity to go to work or school was removed from the EPP-QoL, and that there were no questions relating to the impact of pain, because these aspects were stated by people with EPP to be of great importance to them. The company stated that it had not included a question on how pain affected patient's quality of life because it was not considered to be comprehensive in describing symptoms during a reaction. Following consultation, the company also stated that, because patients avoid light, it is rare for them to experience pain and so it would not yield useful results. The committee appreciated the nuances of capturing the burden of the condition because of light avoidance but, based on extensive patient testimonies, it maintained that pain was an important outcome. A clinical expert added

that, because of small numbers of patients, there was a limit to how much the tool could be optimised, and that additionally seasonal variations were important in interpreting the results. They explained that, ideally, a quality-of-life assessment should be done during each of the 4 seasons to capture these variations. The committee considered that any quality-of-life measure should capture the aspects of the condition that affect a person's quality of life and, for EPP, this should capture quality of life during and between phototoxic reactions. It also considered that the EPP-QoL did not appear to capture some aspects of EPP that people with the condition and their clinicians report as important. However, the committee was aware of the substantial feedback from stakeholders that EPP-QoL is a relevant tool. The committee concluded that it would take the EPP-QoL into account in its decision-making but that, without full and appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide.

4.11 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 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. 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. Following consultation, clinical experts stated that the DLQI had not been validated

specifically for EPP, whereas the EPP-QoL was developed by experts in EPP and queried the committee's preference for DLQI. The committee noted that DLQI data from the trials had shown a modest but not statistically significant improvement in quality of life with afamelanotide and, in a large observational study, it had been shown to be sensitive to the impact of EPP on people with the condition. The committee noted that the same issue seen with EPP-QoL on seasonal variations (see section 4.10) applied to the interpretation of DLQI scores. Importantly, the committee explained that the DLQI could be mapped, using a validated algorithm, to EQ-5D to generate utility values to be used in a cost-effectiveness model. 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 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. The committee concluded that results based on DLQI were relevant to its decision-making, alongside results based on EPP-QoL.

## *Cost to the NHS and value for money*

### Company's model

4.12 The committee discussed the company's model and noted that a large amount of information relating to the model structure and assumptions was considered confidential by the company. The committee was disappointed that this meant that its discussions and decisions on the model could not be fully described publicly. It noted that the modelled benefits were based on pooled trial data on EPP-QoL collected at 4 months. It also noted that data were collected at 6 months, although from a smaller proportion of the trial population, but these data had not

been presented by the company. The committee considered that the longer follow-up data could be useful to see, particularly because it heard from a clinical expert that the benefits of afamelanotide may take time to become apparent if people adapt their conditioned behaviour gradually. The committee noted that the company had stratified the data to represent mild, moderate and severe disease by splitting the EPP-QoL scores into 3 equal ranges. It heard that, in the absence of validated cut-offs for EPP severity using the EPP-QoL, the company considered the arbitrary division of the EPP-QoL into thirds to be the fairest approach. The committee considered the validity of the EPP-QoL to be uncertain (see section 4.10) and concluded that the company's arbitrary approach to stratifying disease severity added to this uncertainty.

4.13 The committee noted that the company's analyses estimated disability-adjusted life years (DALYs) averted, and the incremental cost-effectiveness ratios (ICERs) were presented as cost per DALY averted. The company stated that, because of the unique nature of the condition and because there was of a lack of available robust data from which to derive utility values, it did not support using utility values to quantify quality of life. Rather, the company noted it was more appropriate to consider the impact of EPP and afamelanotide on people's quality of life in terms of disability. The committee noted that the NICE interim process and methods guide of the Highly Specialised Technologies Programme states that benefits of a technology should be expressed as utility values to determine the impact of a technology on quality and quantity of life, that is, quality-adjusted life years (QALYs) gained. It stated that using QALYs was in the NICE reference case (that is, the preferred methods to be applied consistently across evaluations), and that this was important to allow consistent evaluation across therapy areas. 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. The committee noted, however, that it could consider non-reference case

methods alongside those in the reference case if there is a strong enough 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. The committee questioned further why the company preferred to map from other diseases that may not be fully representative of EPP rather than directly use patient-level quality-of-life data collected in EPP trials. The committee understood from the company that it needed a proxy condition to derive disability weights because these were not available for EPP (see section 4.15). However, it did not consider that the company had made a strong case for using disability weights to justify the added uncertainty of using a proxy condition rather than direct trial data.

4.14 At the second evaluation meeting, the company stated that it did not consider the DALY approach to be more appropriate than QALYs. Rather, it considered that no approach was entirely suitable to reflect the complexities in EPP, and that the DALY model was its attempt to present an alternative approach. The committee was aware that the ERG had provided a simple adaptation of the company's model, which showed that the differences between the DALY and the QALY did not matter in this instance because both approaches produced similar results and so would not affect the committee's conclusions. The committee concluded that, although it would take a DALY-based model into account in its decision-making, its preferred approach was the one aligned with the NICE reference case.

4.15 The committee noted that, in its DALY-based framework, the company had used disability weights from the World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) to model the disability associated with mild, moderate or severe EPP. However, because the GBD survey had not asked about EPP, the company had used weights for a proxy condition it considered similar to EPP in its modelling. The committee noted that the company considered the proxy condition to be confidential. It appreciated similarities between some

important aspects of the conditions but was aware of other important aspects that were not similar. The committee stated that it was unclear about the extent to which the proxy condition reflected the disability associated with EPP and whether it was valid to assume that the disability associated with mild, moderate or severe disease in the proxy condition would correspond with mild, moderate or severe EPP. Furthermore, it reiterated its concerns about the uncertainties surrounding the stratification of people with mild, moderate and severe EPP based on EPP-QoL data collected in the trials (see section 4.12). The committee concluded that the proxy condition used by the company may not fully capture the experience of people with EPP, and the assumption that it is similar to EPP in general and at different levels of severity was not sufficiently robust.

### ERG's exploratory analyses

4.16 The committee discussed the alternative approach taken by the ERG in its exploratory base case to model the benefits of afamelanotide. That is, using DLQI data from one of the clinical trials and mapping this to EQ-5D to derive utility values using a published algorithm. 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. 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.

### Treatment duration

4.17 The committee noted that the company assumed in its modelling that the benefits of afamelanotide would be immediate and would remain constant for the whole year, including after the last implant. It also noted that the ERG had tested some assumptions around this in sensitivity analyses. These included analyses around how long it would take for a person to experience the benefits of afamelanotide and how long the treatment effects of afamelanotide would persist after the last implant of the year. The committee considered that it was likely that it would take some time before patients would experience the benefits of afamelanotide, not least because time would be needed to unlearn conditioned behaviour associated with light avoidance. The clinical experts described how the protective antioxidant effect of afamelanotide needed time to build up after the first implant but would persist for a period of time after the last implant. The committee noted the lack of data to support these assumptions. However, on balance, it concluded that the ERG's analyses assuming that the effect of afamelanotide would build up over the first 2 months (as the ERG had modelled in its base case), and that the treatment effect would slowly decrease over 6 months after the last implant, used plausible assumptions.

### Dosage of afamelanotide

4.18 The committee discussed the likely use of afamelanotide in clinical practice. It was aware that the marketing authorisation recommended administering an implant every 2 months before expected, and during increased, sunlight exposure from spring to early autumn, and recommended a maximum of 4 implants per year. 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 (based on what had been seen in

expanded access and commercial distribution of the drug across the expected EPP population; this number is not reported because the company has deemed it to be commercial in confidence) but had provided no detail on whether it was generalisable to people using afamelanotide in clinical practice in England. The committee concluded that it should take into account that people may have up to 4 implants in its decision-making.

### Cost-effectiveness results

4.19 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained. The committee discussed the QALY gains associated with afamelanotide, noting that EPP is not associated with a reduced life expectancy and, as such, afamelanotide does not extend life. The QALY gains were therefore driven by improvements in quality of life, which were relatively modest in both the company's base case and ERG's exploratory analyses. The undiscounted incremental DALYs in the company's base case and the ERG's estimated incremental QALYs based on the company's use of a proxy disease cannot be reported because the company has stated that these are commercial in confidence. Over the life-time of a patient, the undiscounted QALYs gained with afamelanotide in the ERG's exploratory base case were 0.56, and did not exceed 0.8 in the ERG's sensitivity analyses. The committee recalled that there was uncertainty around the utility estimates (and the disability estimates in the company's model), and that the full benefits of afamelanotide were not quantified. However, it concluded that accounting for this was unlikely to result in an incremental QALY gain of at least 10.

The committee concluded that the criteria for applying a QALY weight was not met.

4.20 The committee noted that the following key ICERs were all over £100,000 per QALY gained:

- the company's base case: £278,471 per DALY averted (£278,386 per QALY gained when converted to a QALY-based ICER using the ERG's simple QALY adaptation)
- the ERG's exploratory simple QALY adaptation using utilities from the literature for the company's proxy condition: £1,726,802 per QALY gained
- the ERG's exploratory base case assuming 3 implants per year, gradual onset and 2-month attenuation of the relative treatment effect (see sections 4.17 and 4.18): £1,605,478 per QALY gained
- the ERG's exploratory base case with the committee's preferred assumptions on gradual onset and 6-month attenuation of the relative treatment effect: £1,343,359 per QALY gained
- the ERG's exploratory base case assuming 2 implants per year: £1,337,494 per QALY gained
- the ERG's exploratory base case assuming a maximum of 4 implants per year: £1,785,957 per QALY gained.

The committee concluded that the ICERs based on its preferred methods and assumptions were likely to be between £1,343,359 and £1,785,957 per QALY gained. The committee noted that the ICERs based on EPP-QoL, and 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. The committee considered this to be very similar to the ERG's exploratory base-case ICERs.

### *Impact of the technology beyond direct health benefits and on the delivery of the specialised service*

4.21 The committee discussed the impact of afamelanotide beyond its direct health benefits and the testimony of the patient experts. It noted that people with EPP might alter their career plans to accommodate the effects of their disease and might be unable to take up enhanced career opportunities. The committee considered that people who had already taken a certain career path because there had historically been no treatment options would not necessarily change career if they had afamelanotide, but appreciated that it would allow them the freedom to pursue more opportunities. Additionally, people diagnosed with EPP starting out in their careers may not need to alter their preferred career plans to accommodate managing their EPP. Furthermore, the committee was unclear about the financial implications of these career choices. It acknowledged that afamelanotide reduced phototoxic reactions in the clinical trials and that this could affect a person's ability to work and study. However, 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. It also noted that only 1 scenario reduced the ICER from £278,471 per DALY averted in the company's base case to less than £100,000 per DALY averted. This was based on the assumption that people having afamelanotide receive 90% of the mean wage whereas people having standard care earned only 10% of the mean wage. The committee noted that this assumption was very strong and was not in keeping with the findings on choice of occupation from Holme et al. (2006; see section 4.2). The committee concluded that afamelanotide would have an impact beyond direct health benefits but that quantifying this was difficult. It concluded that it was highly unlikely the impact would be sufficient to overcome the committee's concerns about value for money

(see section 4.20), and also unlikely to bring the most plausible ICERs to a level considered to be an acceptable use of NHS resources.

### Managed access agreement

4.22 Following consultation, the British Association of Dermatologists queried the possibility of developing a managed access agreement (MAA) to address the uncertainties. The committee noted that it could consider an MAA proposal if all stakeholders collaborated to develop and support it. The committee noted that it had not been presented with a proposal but discussed whether a proposal could potentially address the 2 main elements of an MAA:

- Data collection to reduce uncertainty at the end of the MAA: the committee was aware of the significant uncertainties in this evaluation and discussed whether further data collection would address the uncertainties. It heard from the company that there was a lack of appropriate instruments to enable robust data collection and it was not in support of redesigning clinical studies. The company also highlighted that the EMA considered it to be unethical to conduct further clinical trials in patients. Instead, the company stated that they intend to collect post-authorisation safety data and to validate the EPP-QoL tool and use it to collect further data in the UK. 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.

- Sharing of financial risk during the MAA: the committee noted that an MAA would typically include financial components that would apply while it is in force to share the financial risk with the NHS. The company stated that it offered a single price across countries and there was no scope for this to differ in England. However, it was willing to enter into discussions with NHS England to cap

financial risk to the NHS. The committee considered this in the context of the cost-effectiveness estimates discussed in section 4.20. The committee was aware that these estimates (ranging between £1,343,359 and £1,785,957 per QALY gained) were very much above what could be considered an acceptable use of NHS resources, making it highly unlikely that afamelanotide has a plausible potential to be considered cost effective.

## *Conclusion*

4.23 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 without a phototoxic reaction 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. 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 substantial difference between the trial results and the expert testimonies, anecdotal evidence of those present at the meeting, and the consultation comments. The committee agreed that afamelanotide was effective and that the true benefit 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. On balance, it concluded that the ERG's modelling approach was more plausible than the company's because it used trial data in a more direct way. The committee also concluded that it was unclear on how to interpret the non-validated EPP-QoL data and proxy-condition weights, which the company had used to model the benefits of afamelanotide. It concluded that the ERG's exploratory results were also highly uncertain because the

benefits of afamelanotide may not have been fully captured by the DLQI measured in the clinical trials.

4.24 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. It also considered that afamelanotide did not meet the criteria for QALY weighting to be applied, even if qualitative evidence on the extent of benefit and impact beyond direct health benefits was taken into account. The committee considered that an MAA would not have the plausible potential to reduce the uncertainties identified during the evaluation or to reduce the financial risk to the NHS. The committee was therefore unable to recommend afamelanotide for use in the NHS in England.

# 5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
May 2018

# 6 Evaluation committee members and NICE project team

## *Evaluation committee members*

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## *NICE project team*

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Mary Hughes, Aminata Thiam**
Technical Leads

**Raisa Sidhu**
Technical Adviser

**Joanne Ekeledo**
Project Manager

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**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**HIGHLY SPECIALISED TECHNOLOGY EVALUATION**

**APPEAL HEARING**

# Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927]

# Decision of the panel

## Introduction

1. An appeal panel was convened on 30 July 2018 to consider an appeal against NICE's final evaluation determination, to the NHS, on afamelanotide for treating erythropoietic protoporphyria (EPP) [ID927].

2. The appeal panel consisted of:

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| • Prof Jonathan Cohen | Chair |
| • Mr Tom Wright | Non-executive director |
| • Dr Biba Stanton | NHS representative |
| • Mr Uday Bose | Industry representative |
| • Mr Colin Standfield | Lay representative |

3. None of the members of the appeal panel had any competing interests to declare.

4. The panel considered appeals submitted by the British Association of Dermatologists, the International Porphyria Patient Network, the British Porphyria Association and CLINUVEL (UK) Ltd.

5. The British Association of Dermatologists (BAD) was represented by:

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| • Dr Robert Sarkany | Consultant Dermatologist |
| • Prof Lesley E Rhodes | Professor of Experimental Dermatology, Honorary Consultant Dermatologist, Director of the Photobiology Unit |

6. The International Porphyria Patient Network (IPPN) was represented by:

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| • James Rawnsley | EPP patient representative |
| • Emily MacKenzie | Brick Court Chambers |
| • Dr Jasmin Barman-Aksözen | Co-founder and Vice-Chair of the International Porphyria Patient Network |

7. The British Porphyria Association (BPA) was represented by:

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| • John Chamberlayne | BPA Chair |
| • Dr Geoff Sloan | EPP patient representative |

8. CLINUVEL (UK) Ltd was represented by:

| | |
|---|---|
| • Lachlan Hay | General Manager, CLINUVEL (UK) Ltd |
| • Marie Manley | Sidley Austin LLP |
| • Sarah Love | Brick Court Chambers |

9. In addition, the following individuals involved in the evaluation were present and available to answer questions from the appeal panel:

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| • Dr Peter Jackson | Highly Specialised Technologies (HST) Evaluation Committee Chair |
| • Mrs Sheela Upadhyaya | Associate Director – HST, NICE |
| • Mr Meindert Boysen | Centre for Health Technology Evaluation Director, NICE |
| • Miss Aminata Thiam | Technical Lead, NICE |
| • Mr Francis Pang | HST Evaluation Committee Member |
| • Mr Jeremy Manuel | HST Evaluation Committee Member |

10. The appeal panel's legal adviser Alistair Robertson was also present.

11. Two members of the NICE appeals panel (Mr Christopher Rao and Prof Ruairidh Milne) were present as observers but did not participate in any of the discussions of the appeal panel, or in the decision-making.

12. Under NICE's appeal procedures, members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

13. There are two grounds under which an appeal can be lodged:

1) **<u>Ground One</u>: In making the assessment that preceded the recommendation, NICE has:**
   **(a) Failed to act fairly; and/or**
   **(b) Exceeded its powers.**

2) **<u>Ground Two</u>: The recommendation is unreasonable in light of the evidence submitted to NICE.**

14. The Vice Chair of NICE (Dr Rosie Benneyworth) in preliminary correspondence had confirmed that:

- The British Association of Dermatologists (BAD) had potentially valid grounds of appeal as follows: Ground 2.

- The International Porphyria Patient Network (IPPN) had potentially valid grounds of appeal as follows: Grounds 1(a), 1(b) and 2.

- The British Porphyria Association had potentially valid grounds of appeal as follows: Ground 2.

- CLINUVEL (UK) Ltd had potentially valid grounds of appeal as follows: Grounds 1(a) and 1(b).

15. The evaluation that is the subject of the current appeal provided advice to the NHS on the use of afamelanotide for the treatment of EPP.

16. EPP is a genetic disorder. It is caused by impaired activity of the enzyme, ferrochelatase. The condition results in excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma and red blood cells. EPP is a cutaneous porphyria, and the major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and some types of artificial light. The skin may become painful, swollen, itchy and red, and skin erosions can also occur. A phototoxic reaction typically lasts between 2 days and 3 days. However, it can last 10 or more days, with severe pain and loss of sleep. These symptoms, along with anxiety and social isolation because of sunlight avoidance, can have a profound impact on quality of life.

17. During the appeal hearing, Dr Sloan, Dr Barman-Aksözen and Mr Rawnsley gave personal testimony about their experience of EPP as patients. They emphasised the profound suffering caused by EPP and the pervasive impact of the disease on their lives. They also discussed their own experiences of treatment with afamelanotide. The panel found their testimony powerful and moving, and would like to thank them all for their particular efforts to attend the hearing. The panel also wishes to acknowledge the arrangements made by NICE to ensure that patients were not exposed to direct sunlight during the hearing.

18. Before the appeal panel inquired into the detailed complaints, the following preliminary statements were made: Emily MacKenzie on behalf of the International Porphyria Patient Network (IPPN), John Chamberlayne on behalf of the British Porphyria Association (BPA), Dr Robert Sarkany on behalf of the British Association of Dermatologists (BAD), Sarah Love on behalf of CLINUVEL (UK) Ltd and Dr Peter Jackson on behalf of the evaluation committee.

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

**Appeal by International Porphyria Patient Network (IPPN)**

**Appeal Ground 1a.1: The committee failed to act fairly by demonstrating consistent discrimination against IPPN as a stakeholder group**
(This appeal point was named IPPN 1a6 in initial correspondence and during the hearing).

19. Dr Barman-Aksözen, for IPPN, stated that the specific circumstances of this evaluation made the involvement of her organisation as a consultee vital. Specifically, it was important for the committee to hear evidence on the long term experience of treatment with afamelanotide in a real world setting, and this is available only from international patients.

20. Ms MacKenzie, for IPPN, explained that the IPPN had participated as a stakeholder at the scoping stage but had then been told by NICE that they could not be a consultee for the remainder of the process. It was only after protracted correspondence that they were once again recognised as a consultee. Despite this, they did not have the opportunity to participate in the second meeting of the committee held on 20 February 2018.

21. Mrs Upadhyaya, for NICE, agreed that the IPPN had been consulted during scoping before being excluded and later readmitted as consultees. She explained that the rationale for this initial exclusion had been that they might not have access to UK patients. In response to questions from the panel, she agreed that the process guide does not specifically exclude international organisations as consultees but said that patients with experience of the UK system are generally preferred as patient representatives.

22. It was pointed out during the hearing that the IPPN was represented by patients from the UK at the scoping meeting.

23. Dr Jackson, for NICE, said that the Chair of the evaluation committee is responsible for selecting which of the patient and clinical experts nominated by consultees should attend the second committee meeting. Given that the size of meetings is limited, he would usually prefer patients from England as they know the English health service well and, of particular importance for this appeal, experience the weather in this country. He said that IPPN had been able to comment at all stages of the process and that their input had been very helpful.

24. In response to a question from the panel, Dr Barman-Aksözen, for IPPN, said she hoped the final decision of the committee would have been different if an IPPN patient representative had been able to participate in the second committee meeting because they would have highlighted additional information about patients' experience from long term treatment. She also confirmed that the BPA and IPPN are the only patient groups for EPP that she is aware of.

25. The appeal panel concluded that the IPPN had an important role to play in this evaluation. Whilst recognising that UK patient representatives are often the most appropriate to include, in this particular case, the panel judged that the lack of UK patients with experience of long term treatment with afamelanotide made it important to include international patients. In addition, for this rare disease where there are only two patient groups who represent UK patients with EPP (BPA and IPPN), it would seem logical to include both of these patient groups as consultees throughout the process. The panel did not accept that the IPPN suffered discrimination, and noted that the IPPN did have opportunities to contribute to the evaluation process. However, the appeal panel judged that excluding the IPPN from the second committee meeting was an unfair approach, as they had an important contribution to make.

26. The appeal panel therefore upheld the appeal on this point.

**Appeal by CLINUVEL (UK) Ltd**

**Appeal Ground 1a.1: NICE acted unfairly by failing to give the Company an opportunity to discuss and negotiate its proposed MAA to NHS England before presenting it**

(This appeal point was named CLINUVEL 4 in initial correspondence and during the hearing).

This part of the appeal was held in private at the request of the appellant.

27. Sarah Love, for CLINUVEL, stated that the use of Managed Access Agreements (MAAs) as part of the highly specialised technology (HST) evaluation process is relatively new and pointed out the HST process guide does not set out in detail the procedural details regarding MAAs. She argued that the company was therefore reliant on advice given by NICE about the procedure to follow. She went on to say that because an MAA is a multi-party agreement, it seems unlikely that a company could arrive at an acceptable MAA alone, in the absence of an iterative process. Ms Love stated that the process that occurred did not allow CLINUVEL a fair opportunity to propose an acceptable MAA. In particular, she stated that NICE told the appellant that they would facilitate a meeting with NHS England and then did not follow through on that assurance.

28. Sarah Love, for CLINUVEL, went on to state that in CLINUVEL's opinion, the MAA the company submitted did address both of the concerns expressed by the committee in paragraph 4.22 of the FED concerning data collection and the sharing of financial risk.

29. Ms Love went on to state that NICE invited CLINUVEL to submit an MAA on 13 April 2018. She argued that if the high Incremental Cost-effectiveness Ratios (ICERs) in the FED were an insurmountable barrier to an acceptable MAA, this invitation should not have been made so that CLINUVEL did not waste time and resources pursuing it.

30. Lachlan Hay, for CLINUVEL, provided a detailed timeline of the interactions between NICE and CLINUVEL regarding an MAA, as set out in an appendix to their original appeal letter. He stated that the company was keen to engage with the process of negotiating an MAA and emphasised that the company were expecting NICE to facilitate a discussion with NHS England before submission of the proposed MAA and the publication of the FED.

31. Maria Manley, for CLINUVEL, said that the only meeting between NICE, NHS England and CLINUVEL took place on 30 May 2018 (after publication of the FED). She stated that this meeting consisted of feedback on a decision that had already been made by NICE and NHS England rather than an opportunity for CLINUVEL to engage with a collaborative process.

32. Meindert Boysen, for NICE, stated that NICE is aware that NHS England will not consider an MAA unless there is plausible potential for that MAA to resolve uncertainty in a way that leads to NICE being able to make a decision to recommend a technology as cost-effective. He said that the committee were

aware of the company's policy of only offering a single price for their product and that they do not offer discounts. In this case, NICE had to consider how far away the key ICERs in the FED were from the usual threshold for cost-effectiveness in the HST process. He said that the committee concluded that this distance was so great that it was implausible that any data collected in an MAA could lead to a decision to recommend the technology. Whilst it is not for NICE to seek a change in the price of a product, this was an option that was open to the company throughout the process.

33. In response to questions from the panel, Mr Boysen said that NICE is not a "gate-keeper" to NHS England, and that a company can approach NHS England directly to discuss an MAA.

34. In response to further questions, Mr Boysen said that an MAA was indeed mentioned at the committee meeting of 20 February 2018 by the British Association of Dermatologists and that NICE offered to help the company to understand what NHS England's expectations might be. However, soon after that it became apparent that an MAA did not have plausible potential to result in a decision to recommend the technology.

35. Sheela Upadhyaya, for NICE, said that during the teleconference between NICE, CLINUVEL and NHS England on 30 May 2018, CLINUVEL were advised that they needed to respond to the concern in the FED about the lack of plausible potential for afamelanotide to be considered cost-effective. Meindert Boysen, for NICE, said that if CLINUVEL had offered a proposal that led to plausible potential for afamelanotide to be cost-effective this would have "opened a door" to an MAA that could then attempt to address uncertainties in the evidence base.

36. In response to questions from the panel, Lachlan Hay said that CLINUVEL have always been consistent and transparent about their policy of only offering a single price for their product and that they do not offer discounts. He said that CLINUVEL understood the ICERs to be the material driver of the decision not to recommend the product. However, the company believed the issue of sharing financial risk during the MAA had been addressed by their proposal.

37. The appeal panel concluded as follows:

38. Although the appeal panel had some sympathy with the company's view that there had been a lack of clarity regarding the procedure surrounding the development of MAAs, they did not feel that this was sufficient to make out the ground of appeal.

39. The question is whether the final decision was arrived at fairly. A company must know, during an evaluation, what all of the material drivers of a decision are. The key moment to consider is the moment at which the committee takes its final decision: at that point, has the company been made aware of all of the material drivers, has it had a chance to address them, and has whatever submission it has made informed the committee? Furthermore, the panel were clear that the

company would have had the opportunity to approach NHS England directly at any time. The panel was satisfied that the FED contained adequate reasoning for why an MAA was not judged appropriate, in particular the fact that it was highly unlikely that afamelanotide had plausible potential to be considered cost-effective. CLINUVEL were aware that cost-effectiveness was a material driver for the decision that an MAA was not appropriate, which was clear some time before the finalisation of the FED, and CLINUVEL had opportunities to address this. The appeal panel therefore concluded that CLINUVEL were not disadvantaged by any lack of clarity concerning the MAA procedure and that overall the process followed was fair.

40. Therefore the panel dismissed this appeal point.

**Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.**

**Appeal by International Porphyria Patient Network (IPPN)**

**Appeal Ground 1b.1: The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward**
(This appeal point was named IPPN 1b2 in initial correspondence and during the hearing).

41. In their appeal, the IPPN state that they raised a concern about the equalities impact of the decision during the consultation process. They state that the committee responded by simply stating that “no potential equalities issues have been identified” without providing further justification of this.

42. During initial scrutiny, there was some discussion on whether this was a valid point of appeal. It was accepted on the grounds that another appellant (CLINUVEL) argued that the committee’s decision does not take proper account of equality issues and was put to the appeal panel on this basis. The appeal panel therefore considered this appeal point together with CLINUVEL 1b.1 and this decision letter will deal with these two points together in the section below.

**Appeal by CLINUVEL (UK) Ltd**

**Appeal Ground 1b.1: NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities**
(This appeal point was named CLINUVEL 5 in initial correspondence and during the hearing).

43. Sarah Love, for CLINUVEL, argued that:

(a) NICE is a public authority within the meaning of the Equality Act 2010;
(b) EPP constitutes a disability under the meaning of the Act;
(c) The method used by the evaluation committee to determine cost effectiveness is a 'provision, criterion or practice' within the meaning of the Act;

(d) In this case, the practice adopted was to treat the incremental cost effectiveness ratios (ICERs) as effectively determinative of the committee's decision;
(e) ICERs are derived from quality of life measures, and there is no suitable measure to capture quality of life in EPP;
(f) Therefore use of ICERs (based on such measures) to determine the decision discriminated against all patients with EPP (not just a subset of that group). It put them at a substantial disadvantage to others who do not have EPP, as there is no metric that can produce an accurate ICER. People without EPP could expect to have a treatment for their (different) condition evaluated using metrics that adequately assess that treatment's impact on patients' quality of life, whereas people with EPP could not;
(g) Accordingly reasonable adjustment(s) are required;
(h) The reasonable adjustment to be made in the circumstances would have been to recommend afamelanotide subject to a Managed Access Agreement. Even if NICE was not prepared to go that far, NICE should have changed the methodology adopted.

44. Ms Love emphasised that equalities concerns had been raised by both BPA and IPPN during the consultation, but that the response to these concerns in the documents did not address them adequately. She stated that there was no evidence of the committee considering the need to make a reasonable adjustment to their usual methodology in order to meet their duties as a public authority under the Act. She argued that there was no evidence of consideration of the committee's obligations under the public sector equality duty.

45. Ms Love referred to the High Court judgment in the case of *R(Eisai) v NICE* [2007] EWHC 1941 (Admin), and in particular to the need for proper consideration to be given to NICE's duties as a public authority to promote equal opportunities and to have due regard to the need to eliminate discrimination. Although that case was subsequently considered by the Court of Appeal, Ms Love explained that this part of the High Court judgment was undisturbed by that subsequent consideration.

46. The appeal panel's legal adviser drew the appeal panel's attention to paragraph 92 of the *Eisai* judgment and the "series of simple questions that the appeal panel could have asked both the appraisal committee and themselves" set out in that paragraph. The appeal panel found these instructive and put them to the committee, in particular asking in terms: "has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?"

47. Dr Peter Jackson, for NICE, stated that the HST process was specifically set up to address the particular challenges faced by rare diseases. He commented that measuring outcomes is generally challenging in all rare diseases that the HST evaluation committee considers. He stated that the ICERs were an important factor, but not the only factor in the committee's decision. He explained that they are "an element that gives structure to our thinking. They are one of the things that we think about, and an important thing, but not the only thing we think about".

48. Meindert Boysen, for NICE, said that NICE had completed an Equality Impact Assessment for the evaluation that was signed off on 12 March 2018 but that this was not published on the NICE website or otherwise provided to any other party in error. He apologised for this.

49. Meindert Boysen, for NICE, said that NICE has consistently implemented their positive duty to make reasonable adjustments to protected groups in the way recommendations are implemented, but has not typically considered this relevant to making a recommendation in the first place. He explained this by saying "If we are saying no to everyone, then there is no particular issue within the group and no need to make adjustments".

50. Jeremy Manuel, for NICE explained that the HST process itself was established in response to potential discrimination faced by sufferers of rare diseases. He felt that the same arguments used with regard to afamelanotide in this appeal point (concerning the complexities of capturing the full benefits of treatment) could potentially be applied to any rare disease. He argued that if a different method had been used in this particular case, it could be unfair to those with other rare conditions.

51. In response to the question "has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?" Dr Jackson replied that the committee did not consider EPP as a disability in the meaning of the Act. In response to a request for clarification from the panel, Dr Jackson elaborated by saying that they had interpreted "disability" as referring to a patently visible disability, and that it would be problematic if every disease before them were regarded as a disability.

52. The appeal panel concluded as follows.

53. The panel took the view that EPP very clearly meets the definition of a disability under the Equality Act 2010. It is also clear that NICE is a public authority as defined in the Act. The panel accepted that the Interim Process and Methods of the HST Programme[1] is NICE's institutional response to the problem of highly specialised technologies in respect of which outcomes are difficult to measure and where reliance solely on ICERs would be unreasonable. It is itself a reasonable adjustment made for the benefit of people with rare diseases. In particular, the appeal panel noted paragraph 41 of that document, which states that:

> *41. The Evaluation Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Evaluation Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers*

[1] 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

*and clinical experts who have used the technology being evaluated or are familiar with the relevant condition. In evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions.*

54. However, in this case, the panel were not able to consider the Equalities Impact Assessment said to have been completed by NICE as this had not been published and was not available to either the appellants or the panel. The panel could not see evidence of consideration of NICE's duties under the Act with respect to the use of afamelanotide in EPP specifically, elsewhere in the documents provided. Furthermore, the evaluation committee confirmed during the hearing that they had *not* taken into account any anti-discrimination legislation in reaching their decision. Irrespective of whether ICERs were indeed determinative of the committee's decision, or whether the use of ICERs in this way would constitute a discriminatory "provision, criterion or practice", the panel therefore concluded that NICE had not demonstrated adequate consideration of the legal obligations placed on it as a public authority.

55. The appeal panel therefore upheld the appeal on this point and on the linked IPPN Ground 1b.1 (see paragraph 42). The appeal panel suggests that the Committee may wish to seek further guidance from the Institute, if the Committee considers that it is required, on the relationship between the HST Process Guide and any specific need for reasonable adjustment(s) in relation to a particular cohort of people sharing a protected characteristic.

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

**Appeal by British Association of Dermatologists**

**Appeal point Ground 2.1: The NICE committee have not taken into account the full range of factors.**
(This appeal point was named BAD 2.4 in initial correspondence and during the hearing).

56. Professor Lesley Rhodes, for the British Association of Dermatologists (BAD), stated that real world evidence, clinical expertise and photobiological science were ignored by the committee. She argued that the following factors were not taken seriously by the committee: clinicians' views on the dramatic benefits of afamelanotide, the testimony of non-UK patients, and the evidence of efficacy provided by the high rate of long term compliance with treatment in the observational study Biolcati et al 2015: Br J Dermatol 72:1601.

57. Professor Rhodes stated that conditioned light avoidance probably resulted in the clinical trials under-estimating the benefit of treatment compared with that seen in the longer term.

58. Professor Rhodes also stated that the photo-provocation test used in the clinical trials showed a highly significant increase in light tolerance with treatment.

59. Jeremy Manuel, for NICE, said that all patient and clinician testimony was taken seriously by the committee, who spent time discussing the potential wider benefits of treatment for patients' lives and activities.

60. Dr Jackson, for NICE, said the committee had considered whether conditioned light avoidance was likely to have resulted in the clinical trials substantially under-estimating the benefit of treatment. They concluded that this was unlikely, because in the observational study by Biolcati et al (2015) there was a substantial improvement in quality of life over the first 6 months of treatment with no additional substantial change thereafter.

61. The appeal panel concluded that both the FED and the responses of the evaluation committee during the hearing indicated that the committee had considered the full range of factors put forward by the BAD in this appeal point. Whilst opinions might differ on whether all these factors were given sufficient weight by the committee, the panel judged that the committee's approach to weighing up the importance of all these factors was reasonable.

62. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.2: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide**
(This appeal point was named BAD 2.1 in initial correspondence and during the hearing).

*And*

**Appeal point Ground 2.3: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide**
(This appeal point was named BAD 2.5 in initial correspondence and during the hearing).

63. These two grounds of appeal from BAD, together with IPPN 2.2, (see paragraphs 84-85) overlapped to the extent that it was difficult to disentangle separate points, and they have been considered together in this decision letter.

64. Professor Rhodes disputed the committee's view that the clinical trial results suggest "small" benefits with afamelanotide. She stated that the average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). She argued that this increase puts patients with EPP who are on treatment into the normal range for this measure. (She quoted data that showed that healthy indoor workers spend an average of 22 minutes in the sun between 10am and 3pm). She also pointed out that the figure of approximately 10 minutes extra per day of sun exposure represents an <u>average</u> daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest.

65. James Rawnsley, for IPPN, explained that for a patient with EPP, a small absolute change in the number of minutes in the sun could be life-changing. He commented that when he took part in the trial he was able to spend a whole day outside in the sun without any reaction, but that sometimes the feedback in his trial diary about how much time he had actually spent in the sun appeared less positive because of poor weather or his own work commitments.

66. Dr Jasmin Barman-Aksözen, for IPPN, referred to data from an observational study by Biolcati et al (2015) which found improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first six months of treatment.

67. Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.

68. Dr Jackson stated his view that the differences in minutes per day of time in the sun found in the randomised controlled trials were indeed numerically small. He mentioned that the European Medicines Agency (EMA) had also referred to the magnitude effect of afamelanotide seen in the clinical trials in this way. In response to a question from the panel he stated that there is no established minimally important difference for the outcome measures used in the trials, including minutes per day of time in the sun. However, he emphasised that the committee did not intend to imply that the overall benefit experienced by patients was small[2].

69. The appeal panel concluded as follows:

70. Whilst the panel noted Dr Jackson's comment that the term "small benefits" was intended to refer to the randomised trial results rather than the overall benefit of treatment, it also noted that this term was used repeatedly both in the FED and during the hearing. The panel was persuaded by Professor Rhodes' argument that whether an increase of 10 minutes represents a small or a large change can only be interpreted with regard to the normal range for this measure. The panel noted that FED paragraph 4.7 cites differences in the amount of time spent in daylight and decreases in phototoxic reactions that would not necessarily sound small to someone reading the document. The panel judged that describing these differences as small lacks face validity. Whether or not this choice of words was relevant to the final recommendation made, it is important that the FED describes the results of the trial data in a way that appears to "add up". Overall, the panel concluded that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide.

71. The appeal panel therefore upheld the appeal on these two points (and IPPN point 2.2, see below paragraph 85).

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[2] The panel noted a minor typographical error in the FED, page 5 paragraph 4.2 where "47% (n=66/127") should read 47% (n=60/127)" as written in the original Holme paper.

**Appeal by International Porphyria Patient Network (IPPN)**

**Appeal point Ground 2.1: The committee failed to act fairly by not acknowledging the evidence provided in patient testimonies and by expert physicians on the overwhelming clinical benefit**
(This appeal point was named IPPN 1a1 in initial correspondence and during the hearing).

72. Dr Jasmin Barman-Aksözen, for IPPN, emphasised the importance of patient testimonies for understanding the real world impact of rare and poorly understood conditions like EPP. She illustrated this with her own powerful personal testimony. She said that every patient treated with afamelanotide reports life-changing benefits.

73. James Rawnsley, for IPPN, also described very eloquently the devastating impact that EPP has had on his own life, and the dramatic benefits he experienced with treatment.

74. Emily MacKenzie, for IPPN, said that the committee themselves acknowledge that the existing measures of quality of life used in EPP (the DLQI and EPP-QOL) are unsatisfactory. Ms MacKenzie said that the committee also acknowledge in the FED that the trials are likely to have under-estimated the true clinical benefit of treatment. She argued that this means patient and physician testimony should have been given greater weight but this was not done. She expressed concern that the committee were "paying lip service" to acknowledging the importance of patient and expert testimony, whilst at the same time demonstrably preferring the trial data.

75. Ms MacKenzie referred to paragraph 41 of the HST process guide which requires the committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical experts. She argued that the committee had rejected evidence from patient and clinician testimony simply because these factors could not be quantified. She stated that it was inappropriate to use patient testimony only at the stage of judging whether the usual threshold for an ICER could be applied flexibly. Rather, patient testimony should have been given greater weight throughout the process as an alternative approach to one based on economic modelling.

76. Ms MacKenzie referred to paragraph 46 of the HST process guide regarding QALY weighting. She rejected the committee's conclusion that even accounting for the patients' and clinicians' testimony would be unlikely to result in an incremental QALY gain of at least 10, as being based on "woefully inadequate data".

77. Ms MacKenzie referred to paragraph 55 of the HST process guide, which concerns the circumstances in which the usual ICER threshold can be "flexed". She stated that in this case there is a strong reason to indicate that there are substantial uncaptured benefits. She argued that the committee have not shown evidence that they took this into account in making their final decision not to recommend treatment.

78. Dr Peter Jackson, for NICE, explained that the HST evaluation committee have substantial experience in evaluating treatments for rare diseases where because of small sample sizes it is indeed often more challenging to capture all the benefits of treatment with quantitative tools. He said that the HST evaluation committee must apply a rigorous approach to evaluating information from patient and clinician testimonies. This would include consideration of the range of responses, how respondents were elicited and any potential biases. In response to a question from the panel about whether the patient and clinician testimony was unusually compelling and uniform in this case, Dr Jackson replied that the HST evaluation committee very commonly sees a similar picture of very positive responses with technologies that come before them. When the committee looked at descriptions of EPP in the literature, they felt that while the testimony of the nominated patients and clinicians was very powerful, this might not be a complete picture. Dr Jackson said the committee have considerable experience of using a process of deliberative discussion to gauge patient testimony against that from other diseases, but acknowledged that the nature of this discussion can be hard to capture in a simple description.

79. Dr Jackson stated that whilst the committee recognised the limitations of the outcome measure used to assess quality of life for the economic model (the DLQI) they certainly did not accept it was so flawed that it could not be useful. The DLQI has been widely validated in other conditions. Scores on the DLQI correlate with both biochemical and clinical measures of the severity of EPP, and are sensitive to the impact of EPP on quality of life.

80. Asked by the panel what the committee thought were the most likely reasons for the apparent discrepancy between the trial results and the patient testimony, Dr Jackson gave a detailed response but concluded that they had not reached a satisfactory explanation. He said that the committee had therefore put these two pieces of information together as best they could in reaching a decision.

81. The panel asked about how the committee had incorporated patient and clinician testimony into their decision making. Dr Jackson said that they discussed each factor that had been raised (such as impact on occupational functioning) in detail. They had then considered to what extent this would allow them to "flex" the standard ICER threshold for HSTs (as set out in paragraph 55 of the HST process guide). In response to a question from the panel, Dr Jackson said that the ICERs were an order of magnitude away from the usual threshold. The committee had therefore concluded that, whilst the quantitative data was likely to have underestimated the benefit of treatment, it was not plausible that it had been underestimated to the extent that the treatment could plausibly be cost-effective.

82. The appeal panel concluded that there was evidence both from the FED and the committee's responses during the hearing that they had carefully considered the patient and clinician testimony. The panel judged that the committee had shown detailed consideration of the strengths and limitations of different sources of information as well as possible reasons for apparent discrepancies. The committee clearly stated the process they had used to incorporate patient and clinician testimonies into their final decision, and this process was judged by the panel to be reasonable.

83. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.2: The evidence provided shows that the benefit is significant and not small, as assessed by the committee**
(This appeal point was named IPPN 2.1 in initial correspondence and during the hearing).

84. This appeal point overlapped with BAD Appeal points 2.2 and 2.3 to the extent that it was difficult to disentangle separate issues. They were discussed together at the hearing and considered together by the panel (paragraphs 63-71).

85. The appeal panel therefore upheld the appeal on this point.

**Appeal point Ground 2.3: The evidence provided of the measured trial outcome shows that the treatment is highly effective**
(This appeal point was named IPPN 2.2 in initial correspondence and during the hearing).

86. Dr Jasmin Barman-Aksözen, for IPPN did not accept the perception that there was a discrepancy between the randomised trial results and patient testimony. Rather, she argued that the trial results concur with patient testimony in showing that afamelanotide is highly effective. She highlighted the points made by Dr Rhodes (paragraph 64) about how the absolute change in minutes of sunlight per day should be interpreted.

87. The appeal panel concluded as follows;

88. As described in paragraph 70 of this decision letter, the panel was persuaded by the specific arguments made by Professor Rhodes and Dr Barman-Aksözen (paragraphs 64 and 86). It is for this reason that the panel concluded that it was not reasonable for the committee to describe the magnitude of benefits seen in the trial as "small" and thus upheld appeal points BAD 2.2, BAD 2.3 and IPPN 2.2.

89. However, insofar as it differs at all from IPPN 2.2, this appeal point seems to go further in stating that the trial outcomes showed the treatment to be "highly effective".

90. It should be noted that it is not for the appeal panel to draw its own conclusions on the evidence presented, but only to comment on the reasonableness of the conclusions reached by the committee. From the totality of the evidence presented, the panel were confident that it was reasonable for the committee not to have described the trial evidence as showing that afamelanotide was "highly effective".

91. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.4: The evidence provided shows that quality of life before treatment is low and under treatment with afamelanotide increases dramatically and sustainably**
(This appeal point was named IPPN 2.3 in initial correspondence and during the hearing).

92. Dr Jasmin Barman-Aksözen, for IPPN, emphasised the data from the observational study by Biolcati et al (2015) which found improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first six months of treatment. Dr Barman-Aksözen expressed concern that these findings had not been given sufficient weight by the committee (or perhaps had been misinterpreted by the committee) because no further improvements were seen after six months (even though the improvements were sustained).

93. Dr Barman-Aksözen argued that the EPP-QOL was a more appropriate tool to measure quality of life in EPP than the DLQI because it is disease-specific and designed with input from patients and clinical experts. She said that the EPP-QOL is sensitive to treatment effects and can even detect differences in quality of life between summer and winter. She expressed concern that the DLQI fails to capture non-skin components of EPP such as fatigue and that it has not shown to be sensitive to treatment effects.

94. Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.

95. Dr Jackson explained that the committee had considered in detail the strengths and weaknesses of the two scales used to measure quality of life in the trials. Whilst they recognised the limitations of the DLQI in not capturing all the symptoms of EPP, they noted that DLQI has been widely validated in other conditions. Scores on the DLQI correlate with both biochemical and clinical measures of the severity of EPP, and are sensitive to the impact of EPP on quality of life. In addition, DLQI scores can be mapped onto the EQ5D to generate utility values. They recognised the strengths of EPP-QOL (it being disease-specific and having been developed with patient input) but felt that it was insufficiently validated as a measure of quality of life, and that the fact that pain was not included lacked face validity. Overall, the committee preferred DLQI for their economic model. However, they took account of the fact that the DLQI may not capture all the benefits of treatment in their decision making (see

paragraph 78 of the FED) and also considered exploratory models based on the EPP-QOL.

96. The appeal panel concluded as follows:

97. It was reasonable for the committee to put less weight on data from uncontrolled studies than randomised controlled trials. The lack of further improvement after 6 months in the Biolcati study was highlighted in the FED as evidence that most benefits can be seen within the time frame of the controlled trials rather than to imply that these data were not important. The conclusion drawn by the committee was that these data did not support the assertion that one reason for the apparently modest effect seen in the clinical trials may have been because it takes a considerable period of time for the learned behaviour of light avoidance to change. The concern expressed by IPPN in this regard (paragraph 92) may have been a simple misunderstanding of the wording of the FED by the IPPN.

98. The panel judged that the committee demonstrated (both in the FED and during the hearing) that they had considered in detail the relative strengths and weaknesses of the DLQI and EPP-QOL and that their decision to prefer the DLQI was not unreasonable. The panel noted that the committee had explicitly considered both results from the EPP-QOL and the limitations of the DLQI in their overall decision-making process. This process was therefore reasonable.

99. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.5: The committee failed to act fairly by denying a Managed Access Agreement (MAA) 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** (This appeal point was named IPPN 2.4 in initial correspondence and during the hearing).

100. Dr Jasmin Barman-Aksözen, for IPPN referred to the reasons given in the FED for an MAA not being pursued. She said she was not able to comment on cost, but that she disagreed with the conclusion in the FED that an MAA would be likely to suffer from the same problems as the trials and therefore fail to resolve uncertainty in the data. In particular, she argued that a longer duration of follow-up during an MAA compared to the randomised trials would allow patients to change their light-avoidance behaviour, helping to capture quality of life benefits. She referred to the PASS (post authorisation safety study) being conducted in Europe and pointed out that this is collecting efficacy data, the first year of which has just been accepted by the EMA for the purpose of extending approval of the product.

101. Dr Robert Sarkany, for BAD, said that they had the impression that the decision not to pursue an MAA had been made with undue haste, without adequate consideration and without BAD having a full opportunity to suggest how uncertainty in the existing evidence could be resolved.

102. Dr Peter Jackson, for NICE, said that because MAAs are burdensome to patients and costly to NHS England they are only recommended where they are likely to be helpful. He argued that there seemed to be agreement on the difficulty of capturing treatment response in EPP and there was no suggestion that an alternative tool was being developed that would allow this to be done better in an MAA than it had been in the trials. In response to a question from the panel, he said that he did not believe that any of the data being collected in the PASS study was likely to resolve the substantial uncertainty which the committee had identified.

103. Dr Jackson said that an even more important consideration was where the ICER was in relation to the threshold. The committee had to ask themselves whether it was possible that data from an MAA could reduce uncertainty sufficiently to bring the ICER to within an acceptable range. They considered the range of ICERs from all models as well as the degree of uncertainty around this and they concluded that this was not plausible.

104. Dr Jackson was asked by the panel whether the appellants were made aware of the nature of the uncertainty in the evidence base. He replied that the FED was clear that the fundamental uncertainty related to whether existing outcome measures are able to capture the full benefit of treatment.

105. Asked by the panel whether the committee engaged with appellants in any discussion about alternative ways of measuring outcome, Dr Jackson said that they had enquired of the company what future steps they were proposing to reduce uncertainty.

106. Sarah Love, for CLINUVEL, said that they had suggested that CLINUVEL and NICE could collaborate to develop a better outcome measure.

107. The appeal panel concluded that although an MAA was ultimately not felt by the committee to be a useful way forward, it was clear that this had been considered and discussed. The panel judged that the FED gave clear reasoning for the decision not to recommend an MAA. The panel thought that both the difficulty in resolving uncertainty and the very large distance between current ICERs and the threshold were reasonable considerations in reaching this decision.

108. The appeal panel therefore dismissed the appeal on this point.

**Appeal by British Porphyria Association**

**Appeal point Ground 2.1: There is a huge gulf between the results of clinical trials that are communicated by NICE as "small" and the benefits that patients in receipt of Afamelanotide repeatedly report as life changing … Despite this recognition, the FED recommendation has been made primarily on the grounds of the ERG economic analysis that was published before this information came to light, which we consider to be unreasonable.**

109. There was some overlap between this appeal point and IPPN appeal point 2.1. The additional comments made at the hearing specifically in relation to BPA 2.1 are set out here, but this should be read in conjunction with the discussion of IPPN 2.1 above.

110. Dr Geoff Sloan, for BPA, emphasised the discrepancy between the notion that the trial showed small benefits and his own experience of the drug as life-changing.

111. Asked by the panel to clarify which information they felt had come too late in the process, John Chamberlayne said that this referred to the patient and clinician testimonies being heard after the ERG economic model was produced.

112. Dr Peter Jackson, for NICE, said that the committee had listened with great care to input from patients and were indeed impressed by their testimony. Dr Jackson explained in detail the committee's view on the strengths and limitations of both the economic modelling and patient/clinician testimony, and how both of these factors were incorporated into this decision making process. This is described in full in paragraphs 78-81 of this letter.

113. The appeal panel concluded that there was evidence both from the FED and the committee's responses during the hearing that they had carefully considered the patient and clinician testimony. The panel judged that the committee had shown detailed consideration of the strengths and limitations of the trial data and information from patients as well as possible reasons for the apparent discrepancy between these. The committee clearly stated the process they had used to incorporate patient and clinician testimonies into their final decision, and this process was judged by the panel to be reasonable.

114. The appeal panel therefore dismissed the appeal on this point.

**Appeal point Ground 2.2: The economic decision has been made using a flawed model that means the decision is unreasonable in light of the evidence submitted to NICE.**

115. There was some overlap between this appeal point and IPPN appeal points 2.1 and 2.4. The additional points made at the hearing specifically in relation to BPA 2.2 are set out here, but this should be read in conjunction with the discussion of IPPN 2.1 and 2.4 above.

116. John Chamberlayne, for BPA, stated that the economic model had been developed without any input from stakeholders. He argued that the flaws in the model were such that its conclusions could not be considered reliable.

117. Dr Peter Jackson, for NICE, acknowledged that the sensitivity of the DLQI to capturing benefit was a limitation of the model used. However, the alternative model using the EPP-QOL used an indirect method to determine cost effectiveness. The committee had carefully considered different approaches before choosing their preferred model.

118. Mr Francis Pang, for NICE, further described the limitations of the company's proposed model (which used DALYs in place of QALYs and relied on proxies for developing disability weight) but explained that nevertheless this was given due consideration.

119. The appeal panel concluded that the committee had shown careful consideration of the limitations of the economic modelling performed. The appeal panel judged that the limitations of the preferred model were not so severe as to make it unreasonable to use it in decision making. The panel noted that the committee had made efforts to take account of these limitations and incorporate other sources of evidence into their final decision.

120. The appeal panel therefore dismissed the appeal on this point.

**Conclusion and effect of the appeal panel's decision**

121. The appeal panel therefore upholds the appeal on the grounds IPPN 1a.1, CLINUVEL 1b.1, IPPN 1b.1, BAD 2.2, BAD 2.3, IPPN 2.2. The appeal is dismissed on all other grounds.

122. The evaluation is remitted to the evaluation committee who must now take all reasonable steps to address the following issues:

    i) The failure to include an IPPN representative at the second committee meeting (IPPN 1a.1).

    ii) The failure to demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act (CLINUVEL 1b.1 and IPPN 1b.1). The appeal panel considers that this is likely to include express consideration of whether the methodology used in the evaluation discriminates against patients with EPP and if so what reasonable adjustments should be made.

    iii) The appeal panel's conclusion that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide (BAD 2.2 and 2.3, IPPN 2.2).

123. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.

**PRIVILEGED & CONFIDENTIAL**

Dr Peter Jackson
Chairman, Highly Specialised Technologies Committee
National Institute of Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT
Sent via HST@nice.org.uk

CC: Marie Manley, Sidley Austin LLP (mmanley@sidley.com)
Martin Chamberlain QC, Brick Court Chambers (martin.chamberlain@brickcourt.co.uk)
Sarah Love, Brick Court Chambers (sarah.love@brickcourt.co.uk)
Stan McLiesh, CLINUVEL Group (Stan.McLiesh@clinuvel.com)

21 January 2019

**Re: HST 2nd Appraisal following the decision by the NICE Appeal Panel following the hearing of 30 July 2018 – SCENESSE® (afamelanotide 16mg) for the treatment of EPP**

Dear Dr Jackson,

We note that NICE has not responded to all our queries addressed in the letter of 06 November 2018.

In reply to the correspondence received from the National Institute of Health and Care Excellence on 29 October 2018, CLINUVEL kindly adds the following considerations to the previous submissions made to the Highly Specialised Technologies (HST) Committee from 08 March 2016 to 23 April 2018, during the process leading up to the 30 July Appeal Panel hearing, and in various other correspondence to date.

**BACKGROUND MARKETING AUTHORISATION SCENESSE®**

In October 2014 the European Medicines Agency (EMA) explicitly ruled in favour of SCENESSE® (afamelanotide 16mg) as an innovative photoprotective therapy, a controlled-release hormonal therapy in erythropoietic protoporphyria (EPP), a disease which had not been well characterised by medical experts in literature and text books to that point and for which there had not been an available and effective treatment.

Under EC 726/2004 Article 14(8), the Committee for Medicinal Products for Human Use (CHMP) of the EMA stated that under the current state of science no instruments existed to adequately quantify the impact of EPP treatment and the nature of the disorder (orphan) prohibited further exposure of patients in breach of medical ethics, and SCENESSE® was granted approval under *exceptional circumstances*. Further to the marketing authorisation, the EMA (Pharmacovigilance Risk Assessment Committee; PRAC) and CLINUVEL set out to develop a Post-Authorisation Safety Study (PASS), a non-interventional study to follow up patients for a minimum of eight years. In the deliberations of the EMA, a limited number of eligible adult EPP patients in the European Union would receive drug treatment.

**HST APPRAISAL TO DATE**

On 08 March 2016 CLINUVEL submitted to the HST Committee its estimated EPP patient numbers in England. The numbers communicated to the HST were based on a prevalence of 1:140,000 and CLINUVEL's deep knowledge about the EPP community. CLINUVEL communicated a maximum number of 513 EPP patients in England.

On 13 October 2016 it was communicated to CLINUVEL that the HST Committee rejected this number on the basis of an internal assessment of 1,300 patients and therefore rejected CLINUVEL's application for HST assessment, referring SCENESSE® back to a Single Technology Appraisal (STA). After incessant correspondence by CLINUVEL, the HST admitted some five months later that its own assessment of the patient population had been erroneous, despite having in hand the evidence on available patient population in the UK as well as references to the prevalence of disease. The mistake of the HST Committee and its reluctance to respond earlier caused a delay of 16 months prior to the Committee referring the subject back for HST assessment, without further apologies or rectification, but a mere admission that an error had been made.

The Committee eventually referred the subject matter back to a pathway leading to the HST appraisal process, restarting this process from the beginning under a new guidance document and review methodology.

In the correspondence, and as presented during the scoping meeting on 08 March 2016, CLINUVEL clarified that a number of factors would provide ample evidence and assurance for a limited prescription and distribution of SCENESSE® exclusively to specialised university hospitals in the UK, these are:

(i) the burden of clinical compliance with the PASS protocol;

(ii) mandatory enrolment of EPP patients in the European EPP Diseases Registry (EEDR);

(iii) limited number of prescribers available;

(iv) Real World Experience from other European countries; and

(v) previous experience from compassionate use and Special Access Programs.

**MANAGED ACCESS AGREEMENT AND FINANCIAL RISK**

On 12 July 2017 NICE Director Mr Boysen stated on the one hand that leeway could be applied to the appraisal of SCENESSE®, yet, on the other hand – knowing that the quality of life tools and other scientific instruments were not applicable and appropriate to assess the economic benefit of the treatment of SCENESSE® – insisted that CLINUVEL was to submit a QALY model before the HST could engage in a dialogue with CLINUVEL.

On 12 September 2017 NICE submitted financial data on a Budget Impact Test to CLINUVEL. NICE concluded that CLINUVEL was exceeding the budget(s) in some scenarios and therefore would not be meeting the test, despite CLINUVEL's clear and unambiguous data showing that SCENESSE® was not exceeding the threshold of £20 million per annum.

On 06 November 2017, CLINUVEL responded to the Budget Impact Test with modelling demonstrating SCENESSE® would not exceed the £20m threshold in the UK.

On 23 November 2017 in the first HST Committee Meeting in Manchester, NICE suggested in a public meeting that a Managed Access Agreement between all relevant stakeholders (particularly CLINUVEL and the National Health System England), whereby financial risk to the NHS would need to be mitigated or addressed, may be appropriate for this HST appraisal.

In summary of all facts provided and deliberations by CLINUVEL, the financial risk of adopting SCENESSE® by the NHS England is zero for the following reasons:

(i) CLINUVEL has provided an accurate and detailed breakdown of distribution year on year, projected for five years. Since the Company is intimately familiar with logistics and distribution to the European EPP medical community, and therefore knows the national numbers of eligible adult patients per country, it is confident it can reach a financial agreement with NHS England on treatable patients per

annum per centre, without the risk of exceeding budgets or renouncing a commercial agreement made.

(ii) CLINUVEL has projected accurate number of patients treated and product distributed in eight other European countries without exceeding agreed budgets, and in all instances the Company has remained well under the volume threshold agreed during the past three years.

(iii) CLINUVEL is willing to set and agree strict rules on the use of the product and, as reported in the EEDR, is able to provide feedback on effectiveness of the product from rate of discontinuation annually. A financial agreement can be reached in the event of reported lack of effectiveness or discontinuation due to lack of effectiveness (see below for Managed Access Agreement).

(iv) CLINUVEL is willing to evaluate new scientific instruments to be implemented over time to assess the clinical effectiveness of the therapy other than from clinical feedback by expert centres and patients, and from a validated questionnaire, an Inventory of Daily Activities. A validated questionnaire – agreed by expert physicians and patient organisations – is the only measure to quantify how the lives of patients are facilitated by the treatment.

(v) CLINUVEL is willing to evaluate the use of SCENESSE® bi-annually and provide NHS England with access to data on conditions of use and registered directly in the EEDR by the expert centres in England.

**CLINUVEL'S APPROACH TO COMMERCIAL DISTRIBUTION OF SCENESSE®**

From all discussions held with the HST Committee, and from the considerations by the Appeal Panel convened on 30 July 2018, it is sufficiently apparent to all attendees and consultees that SCENESSE® constitutes an exception to other therapies and is therefore a unique case in its health economic assessment.

The Company has approached the product distribution in a transparent manner which differs from the commercial attitude of most peer pharmaceutical companies.

First, in order to allow drug distribution to occur without bias or the Company's intervention, both the clinical demand and willingness to prescribe SCENESSE® dictate the rate of continuation on treatment in all European countries. While it is usual to promote or market pharmaceutical products in the sector, in order to be able to gauge the genuine rate of prescription the Company does not institute a sales force or commercial campaigns. The demand for the drug occurs on an "as is" basis following the clinical assessment by a handful of university centres, and patients themselves, following each treatment. Therefore, the rate of continuation year on year provides an accurate indication of effectiveness, since EPP patients need to seek cyclical treatment every two months. The clinical visits require patients to travel during the night and, in many instances, sleep in the proximity of hospitals at their own expense. EPP patients often take one day off work, forgoing their earnings to be able to receive the implant injection every 60 days. The motivation to continue treatment has proven very high among the treated patients in European countries as seen from real world experience and data. The rate of continuation – as listed in the Company's obligatory Annual Report to the EMA – was 98.5% in 2018 compared to 2017. At the time of print the rate of continuation is 94.5% for those patients seeking treatment at the beginning of 2019.

Second, the Company has been determined to mitigate and annihilate the possibility of off-label use, and self-distributes the product to each European hospital. The product requires special handling through cold-transport at 2-8 degrees. The controlled-distribution precludes off-label use of the product. During three years of past distribution, only one instance of off-label use was permitted to a moribund Congenital Erythropoietic Porphyria (CEP) patient who requested to enjoy one last summer seeking light exposure before giving in to his disease. MHRA permission was obtained to treat through an unlicensed medicines program. There have not been any other cases of off-label indication use in any European country.

Third, through the PASS protocol supervised and controlled by the EMA (PRAC) a non-interventional study is conducted whereby only trained and accredited expert centres, a limited number of university centres throughout the European Union, are allowed to treat EPP patients in a multi-disciplinary team.

Fourth, the use of a European EPP Disease Registry (EEDR) allows for direct control on clinical use of the product, whereby the EMA imposed risk minimisation measures, such as the prevention of off-label use.

**CLINUVEL'S FINAL PROPOSAL 2019**

Following the hearing on 30 July 2018, the Appeal Panel upheld appeals on the grounds IPPN 1a.1, CLINUVEL 1b.1, IPPN 1b.1, BAD 2.2, BAD 2.3, IPPN 2.2. The Appeal Panel determined that the appraisal should be remitted to the appraisal committee who must take all reasonable steps in the decision letter.

Following its investigation, the Appeal Panel ruled that the HST Committee had failed to properly and justly interpret the magnitude of beneficial effects of the pharmaceutical treatment of SCENESSE®. CLINUVEL is willing to

(i) enter a binding Managed Access Agreement with NHS England on the basis of the agreements made – as laid down above in points (i) to (v) – and on the basis of the similar equitable financial conditions agreed with each other European country,

(ii) agree with NHS England the European pricing of SCENESSE® - £12,020 net per injection – to be fixed for 24 months with no further rebates discounts or cashbacks.

(iii) agree on a structured plan to treat EPP patients on the basis of a total of 513 patients in England based on disease prevalence, and most likely 400 eligible adult EPP patients.

(iv) evaluate together with NHS England on a bi-annual basis the EEDR data generated by English patients and distribution data of the product (longitudinal assessment).

(v) enter a volume agreement with NHS England based on the known centres of expertise willing to prescribe the drug in England (currently only two centres), and adhere to a roll-out plan, whereby minimum and maximum volume of drug units can be determined per annum; at a maximum capacity of 50 patients per annum per expert centre; the first year would lead to a maximum of 100 EPP patients to be treated.

(vi) adhere to the patient and treatment projections provided in the Budget Impact Test (see BIT attached, Addendum 1 - Table 1).

(vii) develop a new scientific instrument to be validated in time to assess the patients' ability to overcome their disability and participate in normal life following the treatment ('Inventory of Daily Activities').

(viii) agree stop-start criteria with NHS, expert centres and patients concerning the treatment.

(ix) agree limited resource use under the NHS by reimbursing expert centres for the additional administrative hours expended per patient on the adherence to the PASS protocol, conform and congruent with the agreements made with other European expert centres.

With this far-reaching Managed Access Agreement for SCENESSE®, zero financial risk would be incurred by NHS England while maximum transparency is provided by CLINUVEL. At this juncture, CLINUVEL has made all rational and reasonable attempts to propose and reach an agreement with NICE and NHS England, while an

excessive amount of time has been unnecessarily lost to provide treatment to a limited group of patients who currently have no alternative therapy.

The CLINUVEL proposal has addressed all financial concerns communicated in the FED on 29 March 2018 and addresses the comments made during the Appeal Panel on 30 July 2018.

Following the Appeal Panel's decision, CLINUVEL now has a legitimate expectation that the HST Committee will adopt a different methodology in the appraisal of SCENESSE®, while we are confident that our proposal for a comprehensive Managed Access Agreement has fulfilled all criteria in reducing the financial risk to NHS England by making the drug available to EPP patients, albeit four and half years after receiving European marketing authorisation.

Please contact us so that we may assist the Committee in the fair resolution of any outstanding issues.

We look forward hearing from you at your earliest, in the meantime, CLINUVEL reserves all of its rights.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

Appended: SCENESSE® Budget Impact Assessment England, October 2017

British Porphyria Association

136 Devonshire Rd
Durham City
County Durham
DH1 2BL
Charity No: 1089609
www.porphyria.org.uk
0300 30 200 30

17 January 2019

We, the British Porphyria Association (BPA), are writing to present additional information for your reconsideration of whether afamelanotide should be approved for use in the NHS, following on from the report of the appeal panel.

Many issues were raised during the appeal procedure that require reiteration here as they were not emphasised in the original evaluation. **That several points of appeal were upheld also reinforces our belief that the way the HST process has been applied to the evaluation of afamelanotide has not correctly reflected either the impact of EPP on patient lives or the efficacy of the treatment.**

The following paragraphs summarise the most significant new learning points with regard to three categories of particular interest.

- Nature of the condition
- Clinical effectiveness
- Impact of the technology beyond direct health benefits

**Nature of the condition**

Disappointingly, and despite all of the evidence previously submitted to NICE, at the appeal hearing, Dr Jackson demonstrated a persisting lack of knowledge about the nature of the condition when he explained that the committee did not consider EPP to be a disability because of the absence of visible symptoms (Appeal Hearing report, para 51). Although later highlighted by the appeal panel to clearly meet the definition of disability, the fact that EPP was mentioned in this way at this late stage of investigation demonstrates a clear dismissal or lack of understanding of the severity and reach of the condition.

Throughout the process and in medical circles the lack of visible manifestation for most of the year is what makes EPP so difficult to diagnose. Patients note that the level of severe pain is entirely disproportionate to the physically visible symptoms.

> *Swelling can be similar to a bad sprain, however having suffered from bad sprains and ligament damage, as well as breakages and trauma associated with taking a 60m uncontrolled fall, during which I was knocked unconscious, I can categorically state that the pain of EPP is way beyond and longer lasting than pain that might be associated with trauma. Having experienced the pain, I can only conclude that it might even be akin to that associated with cancers. Invisible yet extreme. There is no wonder why many patients express that they have experienced suicidal thoughts.* [EPP patient]

These aspects of severe and persistent pain were only gradually recognised by NICE through the meetings and it is unfortunate that even at the later stages in the process, the compelling qualitative evidence of patient and clinician testimony is still not being used to its full potential.

Throughout this lengthy process the understanding of EPP has continued to develop, as more patients have voiced aspects that affect them. This is another key reason why patient testimony is so important. Trial participants (likely to be those who see doctors on a regular basis) only make up one category of patients, people who seek and obtain care (rather than the hidden denominator of those that do not seek or cannot access care). It does not take account of those who have given up on or lost contact with doctors due to a lack of medical options for them, or a lack of faith in their ability to help, or even perceived lack of interest from doctors.

Pain and the impact on the mind and body is a key driver in the behaviour of EPP patients (including avoidance tactics). The physiological impact of this pain, along with the chemical effect on haem production, is also key to the extreme impact of fatigue which affects the capability to perform professionally, physically and socially in the days that follow an episode of exposure. We contend that the impact of fatigue (FED 4.1) is not fully reflected in either the EPP-QoL or the model adopted by the ERG.

**Clinical effectiveness**

In initial submissions and, more significantly, throughout the consultation process, it became clear that there is a huge gulf between the results of clinical trials that were communicated by NICE as being “small” (FED p1; 4.7), and the benefits that patients in receipt of Afamelanotide repeatedly report as life changing. This is iterated in (4.9) as reported by a UK patient, but perhaps more significantly by numerous European patients.

The appeal panel acknowledged that the results of the clinical trial were not small [Appeal Hearing, para 71]. In the appeal, Prof Rhodes quoted data that showed that healthy indoor workers spend an average of 22 minutes in the sun between 10am and 3pm [Appeal Hearing, para 64]. She stated that the average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). She argued that this increase thus puts patients with EPP who are on treatment into the normal range for this measure.

She also pointed out that the figure of approximately 10 minutes extra per day of sun exposure represents an average daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest.

Even in the committee’s recognition that 10 minutes extra in the sun is not small, the way the committee and even medical experts present this is still focused on the behavioural change rather than the benefits. We highlight that it is important to consider more deeply ***what it means to patients*** to spend even just 10 minutes more a day in the sun. Why are patients able to make this change? It is because of the diminution of phototoxic reaction and the associated lack of extreme pain, as well as a decreased impact on haem formation. Not only does this permit more 'normal' behaviour, it does so because the lengthy and painful consequences of spending time in the sun are reduced to the point where prolonged exposure can be tolerated without extreme consequence.

**Impact of the technology beyond direct health benefits**

The extended impact on quality of life for family members of those with EPP appears to still be largely disregarded from the appraisal – evidence relating to the far-reaching effects that trying to

protect a family member from the danger of a phototoxic reaction can have, should be taken into account. Please see the moving family testimonies provided in the Appendix, and in earlier documentation [Committee Meeting 1 papers, p264 - 265].

Having considered the FED and comments made by NICE at the recent appeal, the testimony and measurement of impact on the patients' wider life and that of their families remains largely unconsidered. We find no clear evidence of such impacts being incorporated into the ERG and no documented evidence or record of methodology applied by NICE in considering such impacts in the FED.

Afamelanotide can increase the time that an EPP patient can spend outdoors, making the time of exposure similar to other people, which can substantially decrease (maybe even eliminate) the adverse effect on family members and carers. This gives highly beneficial impacts on a family household, not only socially, but educationally, financially and psychologically too, thus increasing their quality of life. To reinforce the wider social impact of EPP and the opportunities that arise from a treatment that can help normalise the behaviour that has become ever more apparent during committee and appeal meetings, we re-append two of the testimonies included on p264 and 265 of the Committee 1 papers and request that NICE act to understand more fully the testimonies presented in subsequent papers and at the appeal.

**Emerging Evidence**

With regard to new evidence, we are aware of the pending submission to the BMJ of a longitudinal study in the clinical efficacy and long-term safety of afamelanotide[1]. The ongoing study has revealed data that addresses a particular issue of concern raised by the committee. The concern raised by the committee was that the uniformly compelling and powerful patient testimonies, 'might not be a complete picture' [Appeal Hearing report, para 78] indicating that only the positive responses might have been selected.

A BPA committee member recently attended the EPNET[2] General Assembly in Rotterdam, where they observed a presentation by Debby Wensink (Erasmus MC, Netherlands), based on data taken from the EMA Post Authorisation Safety Study (PASS) submitted to the EMA annually. **This data showed 98.3% adherence rates** (see Appendix 3). Furthermore, those who decided not to continue with treatment, did so for reasons such as pregnancy or financial constraints of travelling to obtain the drug. This is a very compelling statistic that demonstrates high levels of treatment satisfaction and quantitatively supports the overwhelming benefit already shown by the qualitative patient testimony. This provides support for the fact that the patient testimonies do provide a complete picture.

The weight of these emerging themes; the consistency of patient testimony; the stark contrast between testimony of patients on the treatment and those not on the treatment; are all clear

[1] Expected authors: Debby Wensink, Margreet Wagenmakers, Edith Friesema and Janneke Langendonk. Porphyria Center Rotterdam, Center for Lysosomal and Metabolic Disease, Erasmus MC, Rotterdam, The Netherlands.

[2] EPNET: European Porphyria Network www.porphyria.eu. EPNET consists of 33 EU specialist centres from 21 European and candidate countries that work together to develop an up-to-date consensus-based approach to the management of patients and families with porphyria.

indicators that the impact of EPP on quality of life has not yet been fully incorporated into either the decision, or the models that underpin it.

**Additional points**

We also bring to your attention to the additional points, which seem not to have been factored into the decision.

Overall, patient testimony should carry much greater weight in a structured and measurable way. There is no demonstrable measure recorded or documented that details the extent to which NICE applied patient testimony. Simply 'discussing each factor' [Appeal Hearing report, para 81] feels like an abstract measure with no detailed record and no scientific basis applied.

In particular, it is vital to consider the patient testimonies of international patients, as there is difficulty in obtaining such patient data in the UK. British patients are largely without experience in the benefits of afamelanotide as very few were involved in the trials or know of people on the treatment. Hence, testimonies received from European patients fortunate enough to be able to access the treatment, especially over extended periods of time, have been imperative to obtain such data [Appeal Hearing, para 19]. This point was highlighted by the patient expert at the February committee meeting. Yet this highly relevant and important point, regarding the difference in experience between UK patients and their European peers, was omitted from the FED.

The patient expert also highlighted that testimony provided by European patients not receiving Afamelanotide, or prior to receiving Afamelanotide, is extremely consistent to that of UK patients in relation to how severely EPP impacts upon their life and the quality of life of those around them. Again, this highly valid point appears not to have been reflected in the FED.

**Information submitted to the appeal**

During a committee meeting last year, the patient experts were asked whether or not they would be willing to receive afamelanotide and participate in further studies to evaluate its efficacy. The patient experts responded positively, but given the impromptu nature of the question, did not feel entirely empowered to respond on behalf of all UK EPP patients. To reinforce those individual patient expert answers, and demonstrate the gravity of the impact that a decision not to approve afamelanotide (or consider an MAA) is likely to have on our members, we include some results of a 2018 survey (Appendix 2): 93% of the 100 people surveyed would want to try Scenesse and a further 6% would consider using Scenesse. Given the responses to previous questions this gives a clear indication that there is almost ubiquitous demand for a treatment that reduces the severe impact EPP has on their life. Responses were limited to one per IP address to help prevent duplication and distortion of data.

The survey data (Q4) also demonstrates, in a visual manner, the severe impact that EPP patients feel the condition has on their quality of life in four areas: family life, engaging with friends, work/study and finance, with three out of four categories measuring 8 or more on a scale where 0 is not affected at all and 10 is severely affected.

Additional patient information is also submitted from the patient organisation in the Netherlands[3]. This was referred to in the very first BPA submission and discussed in the ERG report [p122], however was never submitted for the committee's attention. Please now find this attached in Appendix 4.

**Summary**

We believe the points that were upheld at appeal and the weight of emerging evidence indicate that the economic decision was made using a flawed model that means the decision is unreasonable in light of the evidence submitted to NICE.

Indeed, NICE themselves recognise (FED p.1) that "The true benefit of afamelanotide has, however, not been quantified." Despite this recognition, the FED recommendation has been made primarily on the grounds of the ERG economic analysis that was published before this information came to light, which we consider to be unreasonable.

The FED (throughout) indicates that the strength and validity of the argument for improved measures increased as the consultation proceeded. Despite this, the ERG model remains NICE's preferred basis for assessing value for money; a model that has not been updated in light of the evidence submitted during the consultation process; a model that the committee itself recognises as highly uncertain (FED 4.23) "[the committee] concluded that the ERG's exploratory results were also highly uncertain because the benefits of Afamelanotide may not have been fully captured by the DLQI measured in the clinical trials."

Whilst we acknowledge that the committee made some attempt to extrapolate data, we find no documented evidence of this extrapolation or the methodology applied in determining how such calculations were made. Surely such evidence should be front and centre when making economic decisions on people's lives. The BPA contends that an economic decision made on the basis of a highly flawed model is at best unreasonable, definitely inaccurate, and can even be considered as unscientific in light of the evidence submitted during the consultation process. It is therefore logical to conclude that the recommendation is not truly objective.

**MAA**

NICE have stated during this process that testimony from UK patients is preferred, yet recognised that the rare nature of the condition combined with the design of studies means UK patient experience of afamelanotide is extremely limited in comparison to patients on the continent. Throughout the process the BPA has been supportive of the use of an MAA. We have offered to support such a process, to provide patient input into its design. Although we recognise that an MAA is dependent on agreements between Clinuvel and NICE, points raised at appeal raised significant concern as to how serious NICE have been in pursuing such an option, despite the willingness of Clinuvel, clinical experts, patient experts and ourselves to engage. We would like to see the option of an MAA explored further, and we would be very happy to provide patient support in formulating an MAA if this emerges as a suitable way forward.

[3] Jeroen Verheul (2013): *A Life with EPP*. Investigation by the Dutch patient organisation for EPP. Translated and submitted for the EMA approval process.

**Appendix 1: Family testimonies**

**This testimony is from the wife of someone with EPP**

When your children beg you, “Mummy, why can’t daddy come too???”, The story of our life is summed up in one innocent question.

The massive impact the above statement has on family life is un-measureable. Our family unit is strong because we work relentlessly together to overcome the disadvantages that my husband and father to my two children is subject to being an EPP sufferer.

Despite experimenting with lots of creams, clothing, getting out in the light to try and build some sort of resistance, however little, he has still to find anything that can prevent the severe pain and tiredness he frequently has to give in to.

**Advantages of receiving treatment**

**Physical health:** Treatment will allow my husband to vastly improve his ability to participate in outdoors sporting activities that will help getting and keeping him fit, simply having the opportunity to get out for a run or on a bike or even walking the dog. He has never been able to take part in team sports due to the unreliability of him being able to venture outdoors. This, I believe has a very negative psychological effect on him especially as our children are involved in team sports. He regularly cannot support his children at their sports matches and competitions if he is required to be outdoors, these are for our family; cricket, rugby, tennis and lacrosse.

When our garden needs attention, an outdoor physical activity, my husband would be able to do the simple chores such as mowing the lawn and trimming the shrubs at any chosen time of day rather than in the dusk in the late evening. We often have to hire a gardener to complete these jobs.

**Emotional Wellbeing:** Being the wife of a EPP sufferer has been challenging over the years with regard to the level of inclusion that my husband can be involved in family activities. The children and I have to make compromises and difficult choices that often leave my husband feeling guilty, depressed and sometimes suicidal. Being unable to plan ahead and accept invitations to events with friends and family have definitely had a negative impact. Often just the necessity to have to drive to a gathering place or venue can result in frayed tempers and a stressful atmosphere due to the unpredictable and unpreventable physical and psychological effects that my husband will experience.

**Everyday Life:** Of course, he gets into situations where he gets a hit from exposure to sunlight, this is the consequence of trying to battle against the condition he suffers from, to enable him to maintain some form of normality and social acceptance. However, the whole family then feels the effects as well as my husband. We don’t experience his physical pain but can see the physical effects with the skin swellings and his inability to do anything but lie quietly in a darkened room away from the family. Although we certainly share the emotional devastation of his social isolation, feeling responsible for making him ‘come out to play’ and also have to make contingency plans until the time that my husband can once again be well enough to be involved in day to day family life, going to work and meeting his social commitments.

For years we have been forced to take separate holidays, my husband takes his holiday away from his family in the winter season whilst the children and I love to visit sunny Mediterranean climates or go camping on the coast around Britain. Imagine not having those holiday memories to share together, this is a cause of sadness and anxiety for all of the family. Given the chance to have this

treatment would be life-changing for my husband; giving us as a family simple day to day choices that are currently non-existent with his EPP. He may have missed out on much of his children's early years but with the treatment would be able to make a massive difference to their futures.

**What EPP does to Dad. How does it affect me?**

When we are in the garden on a warm, sunny day, dad sometimes feels pain on parts of his body that are exposed to the sun. Then he can't really play with me on the trampoline, in the paddling pool or just in the sun on the grass with a ball. He regularly gets frustrated and takes out his anger on me and mummy but he doesn't mean to. On holiday, when we go somewhere like Greece daddy has to stay at home so he can't come into the pool to play with me or on the beach and in the sea. He loves to go cycling, but has to go early in the morning and ends up in pain so he can't play with me. But it is hard for him in the strong sun and he can swell very easily which leads to me feeling quite lonely on the beach as my mum normally only sun bathes. Then he feels angry with himself and that makes me feel guilty and that it's my fault he has the condition. If he was my only parent, I wouldn't be able to cope very well as I love water and the sun and heat. When I was smaller I didn't understand why daddy couldn't come and play with me and I felt sad when he would not come.

When my friend Charlie and his family go on holiday or a day trip somewhere, they're going to mostly very outdoorsy and sunny places and we regularly try and go with them. They all have so much fun out and about, but although we go outdoors a lot of the time we still have to make sure dad is safe. Daddy is a little bit different to mum, Charlie's mum and dad Jane and Ed and other families as he tries to do as much as he can with me but also has to look after himself.

If my daddy was given a treatment and did not have to worry about EPP any more, my life would be paradise and every day I would treasure each moment carefully. He would be able to do things normally with me such as:

- camping
- go to beaches and lots of different countries
- help me more with my tennis, swimming and other sports
- regular every day outdoors jobs
- go on the trampoline
- go to visit my brother who is living in Australia
- playing on the lawn
- go on boats
- go to exotic places
- HAVE FUN
- Go in the paddling pool
- Come out on bike rides with me and mummy
- And everything else!!!!!

## Appendix 2: BPA Patient Survey May 2018

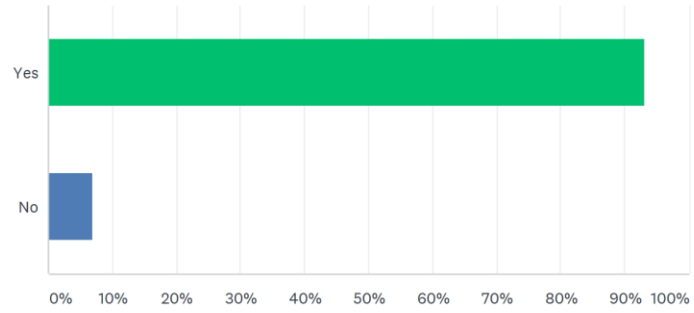
Results from a short SurveyMonkey survey carried out via BPA members in May/June 2018.

Q1

Customize Save As

Do you have a confirmed diagnosis of Erythropoietic Protoporphyria (EPP or XLEPP)?

Answered: 100 Skipped: 20




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Yes | 93.00% | 93 |
| No | 7.00% | 7 |
| TOTAL | | 100 |

Q2

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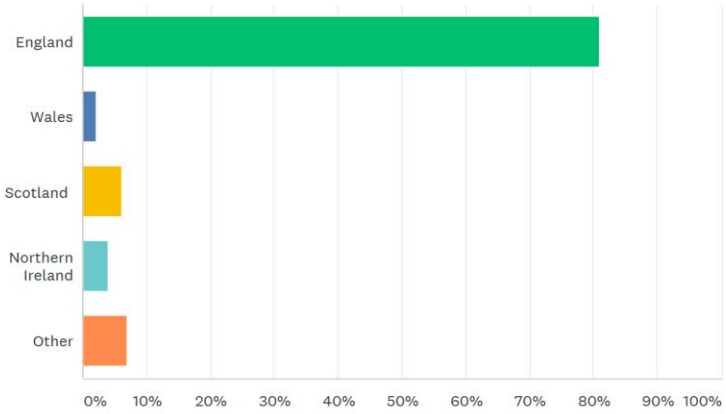
Where do you live?

Answered: 100 Skipped: 20




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| England | 81.00% | 81 |
| Wales | 2.00% | 2 |
| Scotland | 6.00% | 6 |
| Northern Ireland | 4.00% | 4 |
| Other | 7.00% | 7 |
| TOTAL | | 100 |

Q3

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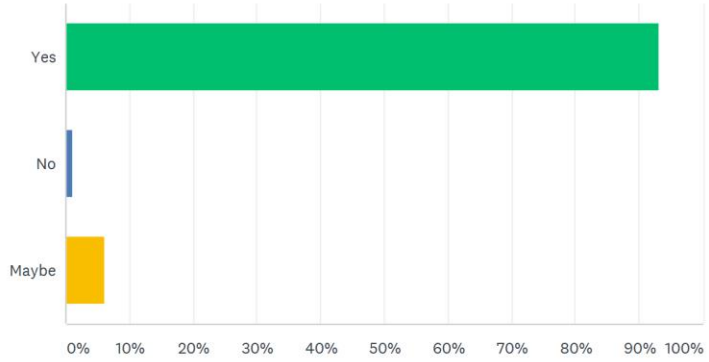
## If Scenesse were to be approved for use on the NHS in the UK, would you try it to see if it worked for you?

Answered: 100 Skipped: 20



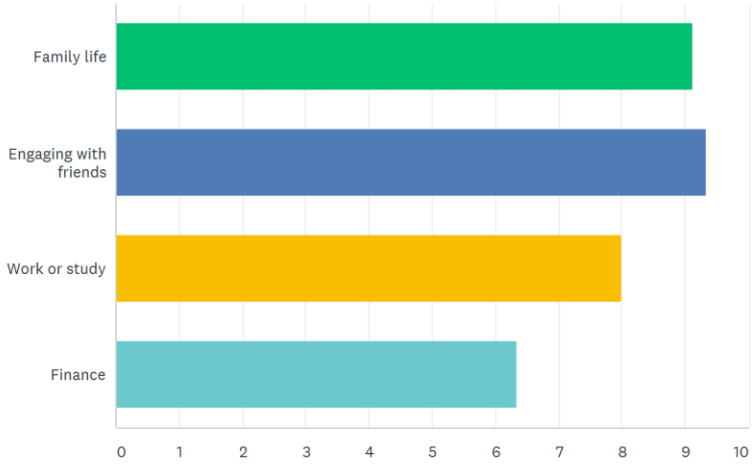

| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Yes | 93.00% | 93 |
| No | 1.00% | 1 |
| Maybe | 6.00% | 6 |
| TOTAL | | 100 |

Q4

Customize Save As

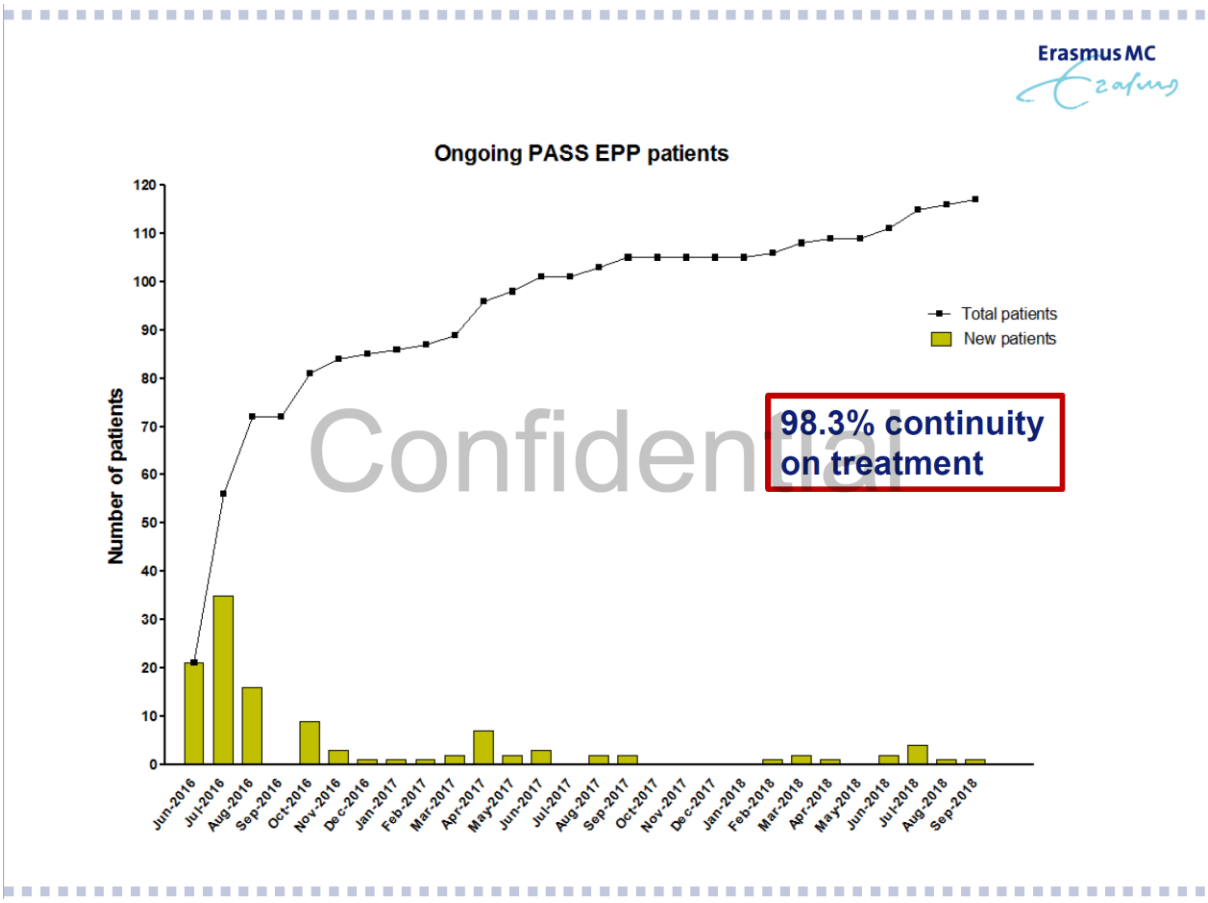
## On a scale of 0 to 10 (where 0 is not affected at all and 10 is extremely affected), how does EPP affect your life in the following categories?

Answered: 99 Skipped: 21



**Appendix 3: Continuity rate of patients being treated with Afamelanotide in the Netherlands**

Statistics kindly provided by Janneke Langendonk and Debby Wensink from Erasmus MC, Netherlands



**Appendix 4: Jeroen Verheul (2013): *A Life with EPP***. Investigation by the Dutch patient organisation for EPP. Translated and submitted for the EMA approval process.

*A group of about 40 patients worked on this paper about EPP. Only their closest relatives and friends know how their lives are influenced by EPP. They felt a great urge to participate in this project and explain their life (A life with EPP) and work (A job with EPP)*

# A life with EPP

## Introduction

It is not possible to simply summarise what EPP means to the 'sufferers' of this condition. Since daylight is present in large quantities at for example the office (due to extended windows) and in public transport, most patients only feel safe in the 'comfort' of their own house. Due to strict regulations for foil in vehicles, that form of protection has partially disappeared too. It is often necessary to apply protective foil to windows, even in homes. Patients suffer from a withdrawn existence mainly out of necessity because they have challenged their limitations with hurtful experiences during their youth. At the same time patients know they have to extend their boundaries to have a normal existence.

The patients suffer worst from April until August when the radiation is at its highest but also when the sun is out longest. Patients are virtually continuously dealing with their limitations and are always trying to plan their days in a way that they are not in danger of exposure. From November to February patients have the best time but still they avoid outdoor activities like ice skating or winter sports holiday.

The physical complaints are sharp pains and can be characterized as the pain one has from stinging nettles with a hairdryer blowing hot air onto it. The pain and burden build up in the course of time and restrain longer and longer. True recovery can only happen after three days of rest in a dark surrounding but one's busy lifestyle does not allow this. The pain level doesn't just drop to zero after a good night's rest. Many patients just keep going and remain hypersensitive during a longer sunny period by virtually every ray of light (also through glass) and even many forms of artificial light. The skin – the radar – keeps giving emergency signals until the weather changes for the worst or there is in fact time to take shelter indoors for a few days. Only then can one say that the pain level is back to zero and a patient will be able to go into the sunlight for anywhere between a few minutes to one hour. If it is partially cloudy outside they may even be exposed for a bit longer but that depends on the light-radiation.



In 40percent of the cases EPP causes unemployment, a considerable larger amount of people calling in sick and it restricts patients in their choice of study and career. Furthermore there is the social and psychological side of the condition. The skin is a sensitive radar which warns a patient at an early stage with painful signals. To avoid isolation and because of obligations towards work, family or social aspects EPP patients will surpass their own boundaries. Social obligations are hardly ever relaxed due to this. Patients feel it on forehand and are held back by the early arising pain and panicky fear they might experience. Without a good social network and understanding from the people around a patient it will lead to more isolation. Even more so for children who suffer from EPP. They have to deal with a lot of pain, anxiety and even panic attacks.

## Children

All EPP patients have at least one childhood memory in common. The burden of the sun: not being able to sleep at night, the itch they experience, the burning agony. Looking for the cool metal of the radiator in the dark. Washcloths to cool with, which turn warm too quickly. The endless hours of not being able to fall into sleep. Staying indoors for shelter 2, 3 days in a row.

And this is just the healing process. Keep in mind the process children undergo before getting to this stage. The pain of the sun on the day in question, but also the fear and anxiety beforehand. The realization you can't escape from the well-intended day-trip in the shade (where there is sun radiation

as well). Sports matches, P.E. or a play date. If one wants to undertake anything, one will be confronted by sunlight. That fear makes matters worse. Like mentioned earlier, the skin functions as a radar. A radar which sends alarm signals on what is coming beforehand. In spite of this children (and grown-ups) keep going because they simply have to go to school, work, shops, sports or the playground with their infants. The sun shines for a long period of time, through windows as well. The light in an ordinary living room is too much with EPP-pain complaints. Being isolated in a dark room is the only remedy. This too is recognised by the patients. Patients claim that sunlight through windows is as harmful as direct sunlight. One does not have to be outdoors to experience the burden of EPP. On that quote, several minutes of sun exposure behind glass e.g. whilst taking public transport can have grave consequences. Therefor patients prefer working on the north side of a building or behind well-functioning sunscreens.

Often children are unable to control their own lives. The limitation, pain and fears caused by EPP form children in the most significant years of their lives. In some cases one can talk about damage ranging from depression to social isolation. Research done by Navarro (1986) and Rufener (1989) have given us founding insight on this matter.

For children in their growth EPP is the worst. During the last patient-day in Utrecht a mother of a nine year old patient emotionally expressed this. In all communication on Scenesse it failed to mention minors. She impressively urged doctors and consultants present to stand together for a prompt realization for children.

**Social aspects**

It is a psychological pitfall not to want to deviate from others, mainly friends. If one wants to connect, one will come along on holiday, also when there is understanding and consideration for the situation. Virtually every time holidays like these will end up in huge painful disappointment and are not really worth repeating. Patients withdraw themselves and calculate whether or not they should turn up at parties. Spending an afternoon on your own in the kitchen is disappointing. Everyone is outside and there you have it; the social norm; one does not want to disconnect from the group and goes beyond their own boundaries. Such a party is hardly ever an event where patients enjoy themselves. Patients are tense when going to the party, mainly because their skin has already been giving warning signals on what is to come. Yet one goes. Even if it is just to please your family. They can't possible become the victim of your limitations? Patients call the effect of EPP on family life severely disruptive. It asks a lot of the partner as well.



**In practise**

As a patient one learns from the many painful experiences from one's youth. One avoids those situations by making conscious decisions about work, sports and social life. When having a family of your own one is forced to adjust to a new rhythm and going outside daily is a part of this. Bringing your child to and from school, sports or play dates. Afternoon sun is unavoidable. Just recently a young single mother (EPP patient) of a two year old alerted us about her burdensome situation. Without a good (social-) network the situation is impossible.

The patient who does go outside under these circumstances needs to wear full protective clothing including gloves. An uncovered hand or stripe of sunlight in the neck or sleeve can cause enough pain to make one turn around and go back inside. The local pain is progressive until it becomes unbearable. A mere sunblock does not protect against the wavelengths of the daylight-spectrum.

Another issue is the holiday; to many a relaxing experience. For patients a fatiguing period. One goes for the family, mainly for the children but the journey and the excursions are a disaster. One sees the surrounding people enjoying the sunlight but the only thought one has is to flee. One patient stated that the children don't tolerate the excuse of work to get out of a holiday anymore.

**Patient's opinion on Scenesse**

Patients who have used Scenesse know that the daily routine can go with less worries. Thus now the father can bring his daughter to the ice hockey match and even stick around to watch it. Something he hadn't been able to do for years!

Furthermore, groceries can be done without pain. A mother doesn't has to feel nervous while seeking shelter in the bike shed at the school of her child because the teacher let the children go a few minutes late. A single mother is less dependent on her social network to help with practical matters, because she can take her child to the playground or children's farm.

Some are scared their vehicle might break down. The foil might keep you save, but what if you have to get out of the car?
A parent doesn't have to tell their child 'no' if it wants to go outside to play together. Instead of having tearful face the child will have a smile on its face because the parent can join in for a change!
And how about the patient using Scenesse who doesn't have to leave the football field the moment the sun comes through. Or the patient who is not afraid of going on a cycling trip with the family, even though the sun might break through?

The medicine doesn't only serve its purpose in the summery periods. Even in winter social isolation can occur because patients can't take part in the normal daily activities due to sunny periods.
It's not just the patient who benefits from Scenesse: the entire family, the social surroundings and the working environment do not have to be in dark spaces anymore because the sun has to be kept out.

The absence from work, school or study will be far less because patients do not have to call in sick. This is due to the fact that complaints during the ordinary daily life will reduce significantly!
Furthermore, patients are far less limited in their choice of profession because the working environment does not have to be adjusted completely. An employee can also go outside easier if work has to be done out of the office.



A social improvement in respect to the social position and the development of the talents of the patient.

A patients needs to plan a lot less and this causes inner peace. On social level EPP patients can develop much better. Even the holidays will become more relaxing. Patients have reported to have been to places which where uncommon to them. They enjoyed being there, places like the school playground. If unexpected discomfort does occur the recovery takes much less time. It is not a cure for EPP but it does give back huge aspects of normal life. For the first time EPP patients have felt free and without worry. One patient felt like he was reborn!

# A job with EPP

## 40 percent of the questioned patients lost their (part-time) job due to EPP.

We have asked patients whether they could keep their job despite of EPP.
The question was: "Have you ever lost a job or been unable to keep a job due to EPP?"
Sadly, 40 percent of the patients answered this question with a yes.
Obviously the worry about the work varies. Different reactions rose according to the sort of employment the patient has. Especially during the current crisis it is worse to lose the job on which you rely for bread winning than losing a holiday job. One patient replied that EPP is currently in his disadvantage during reorganisation. Because of EPP he cannot be active all round and therefore he fears for his job.
Some additional remarks sent in with the answers to the question "Have you ever lost a job or been unable to keep a job due to EPP?"

- *"Yes, often and that frustrates me. I am a hard worker and the fact that I just cannot hold on to a job due to EPP frustrate me immensely. It is likely that I will lose my job in healthcare because it is unavoidable that I have to go outside every now and again. It would help tremendously if I had a medicine which allowed me to get into contact with sunlight, outside, even if it is for just an hour".*

- *"Yes, several times in the past"*

- *"Yes, I have lost two jobs due to EPP"*

- *"When I was 13 years old I delivered leaflets. I had to quite this job in the spring because there were complaints about my delivery work. Currently I am a shelve filler at a supermarket. This is going well because the job is inside and near my house".*



- *"When I was 20 years old I couldn't hold down my holiday job. Tarring drainpipes at de Heidemij in the summer."*

- *"Yes, I prematurely had to give up my holiday job in a department store because I couldn't work for three weeks due to sun-exposure in my spare-time."*

The remarks sent in when the answer to the question was I have <u>never</u> lost a job due to EPP show that it is frequently possible to adjust to the handicap. Apparently these patients were able to conform regularly to their limitations.

- *"No, I have always had jobs indoors"*

- *"No, but is has restricted me in my choice of study and carrier."*

- *"I have done my internship specifically from September to January so that I have outdoor experience for the rest of my carrier. I must say; September was quite a challenge."*

## 91 percent of the patients have adjusted their choice of profession due to EPP.

"Is your choice of profession determined by EPP?" Only a very small percentage of the patients who answered this questionnaire actually have a job in their first choice of trade.
A better question would be how many patients cannot work in their profession of choice. It is clear that patients cannot follow their heart but have to think rationally when it comes to their choice of profession. It means that one can never live up to the ideal. Without dramatizing this, it is very clear that EPP patients are limited in their employment choice.
Some additional remarks sent in with the answer to the question: "Is your choice of profession determined by EPP?"

- *"yes, absolutely"*
- *"Yes, I studied something different to my first choice."*
- *"Sure, I used to be interested in work in developing countries and I wanted to study cultural anthropology. Eventually I ended up in tourism and I pushed all the boundaries, in some extend to the impossible. That hurt a lot, but I did not want to accept that some things had to be left alone. I have done rain dances in many tropical locations, I have prayed for clouds and I have often taken shelter in office work.*
- *'Maybe indirectly, I am doing an IT-study and that is indoors''.*
- *"I feel very limited when it comes to my choice of trade. I have considered doing a sports study but that isn't accomplishable. I think it is quite difficult to decide on which study or profession I will do and I realise I can't decide on anything that involves going outdoors a lot (E.g. sports, adventurous professions, fieldwork). I have noticed it is a difficult decision for many of my friends but I feel far more limited because of EPP. I can't make choices based on emotions.*
- *"Partially, yes (indoor functions instead of execution, although I still combine it as much as possible with outdoor activities)."*
- *"Off course. If you suffer from EPP, you know you are limited in your choice of profession.*
- *"Yes, to a degree. Because of my choice for techniques I was fortunate to be able to do the work indoors."*
- *"Yes, I am a lawyer. I could not possibly choose a profession which forced me to be outside in the summer."*
- *"Yes. I now have my own practise as NMI register mediator (mediation for divorce cases, family affaires, labour, inter- and multi cultural affairs, government, neighbour mediation and vicinity) and Coach. Thus I work indoors."*
- *"Yes enormously! I have always wanted to work with animals but the study consisted of a large amount of courses which had to be done outside. This was not possible. Due to this I had to move towards a different study. Next to this, my dream of living in the countryside and having a farm with live stock and land would stay a dream. Because of EPP I could never realize such a dream. I would like to add that I would have loved to be a part of the recent founded animal police force. And again EPP has restricted me in my wishes"*

- *"Initially not. I chose my study because I have always wanted to work with children. However, it turned out that working with children meant being outside. This is now no longer an option for me as I am an EPP patient and can't be in contact with direct sunlight."*

## 46 percent of patients are claiming health-benefits due to (physical) EPP-complaints.

This is the case for nearly half of the patients. For the other half this is not the case but that needs no explanation. Many of the questioned patients stated that they make sure not to become ill by being careful with themselves in their spare time and by staying indoors.
Patients also answered that they go to work despite of the pain they experience while being ill.
Some additional remarks sent in with the answer to the question "On average, how many days have you called in sick due to EPP over the past five years?"

- *"I have never called in sick because I always take into consideration that I have to work the next day, therefore I stay indoors."*
- *"None. I make sure I don't get physical complaints."*
- *"None, I am a self-employed independent entrepreneur and I have completely adjusted my work to my disability.*
- *"5 weeks"*
- *"On average 5 days per year"*
- *"Certainly one third of a year when it comes to these parts of the day..."*



- *"I cycle back and forth to school daily. The journey takes approximately 40 minutes. Despite of my protective garment I still experience discomfort and complaints. During my school years I have been sick quite often and had to miss lessons due to this. It will amount to approximately 25 days per year.*
- *'' 2 - I don't report in sick often".*
- *"2 days"*
- *"None, I stay indoors as much as possible between March and October. If I do feel discomfort I go to work anyway. My job is indoors and cools due to the air conditioning.*
- *"3 weeks"*
- *"I am retired now. I did call in sick during work more than"*

## 35 percent of patients' employers have made some form of adjustments to the working space for them.

This question is about whether the employers or school bear the costs for the adjustments made to the work environment. This is the case for about one in three of the patients questioned.

Surprisingly a number of patients gave negative answers to this question and their explanation is that their employers do not wish to make adjustments. This is a shocking answer and should lead to further and more detailed subject for discussion.

To continue, it has to be said that a number of the patient are in actual fact working indoors and have sufficient protection if they do not have to work on the sunny side of the building.

Some additional remarks sent in with the answer to the question "whether the employers or school bear the costs for the adjustments made to the work environment".

- *"For the last 10 years I have been taken to school in a taxi (from VMBO (lower vocational education), the MBO (intermediate vocational education), and now HBO (higher vocational education)".*
- *"No, I wish for other less strong and warm lamps, but this is impossible".*
- *"The local council gave my junior school window screens".*
- *"No, often these sorts of things are not taken seriously by the employers, this is in my experience".*
- *"At school I sit in the middle of the classroom, so that I can avoid the sun. I receive extra guidance and support through a budget for long-term ill children till the end of this school year".*



- *"I am allowed to change my work time (office hours), if this is sun technically better",*
- *"I asked for a workspace which is not next to a window or on the west side of the building. This was quickly arranged."*
- *"Yes. When dividing the workspace I requested a space on the shadow side of the room. Here there is virtually no sun at all. When any sun does shine in the laminated curtains are closed. When the sun is a problem the temperature is better here. An additional aspect is that all employees doing the same thing as me have to work in the same area as me too.*
  *Other adjustments have an influence on my own work. While I was the head secretary I frequently had to ask my colleagues if they would go and buy flowers, cards, tourist vouchers, cakes etc. because it was too sunny for me to be able to do this myself.*
  *Lastly I would like to quote the social aspect. Because of EPP I have only been able to attend one teambuilding event in the last 6 years. These activities are organized in the spring and autumn and are usually outdoors.*
- *"Windows screens".*

## 28 percent of the patients have adjusted their home with government funding.

It is apparent that not all patients get funding for the necessary adjustments that have been made. Around 28 percent have been able to claim the costs of the adjustments. Sometimes patients were able to get funding for adjustments which were not given to other patients. This shows a difference in local policy; another thorn in the eye of our patient society. Getting local councils to have the same point of view proves to be very difficult. Many patients have adjusted their home or garden, let alone their choice of house adapted to the disability. We have not questioned this point.
Some additional remarks sent in with the answer to the question "have you had adjustments made to your home which have been funded by your employer, the city council or other sources of funding"

- *"No, I paid for everything myself. I installed dark window screens".*
- *"Screens paid for by the city council, also foil for my car window and an extern roof."*
- *"My parents have paid for all the adjustments themselves"*
- *"I have let some adjustments been made, but paid for it myself."*
- *"The sunscreens added to my house have been paid for by the city council."*
- *"Adjustments to windows but no refunds."*
- *"Shutters in front of the windows which I paid for myself. I do have a parking permit for the disabled"*
- *"Shutters all round my house which I paid for myself."*

## All patients avoid using their bike and taking public transport during the Sunny seasons. Their main form of transport is by car.

This is not a very surprising outcome. The question was: "Do you use the car for trips you could have done by bike f you did not have EPP?" The bicycle is an impossible method of transport during spring, summer and autumn. The car is the best option in these periods. If the car is not an option, patients choose to sit on the balcony of the train as there are fewer windows there.
Some additional remarks sent in with the answer to the question "Do you use the car for trips you could have done by bike f you did not have EPP?"

- *"Yes, otherwise I would not be able to leave the house and I had to cancel my appointments".*
- *"Yes, but I use public transport. I live 5 kilometres from my work. The distance is easily done by bike, but I am forced to take public transport because I then am better protected from the sun. Going by car is not an option because there is no close parking space for me. I don't want to apply for one on medical grounds because I don't wish to be an exception".*
- *"I use public transport to do the groceries at the shops 2 kilometres from here. Something I would normally do by bike.*
- *"Very often in the summer. I am guaranteed to become ill otherwise".*
- *"Yes, this happens a lot in summer.*
- *"Yes, all the time!"*
- *"I am bound to use the yellow-foil-car. I can't take the risk of going by bike. If the sun is not shining when I leave, I have no guaranties it will remain that way. An hour later the sun could be out".*



- *"Yes, my friends live near but it is always uncertain whether I can be exposed outside".*
- *"I live in the city centre and never have to cycle far. Recreational cycling with friend or family is out of the question. I simply can't".*
- *"Very often. Daily in the summer".*
- *"I got my motorcycle drivers license especially because I can cover myself up completely whilst on a motorcycle. I can't do that on a scooter or a moped. It makes me look like an idiot.*

**Submission of the International Porphyria Patient Network (IPPN) on long term effectiveness and new and additional evidence that addresses concerns raised by the HST Committee and/ or the Appeal panel during the Highly Specialised Technologies Evaluation for Afamelanotide for treating erythropoietic protoporphyria [ID927]**

**Short title: IPPN submission of new evidence [ID927]**

Authors: [redacted] [1], [redacted] [2], [redacted] [3], [redacted] [4]

[1] [redacted] International Porphyria Patient Network (IPPN)
[2] [redacted] Officer International Porphyria Patient Network (IPPN)
[3] [redacted] International Porphyria Patient Network (IPPN)
[4] [redacted] International Porphyria Patient Network (IPPN)
Correspondence: [redacted]

## Outline of the submission

On 27 November 2018, IPPN received an e-mail from Helen Knight, Director for the TA, HST and CSP programs at NICE further informing us of the next steps NICE and the HST committee will undertake in order to address the upheld appeal points in the case of afamelanotide:

“The HST committee will meet to discuss this HST evaluation on Wednesday [later corrected to Thursday] 14 March 2019.

In order to support the committee in its reconsiderations, as a participating stakeholder in this technology, we would like to invite your organisation to submit the following:

- New or additional evidence not submitted during the original evaluation, particularly regarding anything that supports long term effectiveness of the treatment.
- Further evidence that addresses the concerns raised by the committee and/or the appeal panel.”

As suggested, we considered in our submission how to demonstrate where some of the benefits of afamelanotide in the 4 categories below may not have been captured in the committee’s previous deliberations:

- Nature of the condition
- Clinical effectiveness
- Impact of the technology beyond direct health benefits
- Value for money

As the ongoing appraisal process in part builds on the decisions made by the Appeal panel, we first outline briefly by way of introduction our understanding of the implications of the Appeal decision.

The Appeal Panel upheld three appeal points raised by the stakeholders:

“The evaluation is remitted to the evaluation committee who must now take all reasonable steps to address the following issues:

i) The failure to include an IPPN representative at the second committee meeting (IPPN 1a.1).
ii) The failure to demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act (CLINUVEL 1b.1 and IPPN 1b.1). The appeal panel considers that this is likely to include express consideration of whether the methodology used in the evaluation discriminates against patients with EPP and if so what reasonable adjustments should be made.
iii) The appeal panel's conclusion that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide (BAD 2.2 and 2.3, IPPN 2.2).”

(Appeal Decision p.20; ¶ 122)

It is worth outlining briefly the implications of the second two issues identified by the Appeal Panel, which in our view have particular implications for the further appraisal process.

Appeal point ii)

“The panel took the view that EPP very clearly meets the definition of a disability under the Equality Act 2010” (Appeal Decision p. 9; ¶ 53).

The British Government defined disability under the Equality Act 2010 as: “You’re disabled under the Equality Act 2010 if you have a physical or mental impairment that has a ‘substantial’ and ‘long-term’ negative effect on your ability to do normal daily activities.” https://www.gov.uk/definition-of-disability-under-equality-act-2010 (Last accessed 13 January 2019)
Therefore,

(1) EPP is a more severe condition with more implications than previously assumed by the Committee. The HST guide “Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes” lists severity of a condition and disability as criteria considered in the cost-effectiveness analysis which should be adjusted accordingly. The severity of the condition is addressed further below.
(2) The Equality Act 2010 requires NICE to make reasonable adjustments, as well as to give due regard to the need to advance equality of opportunity between those with EPP and those without it, including encouraging persons with EPP to participate in public life. In addition, the UN Convention on disability rights, to which the UK is a signatory specifically provides that States must take “appropriate measures to ensure to persons with disabilities access, on an equal basis with others, to the physical environment” (Art. 9). In addition, it provides that reasonable adjustments have to be made to prevent social isolation and segregation from the community (Art. 19).

To meet these legal duties, our view is that NICE cannot do other than permit access to afamelanotide, which enables patients with EPP to lead an almost normal life, which includes accesses to the physical environment and less isolation and segregation from the community.

Appeal point iii):

"[…] it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide (BAD 2.2 and 2.3, IPPN 2.2)."

(1) The benefit is not only perceived, i.e. "believed" (FED p.9) or "valued" (FED p.10) by the patients, but has to be rated as factual.
(2) Because the benefit is not "small", there are no longer "substantial differences" (FED p.10) between the patient`s testimonies and the trial results and the disease specific quality of life measurements – rather, the testimonies reflect the extent of the benefit of the treatment.
(3) The cost-effectiveness evaluation, which takes the extent of the benefit into account, needs to be adjusted and should become more favorable

We hope to support the Committee in its further considerations with the detailed submission on new and additional evidence provided below.

**Disclaimer:**

The authors of this submission state no financial interest in the manufacturer of the product under appraisal.

Comparisons to other HST appraisals under no circumstances are meant to question the validity of the positive decision for funding for the treatments for those other severe and debilitating conditions.

## 1. Nature of the condition

Erythropoietic protoporphyria (EPP) is an ultra-rare condition (1 person in 150.000 affected) with very limited research history and, consequently, many uncertainties. Up to date, 955 peer reviewed scientific articles have been published concerning EPP of which only 22 feature clinical trials (Pubmed, last accessed 2 Jan. 2019). By reading the documents of the HST appraisal and appeal process, it became clear that the Committee has uncertainties about aspects of the nature and severity of the EPP condition with direct consequences on the value assessment of afamelanotide.

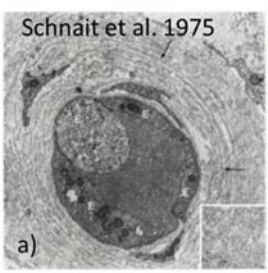
The Committee for example was unsure about the classification of EPP as being a disability because of the assumed absence of visible symptoms in EPP (Appeal Decision p.9; ¶ 51). In addition, EPP is an intoxication-type inborn error of metabolism (Das et al. 2013) and not a dermatological disease as implied by the Evidence Review Group (ERG) which, amongst other things, negatively impacted the economic modeling of the afamelanotide treatment (see section 3 and 4).

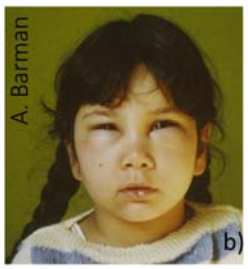
This demonstrates that the Committee was not fully aware of the nature of the EPP condition and, therefore, could not take all factors fully into account when assessing the benefit of the afamelanotide treatment. We address the identified uncertainties by providing the Committee with additional information and evidence not provided before on the nature of the EPP condition, i.e. examples of visible symptoms, behavioral adaptations and the resulting stigmatisation.

### 1.1. Visible symptoms of the EPP condition – physical injuries of the blood vessels

In EPP, visible light interacts with the accumulated protoporphyrin molecules and causes so called “phototoxic reactions”, which are burn-like injuries of the blood vessels (fig.1a; Schnait et al. 1975). Phototoxic reactions lead to a number of severe symptoms, including in an exacerbated phase, immediate burn-like pain in body areas exposed to light – comparable to touching an open flame. While the pain can already be unbearable, alterations on the skin surface however are usually absent or very discrete and might only develop several hours after the light exposure (Lecluse et al. 2008).

If possible, in an early stage of a phototoxic reaction patients withdraw from light exposure to avoid further exacerbation of the EPP symptoms and, therefore, usually do not develop any visible external signs of the phototoxic reaction. However, because of the “invisibility” of the symptoms, patients are often not believed and are sometimes forced to further expose themselves to light, although the pain can already be very severe, which then leads to the rare occasions in which the visible symptoms become very apparent. Due to the physical damage to the endothelial cells surrounding the blood vessels (fig. 1b), the blood fluids leak out into the tissue, which causes swelling of the affected body areas (fig. 2b). Further damage results in blood leaking out into the tissue (fig.1c). In addition, up to second degree burn wounds can develop (fig. 1d), which might even leave scars behind. The provided pictures illustrate the different stages of visible symptoms in EPP:





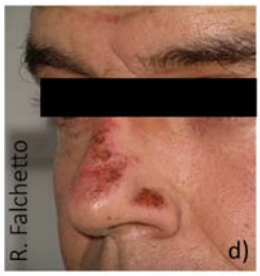


Figure 1: Visible symptoms of EPP: a) Chronic damage to the blood vessels caused by multiple phototoxic reactions in a biopsy from the dorsum of a hand of an EPP patient. Multiple basement membranes, each one resulting from repair process after a preceding phototoxic reaction, surrounding the papillary blood vessels (Schnait et al. 1975). b) Swelling of the tissue after prolonged exposure to visible light, caused by blood fluids leaking into the tissue. c) Massive damage to the blood vessels leads to whole blood leaking into the surrounding tissue. d) Second degree burns and open burn wounds. Visible signs like b)-d) only develop several hours after the acute phototoxic reaction.

### 1.2. Visible adaptations of EPP patients to their condition – protection from light

In order to not have to endure the massive neuropathic pain triggered by phototoxic reactions, which persists for days and does not respond to any known pain medication, EPP patients protect themselves as best as possible from light exposure by physical and behavioral adaptations. As sunscreens and other treatment attempts are not effective in EPP (Minder at al. 2009), the patients use improvised physical light protection as shown in the examples below:


Figure 2: Physical protection against visible light used by EPP patients: Patients use cloth, gloves, hats, umbrellas, masks and other forms of protection when outdoors. As however not all body areas can be sufficiently covered, and light behind window glass and strong artificial light sources can cause phototoxic reactions, the measures are not sufficient to completely protect the patients. In addition, the visible adaptations lead to stigmatisation of the patients, especially since usually visible symptoms of phototoxic reactions are absent.

The pictures provided in figure 1 and 2 demonstrate that EPP are associated with visible symptoms and visible protection measures. The described protection measures are however not sufficient to avoid the symptoms completely, as for example the hands and the face cannot always be covered and the measures cannot be used in indoor settings etc. In addition, they have secondary negative effects as outlined below.

### 1.3. Behavioral adaptation and stigma

Having to wear heavy clothing and other measures for sun protection like umbrellas in bright sunlight exposes patients to stigmatisation by their environment. Moreover, because EPP very rarely presents with visible physical symptoms, the patients are regularly accused of being malingerers and attention seekers who just make up their issues. In order to avoid, on the one hand, the painful phototoxic reactions and, on the other hand, the stigmatisation, from an early age on EPP patients adapt their behavior and restrict their light exposure as much as possible, impacting any social and work-related daytime outdoor activities. In the Committee papers, 16 of the 34 testimonies submitted during the consultation phase directly refer to humiliating experiences due to EPP. Four quotes from the submissions illustrating the behavioral adaptation and stigma associated with the EPP condition are provided below:

Stigma in EPP:

> *"All my life I have been bullied, isolated, misunderstood, shunned, picked on, alone, laughed at, alienated, mistreated and in constant unbearable pain."*
>
> Committee papers p.52; testimony 13

> *"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."*
>
> Committee papers p.56; testimony 18

Quotes demonstrating the behavioral adaptation in EPP:

> *"My life has been completely dictated by EPP with respect to education, career and life style."*
>
> Committee papers p. 58; testimony 22

> *"Isolation has already begun at her young age. We, her parents, dare not imagine what her future will be."*
>
> Committee papers p. 61; testimony 24

The described behavioral adaptations together with the anxiety to be exposed to light and potentially having to endure long-lasting, unbearable pain also affects the way patients react to new treatment options, especially since all other attempts so far have not been effective. The consequences on the afamelanotide trial outcomes are discussed in section 2.

1.4. Severity of the pain – EPP is not just "unpleasant"

During the Appeal Hearing, a Committee member several times described the symptoms of EPP as being "unpleasant". From a patient perspective this wording is concerning because it does not reflect the extent of the suffering experienced by those affected by EPP. Together with the perception of the Committee that EPP would not classify as a disability because of the assumed absence of visible symptoms, it demonstrates an underlying underestimation of the severity of the condition by the Committee during the appraisal process.

Nevertheless, an initial perception of the EPP condition as less serious than it really is closely resembles and reflects the frequent reaction of society to EPP patients and their families. As for the most time physical symptoms are not visible, EPP patients, even if they are already in severe pain, have to permanently justify themselves.

> *"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."*
>
> Committee papers p. 67; testimony 33

The patients during a phototoxic reaction usually stay in a dark and cool place until the symptoms subside, which could take several days. In most cases, they do not visit a physician or an emergency unit - there anyway is no effective pain medication – and therefore even most expert physicians never witnessed a patient in a full phototoxic reaction. We therefore provide the Committee with a short video (30 seconds) of [redacted]

[redacted] mother made the video during an acute phototoxic reaction and we have the permission to share this unique document.

1.5. EPP is a unique, intoxication-type inborn error of metabolism – and not a dermatological condition

We also feel that the unique nature of the EPP condition has not been fully captured by the ERG and, subsequently, the Committee, and want to stress that EPP is not a dermatological condition, but an intoxication-type inborn error of metabolism (Das et al. 2013) which affects the patients already from young age. EPP is characterised by, on the one hand, painful acute phases (the phototoxic reactions) and, on the other hand, by a constantly stigmatising and socially isolating conditioned behavioral adaptation to avoid light and its consequences – a feature not present in any other condition. Stigmatisation is augmented by late diagnosis often delayed for decades (Schneider-Yin et al. 2000; Holme et al. 2006; Wahlin et al. 2006)

1.6. No alternative treatment options

We note that the Committee agreed that no effective treatment options exist for EPP: "The committee concluded that there is no effective treatment for preventing phototoxicity caused by EPP, so there is an unmet need for an effective treatment." (FED p. 6).
Despite this conclusion, we have concerns about the way the ERG described the treatment options in reaching it and so think it is important to correct the record for the purpose of the reconsideration.

The systematic review conducted by Minder et al. (2009) is, to our knowledge, the only publication that systematically compares the scientific evidence of reported treatment options in EPP. Minder and colleagues concluded that "no undisputed and significant efficacy was shown in any of the therapeutic modalities applied in EPP so far" (in 2009). We are particularly concerned that the ERG in its report did not take this publication into account when describing the "treatment options" in EPP (ERG report p.19), although the British Porphyria Association made the ERG aware of it (ERG report p. 126). On the contrary, the presentation of the topic by the ERG creates the impression that, first, effective treatment options exist for EPP and, second, that patients do not pursue them for reasons such as convenience.

| **Treatment options for EPP as presented by the ERG (ERG report p.19)** | **Comment** |
|---|---|
| "Upon discussing treatment options with the ERG's clinical advisors it was noted that beta-carotene compounds (taken orally, on average eight tablets daily) seem to provide some protection for a minority of people. However, it can sometimes be hard to obtain beta-carotene in the UK and it has to be sourced from overseas (e.g. the USA)." | It is not clear why the ERG did not consider the best available evidence on treatment options in EPP, the systematic review by Minder et al. (2009; reference number 49 in the ERGs report), although it was provided by the British Porphyria Association (BPA): "The BPA highlighted a systematic review of treatment options for dermal photosensitivity in EPP, stating that high dose beta-carotene is ineffective.[49]" (ERG report p. 126). |
| "The ERG's clinical advisors also described the use of narrow-band ultraviolet beta (UVB) phototherapy (e.g. 3 x weekly for 4-6 weeks or variations of), which has, according to clinical experience and a few | In addition to the stated marginal effectiveness of the UVB phototherapy, some patients do experience severe phototoxic reactions during the sessions (Minder et al. 2009): The UVB sources |

| | |
|---|---|
| case reports, been shown to marginally increase patients time of exposure to sunlight. Although the ERG's clinical advisors did mention that few patients choose this option due to the practical issues and impact on lifestyle and work routine." | besides emitting UV (which is invisible) also emit strong blue light – the main trigger factor for phototoxic reactions in EPP. This, together with the justified concern about increased risk for skin cancer in case of prolonged usage (as would be necessary for a chronic condition like EPP) are in our experience the reasons why only a minority of patients seek UVB phototherapy. For UVB phototherapy, no prospective, randomised trial data is available demonstrating efficacy (Minder 2009). |
| "The ERG experts state that the use of Dundee cream can also slightly increase the time patients can be exposed to sunlight. However, it tends to be reserved for particular outdoor occasions rather than being used daily. This is because large volumes need to be applied, and it can adhere to clothing. In addition, these creams have an appearance similar to cosmetic make-up and are therefore not always acceptable to some patients (e.g. younger males)." | Sunscreens are of limited effectiveness, most patients do not experience any benefit. For sunscreens, no prospective, randomised trial data is available demonstrating efficacy (Minder 2009). |

From the patient's perspective the main reasons not to use beta-carotene, sunscreen and UVB-treatment is neither "practical issues and impact on lifestyle and work routine" nor "because large volumes need to be applied" nor that "these creams have an appearance similar to cosmetic make-up and are therefore not always acceptable to some patients (e.g. younger males)" as stated by the ERG (ERG report p. 19). The reason not to use these "treatment options" is simply lack of effectiveness, as demonstrated by Minder et al. (2009).

1.7. No "standard of care"

As demonstrated above, protection against light exposure by physical measures and behavioral adaptations are not sufficient to avoid EPP symptoms and, in addition, are associated with negative effects like stigmatisation and social withdrawal. Therefore, there currently is no "standard of care" available for EPP patients in the UK, and the patients are left alone with their condition.

The patient testimonies provided during the consultation phase impressively demonstrate what living with the EPP condition in the UK currently means:

*"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."*

Committee papers p.54; testimony 16

## 2. Clinical effectiveness and impact of the technology beyond direct health benefits – Trial outcomes

Since 2006, afamelanotide has been tested as a treatment for EPP in several clinical trials, collectively including 349 EPP patients. In addition, an eight-year observational study in 115 EPP patients from Italy and Switzerland receiving the afamelanotide treatment during compassionate use and special access programs was conducted. All four randomized controlled trials and the long-term observational study showed significant outcomes regarding the number and severity of phototoxic reactions, time spent in direct sunlight and / or quality of life as measured with a partly validated, disease specific quality of life instrument. (EPAR p. 74 - 75; Langendonk et al. 2015; Biolcati et al. 2015).

During the approval process, the European Medicines Agency (EMA) concluded that because of the rarity and complexity of the EPP condition, i.e. the dependency on external factors and the life-long conditioned behavior of the patients to avoid light, the efficacy of the afamelanotide treatment was not accurately quantifiable in conventional clinical trials (EPAR p.89 - 90). The EMA therefore for the first time in their history involved patients in discussions on benefits and risks of a medicine in a full regulatory meeting with the Committee for Medicinal Products for Human Use (CHMP). The EMA then based their positive recommendation for marketing authorization under exceptional circumstances on the input obtained from patients during the assessment: “The CHMP heard from patients and healthcare professionals involved in an expert group that patients treated with Scenesse [afamelanotide] consistently reported improvements to their quality of life.” (EMA press release, 24 Oct. 2014).

Whilst we acknowledge that NICE is addressing a different question to that asked by the EMA, both entities must consider the extent of the therapeutic effect of afamelanotide on EPP (although the EMA then focusses on balancing this against its risks, whereas NICE has to consider questions of cost). As outlined in our submission, it would be irrational for NICE to require a different kind of proof for effectiveness, especially since the reason put forward by the EMA for basing its positive recommendation for approval on patient input received during the approval proceedings rather than quantitative trial results, was that it is not possible to accurately quantify the benefit of the afamelanotide treatment in EPP because of condition specific characteristics.

During the appraisal for afamelanotide, NICE received 34 written patient statements submitted during the consultation phase, 16 describe first-hand experience with the treatment and provide further insights into the clinical effectiveness and the impact beyond direct health benefits: All 16 testimonies state life-changing effects and that under therapy, patients are able to have an almost normal life. In addition, UK patient representatives and expert physicians during the Committee meetings and the Appeal Hearing contributed first-hand experience with afamelanotide. The International Porphyria Patient Network (IPPN) in addition provides first-hand long-term experience (several Swiss patients receive the treatment since 13 years) on the effectiveness, benefit and the societal value of the treatment (see Appendix C- HST patient expert statement, submitted 4 Jan 2019).

Because of the experiences and conclusion from the EMA approval proceedings the IPPN together with the BPA in the draft scoping documents requested that during the NICE appraisal process patient`s testimonies should be included as an outcome measure (Draft scope and provisional comments table (post referral) p.12, 17 May 2017 (hereafter: Draft scope)). The British Association of Dermatologists (BAD) and the company put forward similar arguments (Draft scope, p.11). Despite the stakeholder’s requests, patient testimonies were not included as an official outcome measure in the final scope (Final scope p.2, 17 May 2017). In the “Action” section of the Draft scope document (p.12), NICE however explains that “the committee can consider a broader range of outcomes during the evaluation” and that “Consultees are encouraged to present evidence of the effectiveness of

the technology, which can come from other sources in addition to the clinical trial data, in their submissions." As the patient testimonies were not assessed as an outcome measure in the appraisal process so far we put forward that for the ongoing process the patient, carers and expert physician`s input should be included as a qualitative outcome measure. Therefore, we below present insights provided by the EPP patients, carers and expert physician's testimonies on the clinical effectiveness and the impact of the technology beyond direct health benefits of the afamelanotide treatment which in our opinion have not been captured in the Committee's previous deliberations because the testimonies were not considered an outcome measure.

Further, we address concerns expressed by the Committee regarding these testimonies, which seem to have prevented the Committee from fully acknowledging the submissions.

2.1. EPP patients are able to assess the clinical effectiveness of the afamelanotide treatment and their testimonies can serve as outcome measure

The European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL) is a group of 15 rare disease experts across seven European countries, including Health Technology Assessment (HTA) practitioners, physicians, patient representatives, academics, politicians and industry representatives. Dr. Sheela Upadhyaya, Committee Member and Associate Director of the HST program at NICE, is one of the 15 experts in the ORPH-VAL working group, which in 2017 published nine principles to help improve the consistency of orphan medicinal product (OMP) pricing and reimbursement (P&R) in Europe and ensure that it reflects the inherent characteristics of rare diseases, the ORPH-VAL recommendations (Annemans et al. 2017).

According to the ORPH-VAL working group, health care professionals, patients and their carers should be involved because they offer "an important insight into the real-world experience of a rare disease." "These stakeholders can help authorities understand what outcomes are relevant in a disease and what level of improvement is clinically meaningful."

In the afamelanotide trials, sun exposure time, and number and severity of phototoxic reactions ("pain") were measured as endpoints (EPAR p.74-75). According to Sullivan (2012) and Vroom (2012) "a clinical meaningful endpoint is an endpoint that directly measures how a patient feels (symptoms), functions (the ability to perform activities in daily life), or survives. Therefore, a primary endpoint should be a direct measure of one of these. A primary endpoint should generally not be a measure of something that is not important to the patient. Who knows better than the patients what is important to them?"

In EPP, a few minutes in sunlight are sufficient to cause massively painful phototoxic reactions:

> *"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."*
>
> Committee papers p. 40; testimony 3

Being able to stay in the light during such situations enables functioning, e.g. to perform activities in daily life, and having to endure less and milder excruciating painful phototoxic reactions is an improvement of the symptoms associated with EPP. Therefore, "more sunlight for less pain" is not a surrogate marker of unknown significance but a clinically meaningful endpoint, which is directly assessable by the EPP patients. The testimonies submitted to NICE illustrate the full extent of the benefit of the afamelanotide treatment:

> "*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."*
>
> Committee papers p. 40; testimony 3, same individual as above

The submissions demonstrate that the effects of the afamelanotide treatment as assessed in the clinical trials are relevant for patients with EPP and their families. The testimonies in addition illustrate "what level of improvement is clinically meaningful" (ORPH-VAL principle 1):

> *"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."*
>
> Committee papers p.39; testimony 1

During the afamelanotide appraisal, the Committee however assumed that "Clinical trial results suggest small benefits with afamelanotide" (FED p.1). The Committee maintained their interpretation, although patient representatives and expert physicians contributed their experience with the treatment at the Committee meetings: "It [the Committee] heard from patient experts and the British Porphyria Association that even small benefits such as being able to spend an extra few minutes in daylight or having fewer phototoxic reactions could have a large impact on people's lives." (FED p.8).
The IPPN and the British Association of Dermatologists (BAD) appealed against the Committee's interpretation of the trial outcome and the Appeal panel "concluded that it was not reasonable for the committee to describe the magnitude of benefits seen in the trial as "small" and thus upheld appeal points BAD 2.2, BAD 2.3 and IPPN 2.2." (Appeal Decision p.15; ¶ 88).

We conclude that the EPP patients, their carers and expert physicians are able to assess the clinical effectiveness of the afamelanotide treatment and can help decision bodies understand what outcomes are relevant and what level of improvement is clinically meaningful. Therefore, the testimonies received during the consultation phase and the inputs from patients at the Committee meetings should be considered and assessed as outcome measures.

2.2. Impact of the technology beyond direct health benefits and on carers and families

While not systematically collected, the impacts of the technology beyond direct health benefits and on carers and families are provided in several written inputs received during the consultation phase. As illustration, we provide one quote:

> *"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."*
>
> Committee papers p. 58; testimony 21

As the direct social environment like parents, partners, children and friends of a patient is affected by the condition in a way that allows them to directly whiteness and assess the benefit of the treatments, their input should be rated as outcome measure for impacts of the technology beyond direct health benefits and on carers and families.

2.3. Are the submissions received by NICE representative?

In general, a valid concern and limiting factor for the reliability of patient testimonies would be a potential selection bias, i.e. that only patients having a good treatment outcome and high treatment satisfaction engage in discussions with and submit testimonies to authorities. However, the experience of expert physicians and patient organisations and the observed high long-term treatment adherence for the afamelanotide therapy indicate that the majority of patients experience the reported life-changing effects:

“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.” (FED p.9)

“The BPA in their submission states that they have not encountered a patient who has not received a significant benefit from afamelanotide.” (ERG report p.127)

“One clinician reported from her experience where 39 out of 40 patients were responding to afamelanotide through increased daily sun light exposure and number of pain free days.” (EPAR p. 88)

“The company and experts stated that an indicator of the effectiveness of afamelanotide was the compliance rate of about 94% despite the cost and time associated with travel for treatment.” (FED p. 10)

We conclude that the descriptions obtained in the 34 testimonies, 16 with experience with the afamelanotide treatment, and the patient and expert physician inputs during the appraisal process are representative.

2.4. Are there “substantial differences” between the trial results and the testimonies?

The Committee was concerned about a perceived “substantial difference” between the trial results and the statements in the submissions received from patients, carers and expert physicians regarding the extent of the benefit: “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 substantial difference between the trial results and the expert testimonies, anecdotal evidence of those present at the meeting, and the consultation comments.” (FED p.22).

We assume that by “substantial differences” the Committee refers to the reported life-changing effects which seem to be in contrast with the perceived small outcomes of the clinical trials. The Appeal Panel however concluded that the trial results shall no longer be assessed as being “small” (Appeal Decision p.12; ¶ 70). It was convinced by the comparison put forward by Prof. Lesley Rhodes about the time normal people spend outdoors which is in the same range as the time EPP patients under treatment were able to spend in direct sunlight without experiencing phototoxic reactions in the trials:

“Professor Rhodes disputed the committee’s view that the clinical trial results suggest “small” benefits with afamelanotide. She stated that the average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). She argued that this increase puts patients with EPP who are on treatment into the normal range for this measure. (She quoted data that showed that healthy indoor workers spend an average of 22 minutes in the sun between 10am and 3pm). She also pointed out that the figure of approximately 10 minutes extra per day of sun exposure represents an average daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest.” (Appeal decision p.11; ¶ 64)

As the trial results are not “small”, consequently, there is also no “substantial difference” between the testimonies and the reported life-changing effects, which are rather a reflection of the therapy’s real benefits.

2.5. Do the testimonies provide the “complete picture”?

The Committee was concerned as to whether the testimonies submitted during the appraisal process would provide the “complete picture” and stated a perceived difference to the scientific literature:

“In response to a question from the panel about whether the patient and clinician testimony was unusually compelling and uniform in this case, Dr Jackson replied that the HST evaluation committee very commonly sees a similar picture of very positive responses with technologies that come before them. When the committee looked at descriptions of EPP in the literature, they felt that while the testimony of the nominated patients and clinicians was very powerful, this might not be a complete picture.” (Appeal Decision p.14; ¶ 78)

To our knowledge, the only publication on real-life and long-term effects of an effective treatment in EPP is the eight-year observational study by Biolcati et al. (2015). The patient testimonies submitted to NICE do reflect the treatment effects described in this publication, e.g. the strong and sustained increase in quality of life and that the benefits of the treatment are relevant and the extent meaningful. In addition, the testimonies also confirm further aspects of the condition, e.g. the social isolation and impacts on family and career choices, the conditioned light avoidance behavior which first has to be overcome to fully test and appreciate the extent of the tolerance to sunlight gained by the treatment.

If the Committee thinks that the descriptions in the submissions from the patients, carers and expert physicians do not represent the complete picture, the Committee should explain which aspects they feel are missing from the testimonies and which literature they refer to.

In addition, the Committee needs to clarify their expectations: Form our perspective it is contradictory to invite submission from patients and expert physicians, who are the individuals with first-hand experience with a condition and the treatment effects, and then invalidate them and their testimonies, because of a perceived difference to unspecified aspects of the condition obtained from undisclosed literature sources.

2.6. Has the conditioned light avoidance behavior influenced the trial results?

During the clinical trials, the behavioural adaptation in EPP patients was one of the reasons why the effectiveness of the afamelanotide treatment was not accurately quantifiable (EPAR p. 89-90). The EMA acknowledged that EPP patients first have to overcome their anxiety and unlearn their conditioned behavior of light avoidance, and approved the afamelanotide treatment under exceptional circumstances because, amongst other reasons, the efficacy is not accurately quantifiable.

The Committee however during the Appeal Hearing questioned the existence of the described effects on the trial results: “Dr Jackson, for NICE, said the committee had considered whether conditioned light avoidance was likely to have resulted in the clinical trials substantially under-estimating the benefit of treatment. They concluded that this was unlikely […].” (Appeal Decision p. 11; ¶ 60). (For further discussion on why the Committee doubted the existence of an effect of the light avoidance behavior on the trial results and further inconsistencies in their assessment of the matter see section 2.7)

We disagree: The unlearning of the behavioral adaptation is best illustrated by a quote from the submissions:

> *"My son (20 years old) has been treated with Scenesse for the last two years, and his life has completely changed for the better! 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."*
>
> Committee papers p. 69; testimony 35

The stated "careful acclimatisation" is partly reflected in the trial results (see figure 3, adopted from EPAR p.71; sun exposure time as measured in the pivotal trial CUV039): During the first 60 days, treatment and placebo group do not perceivably differ in their sun exposure times. However, with the second dose (after day 60), a clear difference is demonstrated between both treatment groups. This picture is best explained by the quote provided above: Patients first need to gain an understanding of the extent of the benefit and need test their new limits in sun exposure that they have under treatment – given the potential massively painful consequences of too much sun exposure an initial reluctance and an adaptation phase is plausible. In addition, as the trials were placebo controlled, patients did not know whether they would experience any effect at all, and since the trials were conducted under real-life circumstances there were significant risks of developing phototoxic reactions, which would have incapacitated trial participants for several days and impacting their ability to function in daily life.

In hindsight, a run-in phase omitting the first 60 days from further analysis would have been an appropriate adjustment for the trial design. This, in addition to other factors not captured during the trials such as the weather conditions and indoor occupation of the individual trial subjects, has affected the trial outcomes and illustrates the challenges in trial design in rare diseases, in which no previous experience with effective treatments options exist.

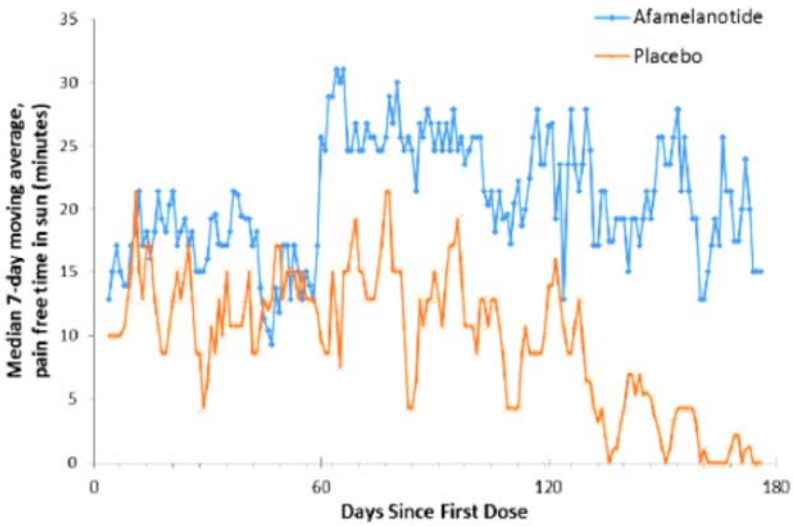



Figure 3: Median of the individual patients' 7 day moving average for pain-free daily exposure to direct sunlight for the CUV039 trial. In the first 60 days of the 180 days study period, no difference in sun exposure times is identifiable between the study groups. After day 60 (2nd dose afamelanotide), the treatment group shows a clear increase in sun exposure times compared to the placebo group. (Figure adopted from EPAR p.71)

Patient testimonies and the trial results measuring time spent in direct sunlight (without phototoxic reactions) strongly indicate that patients with EPP have to first overcome their conditioned light avoidance behaviour and that the trial results have been influenced, amongst other factors, by the patients' behavioural adaptation.

2.7. Impact of the conditioned light avoidance behaviour on quality of life measurements

Interestingly, the Committee on the one hand was concerned that the deeply ingrained light avoidance behaviour increased the uncertainty in the quantification of the benefit to an extent that would not provide sufficient evidence to recommend funding by the NHS or would not even allow for a Managed Access Agreement (MAA):

“The committee was convinced that patients valued the benefits of afamelanotide but remained concerned that no data were available to quantify this impact.” (FED p.10);

“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).

On the other hand, and contrary to the mentioned concerns, during the Appeal Hearing the Committee also fundamentally questioned the effect of the conditioned light avoidance behaviour on trial results:

“Dr Jackson, for NICE, said the committee had considered whether conditioned light avoidance was likely to have resulted in the clinical trials substantially under-estimating the benefit of treatment. They concluded that this was unlikely, because in the observational study by Biolcati et al (2015) there was a substantial improvement in quality of life over the first 6 months of treatment with no additional substantial change thereafter.” (Appeal Decision p.11; ¶ 60)

The sun exposure times measured in CUV039 as shown in figure 3 (see section 2.6) suggest that the patients under treatment needed approximately the first 60 days during the trial to first experience and become confident in the protection by afamelanotide, before they are able to partly overcome their conditioned light avoidance.

The first time point for quality of life measurements (as measured with the disease specific quality of life instrument EPP-QoL) after the determination of the baseline in the referred Biolcati study is on day 180 (see figure 4). During the clinical trials CUV039 (pivotal trial) and CUV029 (European arm of the study), a stepwise increase in quality of life indeed is visible (see figure 5): The biggest increase in quality of life (as measured with the EPP-QoL) is observed between baseline and day 60. After day 60, the quality of life further increases, however the improvement is less pronounced and in both trials levels off at around 80% at day 180.

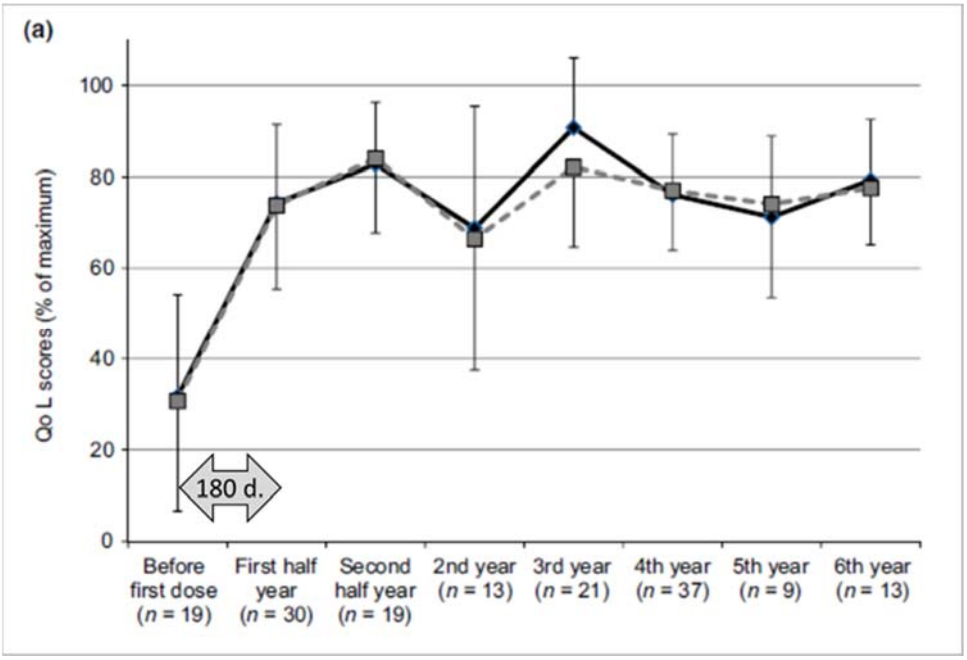



Figure 4: Quality of life as measured with the EPP-QoL in the eight-year observational study by Biolcati et al. (2015). First time point after determination of the baseline (before first dose) is day 180. The stepwise increase in quality of life observed in the clinical trials CUV029 and CUV039 was in the period between baseline and day 180 (figure 4). (Figure adopted from Biolcati et a. 2015 and modified).

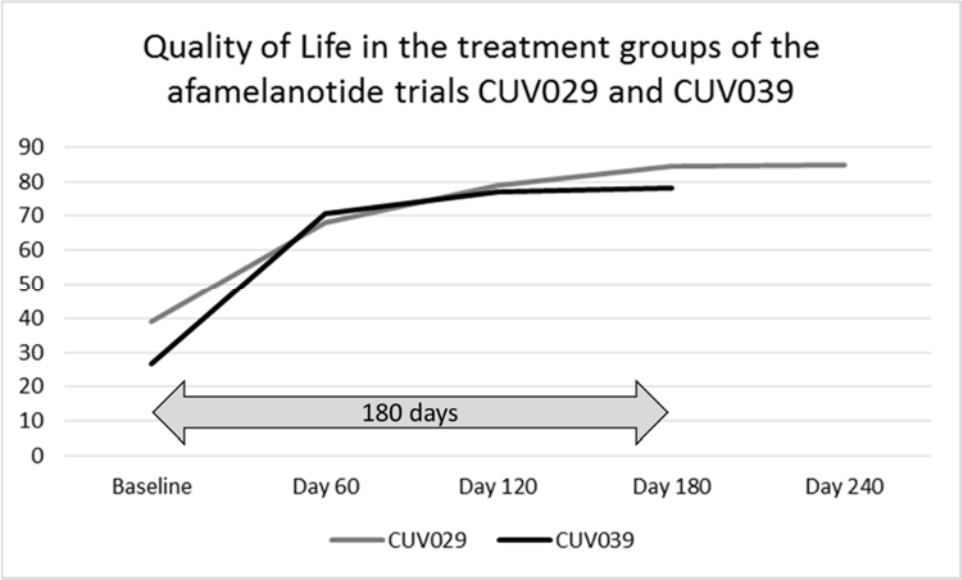



Figure 5: Quality of life as measured with the EPP-QoL in the treatment groups of the afamelanotide trials CUV039 (pivotal trial, duration:180 days) and CUV029 (European arm, duration: 240 days). A period with stepwise increases in quality of life is visible between baseline and day 180. Quality of life seems to level off at around 80 %.

Table 1: EPP-QoL results, excerpt from ERG report p.57

| Treatment | CUV039 | SD | CUV029 | SD |
|---|---|---|---|---|
| Baseline | 26.6 | 19.9 | 39 | 25.8 |
| Day 60 | 70.6 | 24.2 | 68 | 19.1 |
| Day 120 | 76.9 | 22 | 78.8 | 16.2 |
| Day 180 | 78.1 | 24.9 | 84.6 | 12.6 |
| Day 240 | | | 84.8 | 10.7 |

We conclude that the data obtained from the long-term observational study by Biolcati et al. (2015) does not cover the period in which the change in quality of life (further increase) would be visible (figure 4). Therefore, the absence of a further increase in quality of life measurements in the Biolcati study does not indicate that the patients would not need to overcome their conditioned light avoidance behaviour. To further explore how quality of life and the ability to expose to sunlight are connected in EPP, we asked an expert physician from Switzerland on their experience (box 1).

Box 1

Comment of expert physician Prof Elisabeth Minder, MD, who treats EPP patients with afamelanotide since 2006:

QoL und light exposure without pain are independent measurements. QoL is for example influenced by the fact that patients don't need to carry protective measures such as umbrellas, gloves long sleeves and closed shoes during hot and sunny days, which enables them to avoid stigmatization in the public. This effect is perceived comparably fast. Sun light exposure on the other hand is determined to a great extend by the patient's life style, e.g. the patient has chosen a work environment, that does not have a risk of sunlight exposure, his leisure activities he likes and is used to are indoors. Moreover, Swiss patients report that even after years of treatment with afamelanotide, they have consciously to overcome a psychological barrier to expose to light. This is underlined by our experience that it requires years of treatment until patients dare to move to a more rewarding working place that includes higher light exposure than the protected they had before.

E. Minder, January 2019, expert physician Zürich, Switzerland

### 2.8. Would it be unfair to use patient testimonies in the case of afamelanotide? - Patient testimonies in other NICE appraisal proceedings

A Committee member at the Appeal Hearing expressed concerns that using different approaches for the evaluation of afamelanotide would be unfair to those with other rare conditions.

"Jeremy Manuel, for NICE explained that the HST process itself was established in response to potential discrimination faced by sufferers of rare diseases. He felt that the same arguments used with regard to afamelanotide in this appeal point (concerning the complexities of capturing the full benefits of treatment) could potentially be applied to any rare disease. He argued that if a different method had been used in this particular case, it could be unfair to those with other rare conditions." (Appeal Decision p. 9; ¶ 50).

Capturing the full benefits of the afamelanotide treatment by, for example, including the patient testimonies as outcome measures as put forward by IPPN and other stakeholders however would only be unfair in case NICE would not consider patient input in other appraisals.
Staley & Doherty (2016) investigated the use of patient input in NICE appraisal processes and report that "On occasion, the patients' views have had a profound impact on decision-making (see the example of the review of insulin-glargine below) when committee members have drawn conclusions based on the clinical and economic data that do not reflect the reality of the patient experience."

*"We were considering insulin-glargine and the evidence showed that using conventional insulin and insulin-glargine had the same effects on HbA1c [a biomarker for diabetes control] but the glargine cost loads more, but what the committee heard from the patients was that if you have any tendency towards hypoglycaemic events, which can happen with standard insulin, then you literally went to bed every night scared you weren't going to wake up as a consequence of having a hypo. So people wouldn't take their insulin and their base level of HbA1c was much higher. So the committee asked for work to be done to survey patients to see how common this behavioural response was, and what impact the higher HbA1c levels would have on survival. Glargine did not result in hypos so had less behavioural impacts-you could take it and run yourself at the appropriate HbA1c level. With the additional evidence, the committee was convinced that a proportion of patients would respond better that way.* (Committee member 5)". Staley & Doherty (2016)

Diabetes mellitus is not a rare condition, and with over 458.000 peer reviewed publications, approximately 28.000 on clinical trials, a substantial body of evidence exists (Pubmed, last accessed 11 January 2019). Nevertheless, NICE considered patient input when assessing insulin-glargine for the treatment of diabetes mellitus type 1 and 2, to understand patient treatment preferences and behavioural responses.

Also in the HST2 appraisal of elosulfase alfa for the treatment of the ultra-rare condition mucopolysaccharidosis type IVa (MPS IVa), patient input was considered. We quote from the section on "Clinical evidence. Availability, nature and quality of evidence" in the FED of elosulfase alfa:

"The Committee noted that much of the evidence represented anecdotal, patient-reported outcomes. The Committee concluded that some of the true long-term outcomes in people with MPS IVa, such as cardiac and respiratory function and the need for orthopaedic surgery, remained uncertain.
The Committee was aware that the patient experts' opinion was subjective and was at risk of bias because it may represent the experience of only a selected group of patients.
The Committee was aware that the clinical trials measured primarily proxy outcomes, and did not substantiate most of the direct health benefits described by patients. The Committee concluded that data collected within the context of the managed access agreement would help to reconcile the differences between the patient testimonies and clinical trial data when this guidance is reviewed." (FED elosulfase alfa, p.41-42)

In addition, in the HST2 appraisal patient input was considered for the determination of the extent of the benefit:

"A patient expert noted in their submission that the improvement in quality of life associated with elosulfase alfa might be greater than the increase in 6MWT, and noted that even a small improvement in endurance could make a substantial difference to the quality of life of a person with MPS IVa." (FED elosulfase alfa, p.15; ¶ 4.26).

In the HST1 appraisal of Eculizumab for the treatment of the ultra-rare condition atypical haemolytic uraemic syndrome (aHUS), only single-arm, non-randomized trial outcomes were available:

"The key clinical evidence came from 2 published (C08-002A/B and C08-003A/B) and 2 unpublished (interim data from C10-003 and C10-004) prospective studies, and 1 retrospective observational study (C09-001r). No randomised controlled trials were identified. All prospective studies were phase 2, open-label, non-randomised, single-arm studies that included patients with different clinical baseline characteristics."
Guidance for Eculizumab for treating atypical haemolytic uraemic syndrome, https://www.nice.org.uk/guidance/hst1/chapter/4-Evidence-submissions#clinical-evidence (Last accessed 14 Jan 2019)

Also in this case, patient, carers and expert physicians input was considered and Eculizumab was recommended for reimbursement by the HST Committee in charge (appraisal HST1):

“After considering all available evidence, and the opinions of the clinical and patient experts, the Committee agreed that eculizumab represents an important treatment option and effectively decreases thrombotic microangiopathy activity and improves kidney function in most patients with aHUS. The Committee noted that the use of eculizumab would be of significant value to patients with aHUS, but it was aware of its need to consider the extent to which the cost to the NHS of doing so was reasonable.” (FED Eculizumab, p.27)

As patient input was considered in other conditions and the HST program showed flexibility and a sense of proportion when assessing other rare conditions, the consideration of patient input and other reasonable adjustments in the case of the afamelanotide appraisal would not be an unprecedented and unfair act against other rare or common diseases. Rather, the opposite is the case: It is unfair and discriminatory to not take EPP patient input into consideration in the appraisal of afamelanotide.

2.9. New evidence for long-term effectiveness: Treatment adherence rate in the Post-Authorization Safety Study of over 98 %

Treatment adherence is a major concern in all health care systems, causing a significant amount of avoidable complications and costs, also in the UK (Dunbar-Jacob & Mortimer-Stephens 2001; Osterberg & Blaschke 2005; Khunti et al. 2018). The reasons for poor adherence are various but include, amongst other things, lack of (perceived) benefit (Patti et al. 2010). According to Osterberg & Blaschke (2005), missed appointments (“no-shows”) are one of the markers of poor adherence.

For this submission, NICE specifically asked about additional evidence on the long-term effectiveness of the afamelanotide treatment. We think that the exceptionally high adherence rate for the afamelanotide under real-life conditions demonstrates the high treatment satisfaction and should be counted as supporting evidence in the context of the EPP condition.

Already during the eight-year observational study in 115 patients receiving afamelanotide during compassionate use and early access schemes in Italy and Switzerland, a compliance rate of 94 % was noted (FED p.10).
After obtaining marketing authorisation, the Netherlands were the first country which in June 2016 started to regularly treat EPP patients with afamelanotide: Between June 2016 and November 2018, 117 patients started with the treatment at the national porphyria center in Rotterdam. The treatment adherence rate of this cohort is 98.3 % with only a few patients reporting lack of effectiveness as a reason not to continue the treatment (Langendonk and Wensink, personal communication). A detailed list of reasons for discontinuation with the afamelanotide treatment will be published by Langendonk et al. (manuscript in preparation).

The Committee previously “appreciated the compliance rate was high but noted that it was not a quantifiable marker of effectiveness.” (FED p.10). However, the HST can consider a wide range of factors and Barbosa et al. (2012) in a meta-analysis concluded “that greater treatment satisfaction was associated with better compliance and improved persistence.” As “collecting adherence data from subjects is now considered an essential part of clinical trials” (Osterberg & Blaschke 2005), and as the afamelanotide treatment as a condition of approval by the EMA is connected to an obligatory Post-Authorization Safety Study (PASS) to determine safety and efficacy and amongst other outcomes measures treatment adherence, it would be illogical to now not use the data on the adherence rate generated by the PASS.

### 3. Clinical effectiveness- Quality of Life in EPP

The Dermatological Quality of Life Index (DLQI) “was the first dermatology-specific Quality of Life instrument” and developed in 1994 at the University of Cardiff (Finlay et al. 1994). It is a tool validated for many skin disorders and one of the most frequently used quality of life measures in dermatology. Because EPP is associated with painful burns after light exposure and because the lack of a disease specific tool, the DLQI was used in an exploratory way during some of the clinical trials testing afamelanotide for EPP.

However, patients and expert physicians did not feel comfortable using the tool as, according to their assessment, it neither adequately reflected the characteristics of the EPP condition nor captured the treatment effects. Therefore, and because EPP is not a dermatological condition but an intoxication-type inborn error of metabolism and has unique features, the disease specific EPP quality of life instrument named “EPP-QoL” was developed by expert physicians together with Clinuvel. During the development of the EPP-QoL, feedback from EPP patients was collected and the instrument was psychometrically validated by an external company (Biolcati et al. 2015). As the development and validation process was performed while the clinical trials were already ongoing, slightly different versions of the EPP-QoL (18-item, 15-item and 12-item versions) were used in the different clinical trials and for patients receiving afamelanotide in compassionate use and early access schemes.

The quality of life data collected with the EPP-QoL shows a “substantial improvement in quality of life” (as stated by the Committee, Appeal Decision p.11; ¶ 60) which in the observational study in 115 patients receiving afamelanotide during compassionate use and early access schemes was sustained over a period of 6 years (Biolcati et al. 2015). In contrast, the DLQI did not show a significant improvement in quality of life measurements during the clinical trials and was not used thereafter.

Nonetheless, the ERG based their economic model on the DLQI data from the clinical trials, and stated as one of the reasons for their choice that “The DLQI has undergone extensive validation, we believe that it has face validity for use in EPP […]” (ERG report p. 77). The DLQI however has never been validated for EPP. The Committee expressed concerns regarding the ERG`s approach to use the DLQI data, amongst other considerations 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 […]” (FED p.12).

According to the ORPH-VAL recommendations, health care professionals and patients “have the expertise and experience to discuss HRQoL [health-related quality of life], burden of disease and patient preferences [67, 74, 75]. Clinical experts and patients may also help interpret the relevance of trial data, where endpoints might be unusual or not validated in the disease in question.” (Annemans et al. 2017). These ORPH-VAL recommendations have not been met in the ERG evaluation:

During the development of the EPP-QoL, feedback from EPP patients was collected. The patient feedback data collected in the Swiss treatment center between 2010 and 2011 in the Swiss patient cohort demonstrate that EPP patients rate the questions of the EPP-QoL as mainly “appropriate” or “very appropriate”, as elaborated below (Unpublished, 3.1.). Additional questions, e.g. on fatigue, might be considered for inclusion in future versions as the EPP-QoL is further improved in preparation for a full validation.

In addition, we performed a review of the ERG’s “Face validity of content and framing” analysis (ERG report p.94) on the comparability of the DLQI and EPP-QoL tools. Our analysis shows that amongst other issues the ERG was only able to match 5 out of 10 questions of the DLQI with questions from the current version (12-item) of the EPP-QoL. The

comparability of the two tools is further compromised by unspecific questions and the lack of sensitivity of the DLQI for treatment effects in the EPP condition (see 3.2.10).

According to the ERG, “The appropriateness of the DLQI and EPP-QoL questionnaires for EPP is central to the interpretation of the clinical effectiveness and cost-effectiveness evidence.” (ERG report p.94). We therefore put forward that data collected by a tool which knowingly underestimates the benefit of the first effective treatment in an ultra-rare condition is not an appropriate basis to model the cost-effectiveness. As even the Committee expressed their concerns, below we present additional and new evidence on the topic.

3.1. The questions asked in the EPP-QoL are rated as appropriate by the patients

For the development of the EPP-QoL, in the Swiss treatment center expert physicians together with several EPP patients discussed the content and wording of the questions to optimally capture the nature of the condition and the aspects most relevant for the patients. The original EPP-QoL questionnaire had 18 items and an additional global rating of the perceived quality of life on an 11-point Likert-type scale (with 0 being the worst imaginable and 10 being the best imaginable quality of life) for the current time point and, retrospectively, for their adolescence and for their childhood. In addition, in the 18-item version, all patients were asked to rate how appropriate they perceive every questions to capture the symptoms of their EPP condition.The rating was placed adjacent to each specific question. This original version of the EPP-QoL was then further developed and psychometrically validated by an external company (Oxford Outcomes, Biolcati 2015), which also adjusted the scoring algorithm to allow comparability between data obtained by the different versions.

Between 2010 and 2011, 14 Swiss EPP patients received the afamelanotide treatment and were asked to answer the EPP-QoL (18-item version). All patients signed a written informed consent before providing the data and the presented analysis was performed as part of a biobank project and has been approved by the cantonal ethic committee in Zurich (BASEC-No.: 2018-00131). Following, we present the results of the patients’ rating of the appropriateness of the questions for all questions present in the 15-item and 12-item EPP-QoL version (which are the underlying versions for the evaluation by NICE). The wording of the question regarding the appropriateness of each quality of life – question was:

**In order to capture the symptoms of EPP, the questions is[&]:**
**Very appropriate**
**Appropriate**
**Less appropriate**
**Inappropriate**

[&]own translation. Original wording in German: Um die Beschwerden der EPP zu erfassen ist diese Frage: sehr geeignet / geeignet / wenig geeignet / ungeeignet.

Below, we present a summary of the rating for all 15 questions and in addition the rating for each of the questions individually. The wording of the questions was derived from Langendonk et al. (2015), Supplement p.108. Questions with an asterix (*) are only present in the 15-item version of the EPP-QoL, and have been removed from the 12-item version (concerns Q2*; Q3* and Q9*).

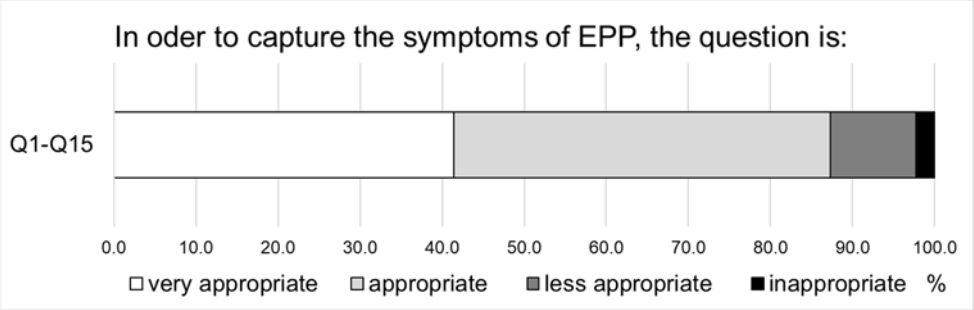
Results

Between 2010 and 2011, in the Swiss treatment center 14 EPP patients (the participants of the CUV010 and CUV017 trials) received the afamelanotide treatment and were asked to answer the EPP-QoL, which contained in addition to the quality of life questions also the rating on the appropriateness of each question. 11 of the 14 patients (73%) provided a rating

of the questions, each person on average assessed 2.9 questionnaires (mean; median 3, range 1 – 6). For each question, on average 31.7 (mean, range 30 – 33) ratings were obtained. Currently, 38 EPP patients in Switzerland receive the treatment, which means that 29 % of the Swiss cohort are covered by the analysis, and we rate the results as representative.

3.1.1. Summary rating on the appropriateness of all questions in the EPP-QoL (15-items):

On average, 87.3 % (mean; median: 90.3 %; range: 67.8 % - 93.7 %) assessments rated the questions as appropriate or very appropriate. The questions were rated as being inappropriate by on average 2.3 % (mean, median: 0 %, range 0 % - 12.5 %) of the answers given.

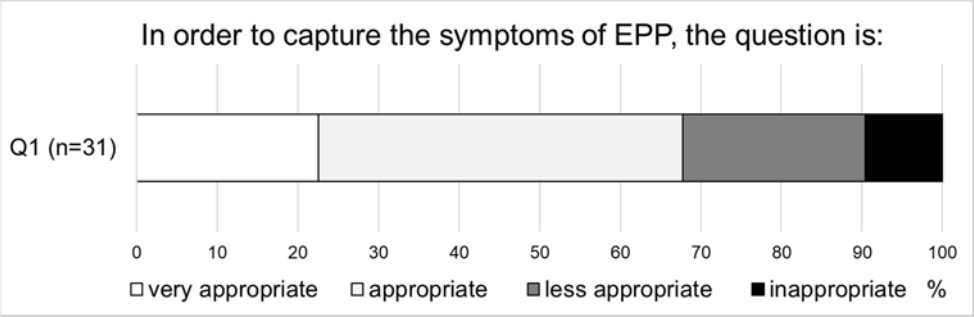



3.1.2. Rating on the appropriateness of single questions in the EPP-QoL (15-items):

Below, we present the ratings for the single questions (Q1-Q15) and highlighted the two questions assessed as being least appropriate and the two questions being assessed as most appropriate.

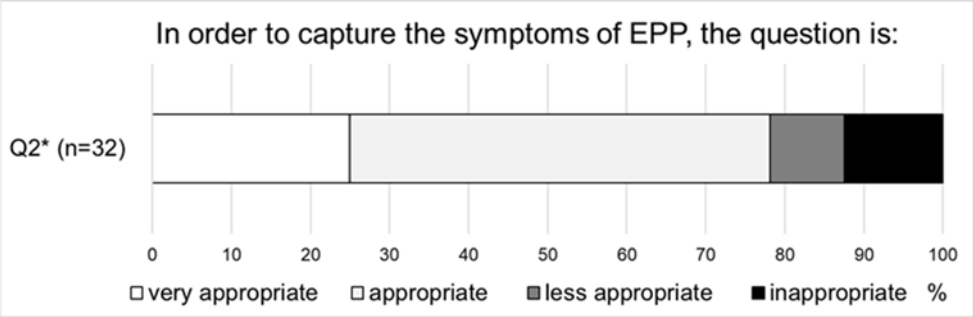
Q1: Over the last two months, how has your well-being been affected by EPP?

With 32.3 % of the answers rating the question as less appropriate or inappropriate (9.7 % of the answers rate the question as being inappropriate) Q1 is the question assessed as the least appropriate by the cohort. Only 22.6 % of the obtained ratings assessed the question as very appropriate.



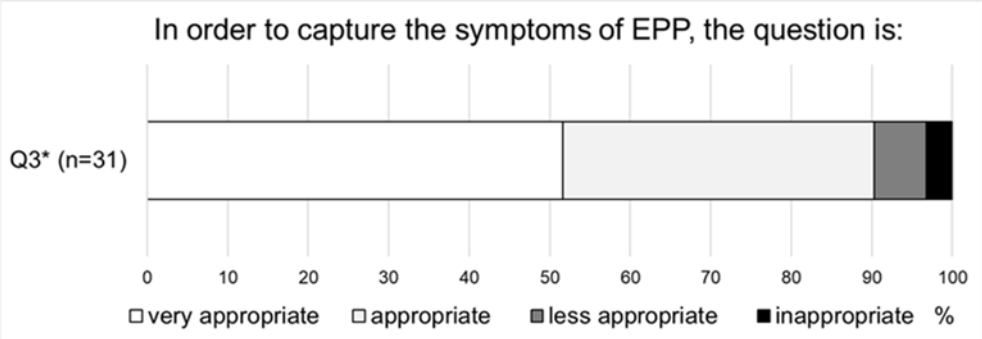

3.1.3. Q2*: Over the last two months, how much has your EPP symptoms influenced your capacity to go to work or school?

With only 78.1 % answers rating the question as very appropriate or appropriate, Q2 has the second worst rating of all questions in the questionnaire. In addition, 12.5 % of all ratings given assess the question on how much EPP symptoms influenced the capacity to go to work or school as inappropriate, which is the highest percentage of negative rating of all questions in the questionnaire.



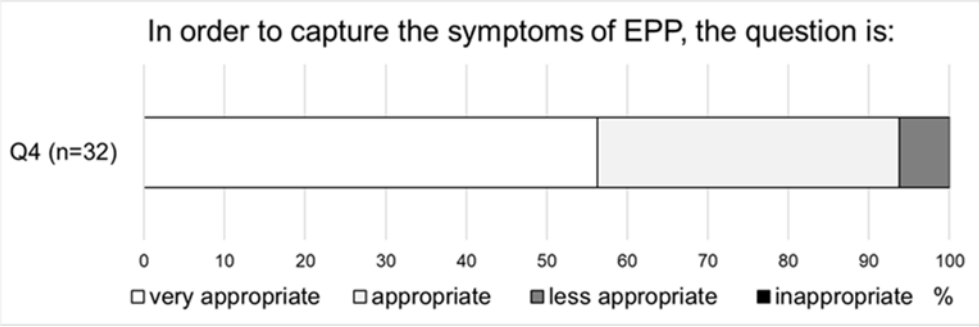

3.1.4. Q3*: Over the last two months, how often did you feel the need to seek out shade?

Seeking shade was rated in 90.3 % of the answers given as an appropriate or very appropriate questions to capture the symptoms of EPP.



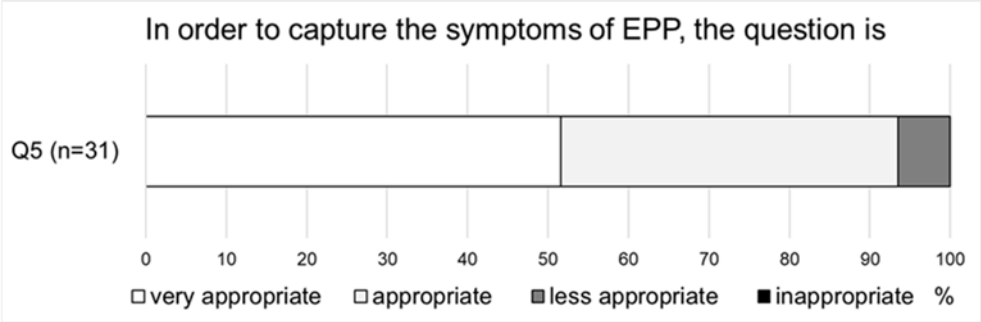

3.1.5. Q4: Over the last two months, how much has EPP influenced the choice of the clothes you wear on a sunny day?

93.8 % of the ratings assessed the question if EPP influenced the choice of the cloth on sunny days as very appropriate or appropriate, and no negative ratings were obtained. Q4 therefore is the best rated question of the EPP-QoL, with 56.3 % of the answers rating Q4 as very appropriate.



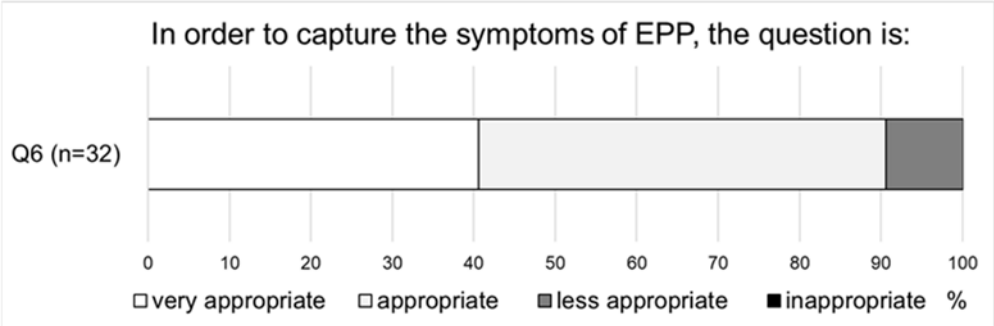

3.1.6. Q5: Over the last two months, how often did you feel you were at risk of developing EPP symptoms?

93.5 % of the ratings assessed the question “Over the last two months, how often did you feel you were at risk of developing EPP symptoms?” as appropriate or very appropriate. No negative ratings were obtained.



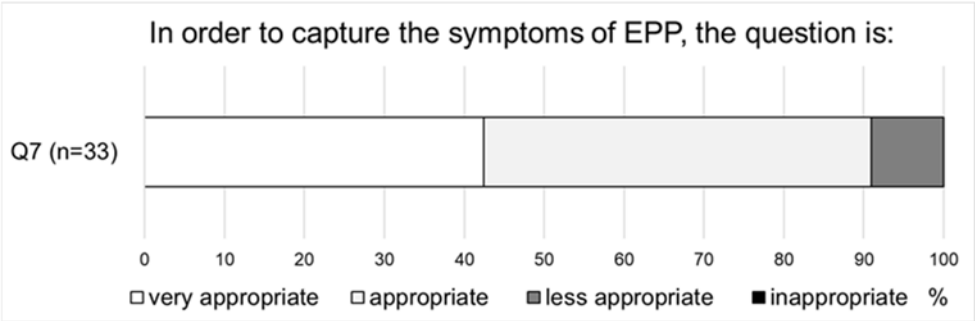

3.1.7. Q6: Over the last two months, how much has EPP affected any social or leisure activities on a sunny day?

90.6 % of the ratings assessed Q6 as very appropriate or appropriate, and 0% as inappropriate.



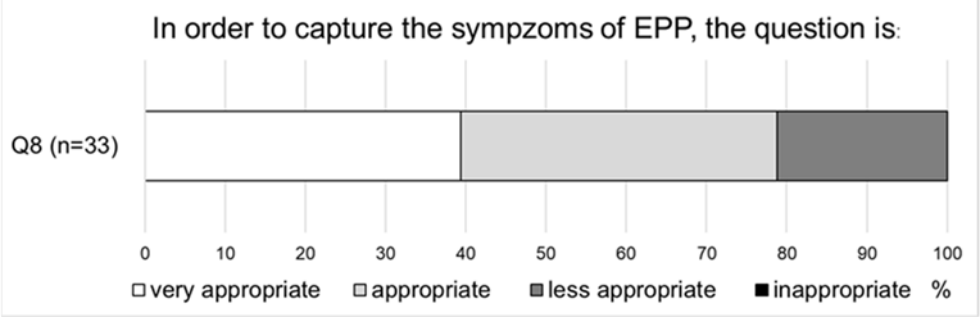

3.1.8. Q7: Over the last two months, how much has EPP influenced your need to plan before leaving your house?

90.9 % of the ratings assess Q7 as very appropriate or appropriate, and 0% as inappropriate.



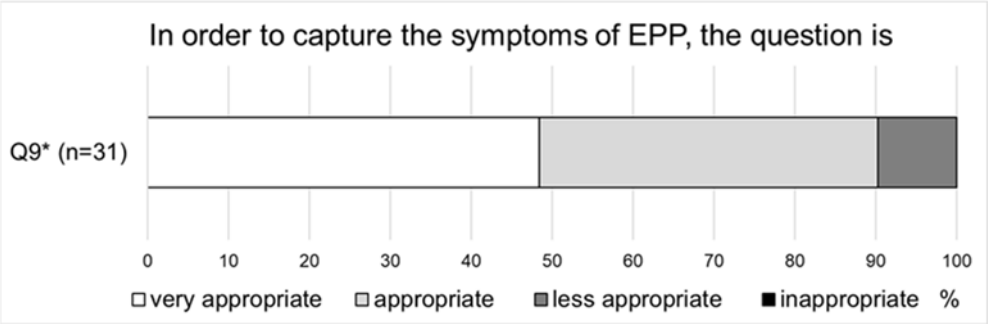

3.1.9. Q8: Over the last two months, has EPP limited your ability to undertake activities in a spontaneous manner?

78.8 % of the ratings assess Q8 as very appropriate or appropriate, and 0% as inappropriate.



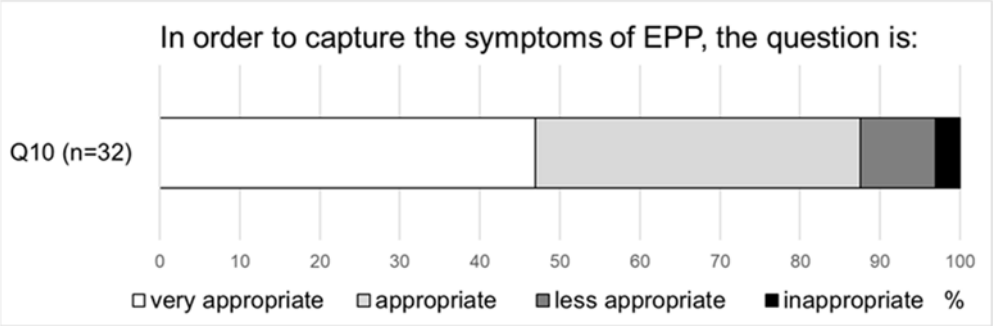
3.1.10. Q9*: Over the last two months, how often have you not worn protective clothing on a sunny day?

90.3 % of the ratings assess Q9 as very appropriate or appropriate, and 0% as inappropriate.



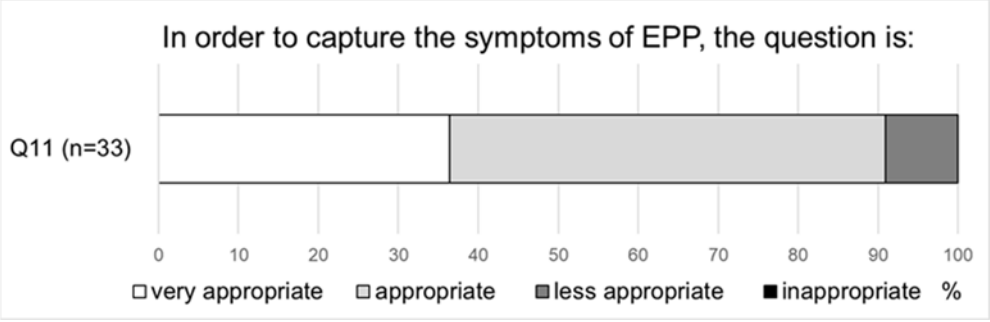

3.1.11. Q10: Over the last two months, how much has EPP interfered with your going shopping or looking after your home (indoors and outdoors) or garden on a sunny day?

87.5 % of the ratings assess Q10 as very appropriate or appropriate, with 3.1 % ratings as inappropriate.



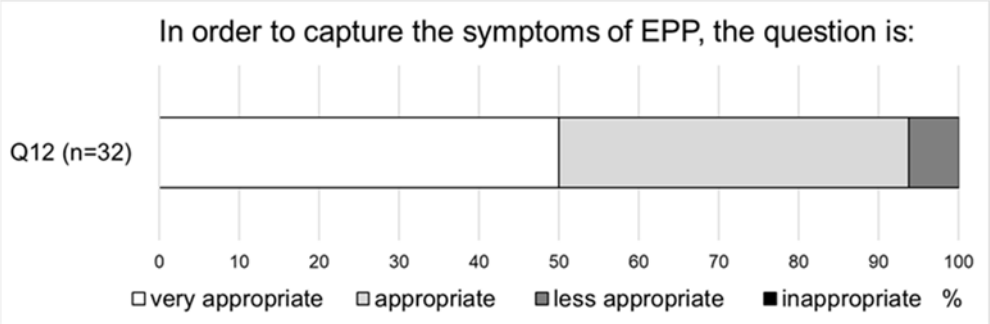

3.1.12. Q11: Over the last two months, how much has EPP prevented you from attending outdoor social activities with family and friends?

90.9 % of the ratings assess Q11 as very appropriate or appropriate, and 0 % as inappropriate.



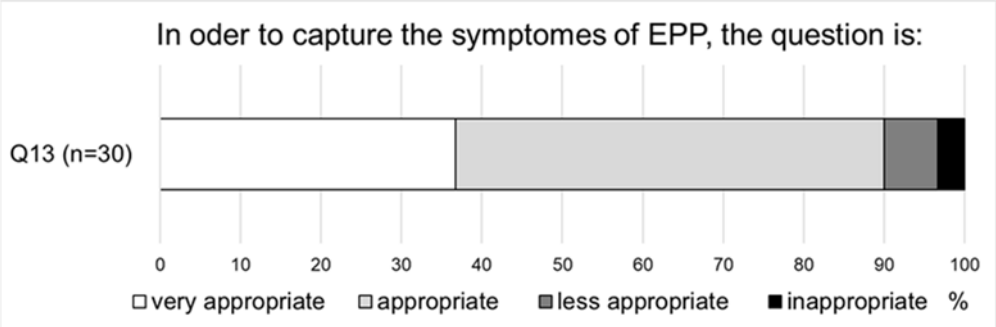

3.1.13. Q12: Over the last two months, how much has EPP limited your amount of outdoor activities?

93.8 % of the ratings assess Q12 as very appropriate or appropriate, and 0 % as inappropriate. Q12 therefore is the second best rated question of the questionnaire.



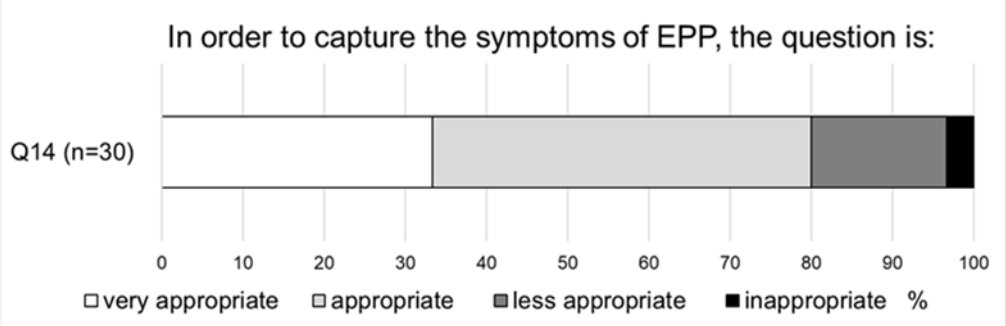

3.1.14. Q13: Over the last two months, how often did you experience typical EPP skin complaints?

90 % of the ratings assess Q13 as very appropriate or appropriate, with 3.3 % ratings as inappropriate.



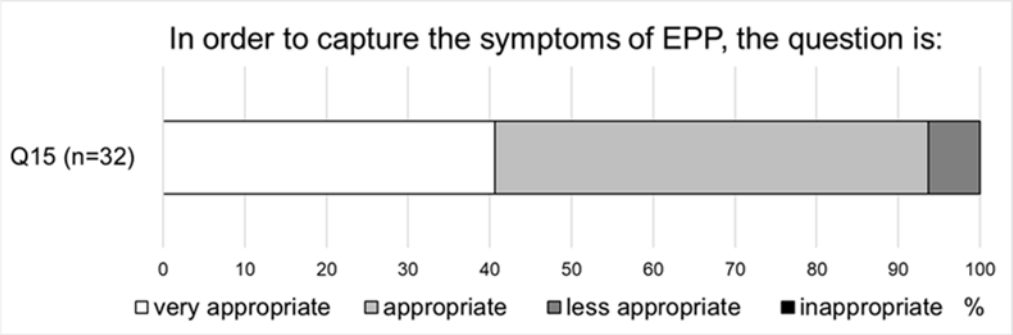

3.1.15. Q14: Over the last two months, how much has your quality of life improved?

80 % of the ratings assess Q14 as very appropriate or appropriate, with 3.3 % ratings as inappropriate.




3.1.16. Q15: Over the last two months, how much has EPP influenced your method of transportation or seating preference during transportation?

93.7 % of the ratings assess Q15 as very appropriate or appropriate, and 0 % as inappropriate.




Discussion:

Summary rating of Q1-Q15

On average, all questions together (Q1-Q15) obtained a rating of being 87.3 % appropriate or very appropriate (mean; median: 90.3 %; range: 67.8 % - 93.7 %). The questions were rated as being inappropriate only by on average 2.3 % of the answers (mean, median: 0 %, range 0 % - 12.5 %).
We in addition analysed the rating of the self-perceived quality of life as assessed by the 11-point Likert-type scale (with 0 being the worst imaginable and 10 being the best imaginable quality of life) for the current time point, which was part of the 18-item EPP-QoL with the outcome of the quality of life measurements (as assessed with the EPP-QoL questions). A Pearson`s r of 0.647 ($p < 0,0001$; Analyse-it v4.51 for Excel) was achieved, which suggests that the self-perceived quality of life in EPP patients is captured to a high degree by the questions in the EPP-QoL.

These results demonstrate that at large EPP patients rate the questions of the EPP-QoL as covering aspects important for their EPP condition. In addition, the detailed analysis of each question provides an overview which of the questions were rated more or less appropriate. Some of the ratings of individual questions are discussed in detail below.

Q1: Over the last two months, how has your well-being been affected by EPP?

With only 67.8 % of the answers rating the question “Over the last two months, how has your well-being been affected by EPP?” as appropriate or very appropriate, Q1 is the question assessed as the least appropriate of the EPP-QoL (15-item version). In addition, 9.7 % of the ratings assessed the question as inappropriate. In the ERG report is noted, that “Unlike the DLQI, the EPP-QoL includes a direct question on well-being” (p. 95), but no further discussion or conclusion is provided.

Q2*: Over the last two months, how much has your EPP symptoms influenced your capacity to go to work or school?

With only 78.1 % answers rating the question as appropriate or very appropriate, Q2* has the second worst rating of all questions in the EPP-QoL (15-item version). In addition, 12.5 % of all ratings given assess the question on how much the EPP symptoms influenced the capacity to go to work or school as inappropriate, which is the highest percentage of negative rating of all questions in the questionnaire. The ERG expressed concerns because “the EPP-QoL (12-item version) excludes questions on feelings and ability to work or study, which are important aspects of life” (ERG report p.95). However, EPP patients themselves did rate that the question is of limited appropriateness in the context of EPP. This may be due to the fact that EPP patients develop coping strategies for compensating their incapability in order to remain able to go to school or work, and subordinate this aim all other aspects of life, such as they limit or suppress their leisure, social and family activities (personal communications). For further discussion see 3.2.

Q3-Q7, Q9:

All questions obtained ratings above 90 % (90.3 % – 93.8 %) as being appropriate or very appropriate, and only Q3 (Over the last two months, how often did you feel the need to seek out shade?) has 3.2 % ratings as being inappropriate.

Q10-Q12 on “outdoor activities”:

The ERG criticized that “The EPP-QoL also emphasises the ability to perform outdoor activities on sunny days, but does not measure the relative importance of these activities to the individual.” (ERG report p.95). Q10, Q11 and Q12 in the EPP-QoL specifically ask about outdoor activities, and our analysis provides evidence that the patients rate this aspect as very important: All three questions were rated by at least 87.5 % of the assessments given as very appropriate or appropriate, and Q12 is even the second best rated question of the EPP-QoL (Q12: Over the last two months, how much has EPP limited your amount of outdoor activities?): 93.8 % of the answers rated Q12 as appropriate or very appropriate. The importance of outdoor activities on sunny days, respectively not being able to perform said outdoor activities can be also depicted from the patient testimonies (see section 2).

Q14: Over the last two months, how much has your quality of life improved?

80 % of the obtained ratings assessed Q14 as appropriate or very appropriate, and 3.3 % of the ratings assessed the question as being inappropriate.
The ERG stated that it was “concerned about the framing of the quality of life question (Q14), which does not allow for the possibility of deterioration” and point out that this represents a potential source for bias (ERP report p. 95). We agree with this critic but point out that the overall impact of the improper wording only affects 1/12 of the results at maximum (12-item version) or 1/15 of the results in the 15-item version.
We examined the German version of the EPP-QoL, which is the one used for the presented analysis. In contrast to the English version, the wording in the German version is neutral, asking not for an “improvement” of the quality of life, but for a “change” in quality of life. Therefore, the possible answers are balanced in regard of improvement or deterioration: “Over the last two months, how much has your quality of life changed: Very much/much/not much/not at all.” (Original wording in German: “Wie stark hat sich in den letzten beiden Monaten Ihre Lebensqualität bezogen auf die EPP verändert?” Sehr stark/ Stark/ Wenig/ Überhaupt nicht).
As the German version of the question was not affected by the improper wording, the presented assessment of the appropriateness is not affected by the wording. In addition, the studies using the German version of the EPP-QoL, which includes the Swiss cohort in the eight-year observational study (Biolcati et al. 2015), is not affected.

Conclusion:

12 of the 15 questions of the EPP-QoL were assessed as being appropriate or very appropriate in ≥ 80 % of the ratings given, and 10 questions even were assessed as being in ≥ 90 % appropriate or very appropriate. While there is room for improvement, and a full validation of the EPP-QoL should be carried out, the questions in the tool already reflect to a very high degree aspects rated as relevant and appropriate to capture the characteristics of the condition by the EPP patient cohort. In addition, as the rating was conducted in patients receiving the treatment, the high ratings also reflect that patients assess the EPP-QoL tool as appropriate to capture treatment effects in EPP.

3.2. The DLQI is inappropriate to measure treatment effects in EPP – review of the ERGs comparison of the DLQI with the EPP-QoL

The ERG claims that because: “The DLQI has undergone extensive validation, we believe that it has face validity for use in EPP and that it has been shown to reflect marked impairment in quality of life for people with EPP [17].” (ERG report p. 77).

However, only because the DLQI “has been shown to reflect marked impairment in quality of life for people with EPP”, it is not automatically a suitable instrument to also measure treatment effects – during the time Holme et al. (2006) performed the cited measurement using the DLQI in a cohort of British EPP sufferers (reference 17 in the ERG report), no effective treatment was available for EPP and no conclusion on the ability to measure treatment effects using the DLQI can be drawn from that study.

The ERG presents “a summary comparison of the content of the DLQI and EPP-QoL”, named “Face validity of contend and framing”. (ERG report p. 94). We reviewed the ERGs analysis on the comparability of the questions in the DLQI (DLQI Q1-Q10) and the EPP-QoL (EPP-QoL Q1-Q15) and present the results for category of questions below. We first discuss the effects of the limited sampling period and the absence of weather specifications (named “concepts”) in the DLQI and later present the analysis for the categories of questions in the order they are presented in the ERG report (table 27, p.97):

3.2.1. Concepts: Absence of weather specification and effect of the sampling period

The sampling period of the DLQI comprises the last week (7 days), while the EPP-QoL has a sampling period of the last two months and in addition specifies that the sampling time only consists of the sunny days and / or the time spent outdoors during those two months.

Table 27, ERG report p. 97: Excerpt on “concepts”

**Table 27 Comparison of questions from DLQI and EPP-QoL**

| Concepts[a] | DLQI questions[b]<br>Over the last week, how much has skin affected... | EPP-QoL questions[c]<br>Over the last two months, how much has EPP affected... |
|---|---|---|

Absent weather specifications

The specification in the EPP-QoL that the sampling period only contains sunny days / time spent outdoors is crucial because the phototoxic reaction in EPP only develop after exposure to light, the main trigger factor is sunlight. Not selecting for sunny days strongly reduces the sensitivity and specificity of the tool: The absence of EPP symptoms could be either caused by the high effectiveness of a treatment - or completely unrelated to the treatment, like for example due to bad weather condition or indoor occupation. This identified limitation concerns all questions in the DLQI.

Sampling period of one week

The sampling period in the DLQI is seven days, however, as the weather conditions are volatile and several other factors might limit the time spent outdoors (for example having a flue, high workload etc.), only including the last seven days of the two-month treatment period is not a representative sample but introduces a substantial sampling error and reduces the sensitivity to detect and quantify treatment effects.

The ERG in its report questioned the reliability of the two-month recall period and assumes a recall bias: “Another important difference between the two questionnaires is the recall period - one week in the DLQI and two months in the EPP-QoL. Again, it is unclear which is more

appropriate, as a longer recall period reduces the risk of missing periods of time when EPP may have had less of an effect on patients' lives, but it does also increase the risk of recall bias." (ERG report p. 95-96). However, the fully validated quality of life questionnaire MetabQoL 1.0 for pediatric patients with intoxication-type inborn errors of metabolism does have a recall period of 12 months (Zeltner et al. 2016). Therefore, while the potential for a recall bias for longer sampling periods (e.g. 2 months) has to be discussed, even considerably longer recall periods (12 months) did not prevent a disease specific quality of life instrument to become fully validated in diseases with similarity to EPP.

For EPP, shorter sampling times are associated with a substantial sampling error by for example volatile weather conditions. The less suitable sampling period and the missing specifications for the relevant weather conditions are limitations concerning all questions in the DLQI and adversely affect both the sensitivity to detect treatment effects and their quantification.

3.2.2. Symptoms: Limited overlap between symptoms in the DLQI and the unique EPP symptoms

ERG report p. 97: Table 27, excerpt on "symptoms"

| | | |
|---|---|---|
| Symptoms | Q1. Itchy, sore, painful or stinging | Q5. Frequency at risk of developing EPP symptoms<br>Q13. Frequency of typical EPP skin complaints<br>~~Q3. Frequency of need to seek out shade~~ [d] |

While "painful, itchy and stinging" could be used to describe the symptoms in EPP, the skin usually does not become "sore" because of the phototoxic reactions. The description "typical EPP symptoms" is more specific and in addition discriminates between EPP symptoms and other skin conditions which the patient might suffer from in addition. Moreover, the question asking for the "risk of developing EPP symptoms" includes not overt manifestations, but the necessity for avoidance strategies that, as we discussed above, impairs the patient's condition to function normally as a subject in the society.

3.2.3. Feelings: No corresponding question

ERG report p. 97: Table 27, excerpt on "feelings"

| | | |
|---|---|---|
| Feelings | Q2. Embarrassed or self conscious | |

"Feelings" like distress or anxiety (ERG report p.69) could indeed be considered as an additional outcome measure, however we stress that when included into a quality of life instrument, also the specific circumstances need to be captured adequately. In addition, in our experience EPP patients conceal their embarrassment by their condition and we have the following explanation: (1) they have frequently experienced to be accused of malingering, (2) they previously have experienced most extreme pain conditions (VAS10/10), so that they suppress the memory of it like observed in persons affected by Post traumatic stress disorder, (3) if they try to protect themselves from light, they are exposed to stigmatization, (4) the diagnosis is often delayed for more than a decade, which together with the above mentioned points (1) and (2) causes the patients to conceal and suppress the feelings of embarrassment.

3.2.4. Daily activities

ERG report p. 97: Table 27, excerpt on “daily activities”

| | | |
|---|---|---|
| Daily activities | Q3. Going shopping, looking after home or garden<br>Q4. Clothes you wear | Q10. Going shopping, looking after home or garden on sunny day<br>Q4. Choice of clothes on sunny day<br>~~Q9. Frequency not wearing protective clothing on sunny day~~ [d]<br>Q15. Transportation method or seating preference |

Relevance of the questions is dependent on the weather conditions

For the questions DLQI Q3 and DLQI Q4 on shopping, looking after home or garden and choice of clothes the same limitations apply as discussed above: Without specification that only the sunny days are relevant, the questions become meaningless in the context of EPP.

EPP-QoL Q15: Transportation method or seating preference are one of the most important factors for EPP patients

For the question Q15 in the EPP-QoL on “transportation method or seating preferences”, no matching questions exists in the DLQI. This question however is an excellent example for the uniqueness of the EPP condition: In skin conditions transportation and seating preference is not a relevant concern and therefore such a question is not included in the DLQI. This is in stark contrast to EPP, a condition in which managing the way from one destination to another (home to school or work, traveling to a conference etc.) is one of the biggest concerns, as those are the moments when EPP patient have the least control over their environment but the most risk to be exposed to sunlight. EPP patients take measures like choosing their flat in vicinity to their workplace, checking out the safest way to a destination in advance for example by google earth research or they travel during night only, many make sure to only sit on the window seat during a flight in order to control the shutter and to never sleep during travels as the vehicle might take a turn and expose the patient to sunlight while sleeping. As not all aspects always can be planed ahead or in accordance with the needs of the EPP patient - for example when traveling in groups or when all seats in the transportation vehicle are occupied - traveling and transportation are some of the biggest stress factors for an EPP patient.

The importance of the aspects asked in EPP-QoL Q15 are reflected in the very high rating on the appropriateness of the question (see analysis 3.1.16): 93.7 % of the ratings assessed EPP-QoL Q15 as very appropriate or appropriate, and 0 % as inappropriate. By using the DLQI only, this important feature is not reflected in the quality of life outcomes.

3.2.5. Social and leisure activities

ERG report p. 97: Table 27, excerpt on “social and leisure activities”

| | | |
|---|---|---|
| Social and leisure activities | Q5. Social or leisure activitites<br>Q6. Sport | Q6. Social or leisure activities on sunny day<br>Q11. Outdoor social activities with family and friends<br>Q12. Amount of outdoor activities<br>Q7. Need to plan before leaving house<br>Q8. Ability to undertake activities in spontaneous manner |

Treatment effects are not captured without a specification on outdoor activities and / or sunny weather conditions

EPP is a chronic condition and the patients are at a constant risk to develop painful phototoxic reactions when exposed to light. Therefore, whenever possible, EPP patients plan their social, leisure or sport activities accordingly. By not specifying that only social and leisure activities and sports outdoors and / or on sunny days should be reported, the treatment effect is missed by the DLQI: “However, patient and EPP experts have confirmed that the increase in outdoor light exposure possible with Scenesse was enabling to alter patients’ quality of life and translated in the uptake of outdoor lifestyle.” (EPAR p.104).

The relevance of the “outdoor” aspect can be also depicted by the rating of the appropriateness of the EPP-QoL questions provided in 3.1. The question EPP-QoL Q12: “Over the last two months, how much has EPP limited your amount of outdoor activities?” is the second best rated question of the EPP-QoL with 93.8 % of the answers rating the question as appropriate or very appropriate.

The EPP specific requirement to plan ahead is not reflected in the DLQI

In addition, EPP is connected with a substantial amount of planning efforts to reduce uncertainties and stress (see also discussion on EPP-QoL Q15 above). No questions related to the need to plan ahead before an outdoor activity for example by checking the weather forecast can be found in the DLQI.

3.2.6. Work and study: No corresponding question (12-item version)

ERG report p. 97: Table 27, excerpt on “work and study”

| | | |
|---|---|---|
| Work and study | Q7. Prevented or problem with work or study | ~~Q2. Capacity to go to work or school~~ [d] |

All aspects of daily life are optimized by the EPP patients in order to not become incapacitated for work and other important duties

The ERG was specifically concerned that the question EPP-QoL Q2* on ability to work or study has been excluded for the 12-item version of the EPP-QoL: “But the EPP-QoL (12-item version) excludes questions on feelings and ability to work or study, which are important aspects of life.” (ERG report p. 95). However, when the patients in the Swiss cohort assessed the appropriateness of this question, it was rated as the second worst question with 22 % of the results of the survey stating that the question is less appropriate (9.4 %) or even inappropriate (12.5 %, see point 3.1.3). The 12.5 % of the answers rating the question as inappropriate is the highest amount of ratings as inappropriate of all questions in the EPP-QoL.

While the capacity to go to work or school might be restricted during an ongoing phototoxic reaction, the question for most of the time is not applicable for adult EPP patients: Most adult EPP patients have adapted their lifestyle according to their chronic condition and optimized their daily life to avoid light – and therefore symptoms – as best as possible. EPP patients would not be able to keep a job in case it would pose the patient at risk for frequent phototoxic reactions. Like persons bound to a wheelchair, most EPP patients have chosen a work compatible with their disability. In addition, EPP patients take precautionary measures to not be exposed to sunlight and therefore being incapacitated for work. This is also reflected in the low frequency of phototoxic reactions during the randomized controlled trials. This question therefore does not give a good estimation on quality of life in EPP, especially not if the sampling period only consists of one week like in the DLQI.

3.2.7. Personal relationships: No corresponding questions

ERG report p. 97: Table 27, excerpt on “personal relationships”

| | | |
|---|---|---|
| Personal relationships | Q8. Problem with partner, close friends or relatives<br>Q9. Sexual difficulties | |

This questions are only marginally applicable to the EPP condition: As EPP is a chronic, life-long condition partners, family members and close friends are usually adapted to the EPP condition as well.

3.2.8. Treatment: No corresponding question

ERG report p. 97: Table 27, excerpt on “treatment”

| | | |
|---|---|---|
| Treatment | Q10. Treatment problems, e.g. making home messy or taking time | |

This question is not applicable for the afamelanotide treatment, as it is a two-monthly slow release formulation with no additional complications. It could be applicable to other treatment options but for the current situation does not give a relevant outcome (noise).

3.2.9. Overall

ERG report p. 97: Table 27, excerpt on “overall”

| | | |
|---|---|---|
| Overall | | Q1. Well-being<br>Q14. Quality of life |

The EPP-QoL is the first attempt to specifically measure quality of life in EPP, and the patients were asked to provide self-perceived quality of life scores in addition to answering questions about specific aspects of EPP. Question Q14 on self-assessed quality of life was rated as being 80 % appropriate or very appropriate, which is one of the lower ratings.

As discussed in 3.1.2., question EPP-QoL Q1 (well-being) was rated as the least appropriate question in the EPP-QoL with 32.3 % assessments rating the question as less appropriate or inappropriate.

3.2.10. Summary comparison of the EPP-QoL and the DLQI. Quantitative assessment – review of the “Face validity of contend and framing”-analysis

Based on the review of the ERGs analysis on the comparability of the DLQI and the EPP-QoL named “Face validity of contend and framing” (ERG report p. 94), we tried to quantify the overall impacts on sensitivity and specificity in case the DLQI is used instead of the disease specific instrument EPP-QoL.

| **EPP-QoL** | **DLQI** | **Impact** | **Comment** |
|---|---|---|---|
| Sampling period 8 weeks (8 out of 8 weeks between the treatments) | Sampling time 1 week (1 out of 8 weeks between the treatments) | 87.5 % loss in sensitivity when using the DLQI | Due to the conditioned light avoidance and the dependence on external factors (light exposure, weather conditions etc.), phototoxic reactions are occasional events and the probability to miss them is |

| | | | |
|---|---|---|---|
| | | | higher, the shorter the sampling time |
| Sampling only on sunny days/ during outdoor activities | No distinction of the weather conditions or in regard to indoor/ outdoor activities | Approx. 20 % loss in sensitivity in the DLQI, 7 out of 10 (70 %) of the questions in the DLQI affected (underlying assumption that 1 in 5 days the weather is not sunny). In addition, the missing distinction between indoor and outdoor activities renders the questions unspecific. | The sampling period is further compromised by volatile weather conditions. This also introduces a substantial sampling error (for example if the weather was cloudy during the week used for baseline determination, all subsequent measurements will be affected by this one week) |
| 12 (15) questions | From the 10 questions in the DLQI, only 5 could be matched by the ERG to questions in the EPP-QoL with related content | 50 % noise in the DLQI: 5 out of 10 (50 %) questions in the DLQI do not have a roughly matched partner question in the EPP-QoL (in the ERGs own comparison; 12-item version) and are of unknown / less significance for the EPP patients (see discussion of those questions above: DLQI Q2,Q7,Q8,Q9,Q10) | Questions in the DLQI without an equivalent in the EPP-QoL are of unknown significance for the EPP patients, and some of the questions (DLQI Q10 on problems with the treatment) are not applicable. Only disease experts should base a comparison on “face-validity”, as disease specific aspects are not known to non-specialists, see question on “work”, DLQI Q7(but even disease experts would need to validate their assumptions).<br>From a statistical point of view, the noise induced by the questions not related to the EPP condition reduces or abolishes statistical significance. |
| Disease specific and relevant aspects present (need to plan ahead: EPP-QoL Q7 and Q8, transportation and seating preference: EPP-QoL Q15) | No corresponding questions | 20 % - 25 % relevant outcomes missed in the DLQI: 3 out of 15 questions (15-item version) or 3 out of 12 questions (12-item version) in the EPP-QoL do not have a corresponding partner question in the DLQI, but cover aspects highly relevant for the patients (like see analysis 3.1.) | Aspects important in EPP are not represented in the DLQI, which makes the DLQI less sensitive and specific for EPP |

Conclusion:

With our review of the “Face validity of contend and framing”-analysis (ERG report p. 94) we showed that the DLQI and the EPP-QoL are not interchangeable, as assumed by the ERG. In the comparison provided by the ERG only 5 of the 10 questions of the DLQI do have a counterpart from the EPP-QoL, which means that 50 % of the DLQI questions give unspecific readouts of unknown significance (“noise”). In addition, disease specific aspects rated as relevant by the patients like seating preferences, transportation method and the need to plan ahead are not covered by the DLQI. On top of that, the sampling period of the DLQI questions only covers the last seven days, and does not differentiate if those days were sunny (relevant) or not (not relevant), which introduces a substantial sampling error. Only disease experts should base a comparison on “face-validity”, as diseases specific aspects are not known to non-specialists (see question on “work”, DLQI question Q7), but even disease experts would need to validate their assumptions.

We therefore strongly disagree with the assumption of the ERG that the DLQI data sufficiently reflects treatment effects in EPP and can be used for economic modelling of the benefits. While the EPP-QoL needs further development and a full validation, the DLQI clearly cannot be rated as an appropriate tool in EPP. Moreover, the DLQI data should not be used because it would be illogical to use a Patient Reported Outcome Measure which is not accepted by the patients.

3.3. Further concerns and uncertainties

Further concerns and uncertainties expressed by the Committee and /or the Appeal Panel and benefits of afamelanotide which may not have been captured in the committee’s previous deliberations in relation to quality of life in EPP are discussed below:

3.3.1. The EPP-QoL is only partly validated – but the DLQI is not validated for EPP at all

The Committee expressed concerns that the EPP-QoL tool is not yet fully validated: “The committee concluded that it would take the EPP-QoL into account in its decision-making but that, without full and appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide.” (FED p.12)

However, the DLQI has not been validated for EPP at all. EPP is a unique, intoxication-type inborn error of metabolism and not a dermatological condition. The EPP-QoL not only was developed together with disease experts and feedback from patients was obtained, it also is psychometrically validated by an external company (Biolcati et al. 2015). The validation of a quality of life instrument is a multi-step approach which has to be undertaken for each condition separately.
EMA’s “Guideline on Clinical Trials in Small Populations” (p.6) states “if quality of life is measured, it should always be assessed using scales validated for the particular indication being treated”. It is also recognised in the guideline “that sometimes there are too few patients for validation exercises as well as separate treatment evaluation”.

While we support that the EPP-QoL should be further developed and fully validated, the same concerns expressed by the Committee apply to the DLQI: Without full and appropriate validation, there is substantial uncertainty about how the DLQI could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide.

In addition, the HST has experience in the evaluation of disease specific quality of life questionnaires which are not fully validated, for example in the appraisal HST2 of elosulfase alfa for mucopolysaccharidosis type IVa (MPS IVa):

“QoL was measured using the MPS HAQ [MPS Health Assessment Questionnaire] in MOR-004, which is a disease-specific instrument developed to measure disability in patients with MPS over 8 years of age. It should be completed by the parent/care giver for children less than 14 years of age. There is no validated tool to evaluate QoL in MPS IVA.” (ERG report elosulfase alfa p.29).

Elosulfase alfa was recommended for reimbursement by the NHS within a Managed Access Agreement.

3.3.2. Clinical significance of the changes observed by the EPP-QoL and the DLQI

Holme et al. (2006) measured an impairment in quality of life in patients with EPP in the UK by using the DLQI. Based on these results, the ERG argues that the DLQI would be also an appropriate tool to capture treatment effects in EPP. However, only because the DLQI “has been shown to reflect marked impairment in quality of life for people with EPP” (ERG report p. 77), it is not automatically a suitable instrument to also measure treatment effects – during the time Holme and colleagues performed the cited measurement using the DLQI in a cohort of British EPP sufferers, no effective treatment was available for EPP and no conclusion on the ability to measure treatment effects using the DLQI can be drawn from that study.

The ERGs reasoning in the case of the DLQI is in stark contrast to their evaluation of the EPP-QoL, in which the ERG criticises for example that “The clinical significance of the changes in EPP-QoL results was unclear as minimal important differences have not been established.” (ERG report p.11).

As also no clinical significant changes have been established for the DLQI in the context of EPP, the ERG clearly applies different measures in their assessment of the two tools. Again, we support that the EPP-QoL has to be fully validated, however we are concerned by the inconsistencies in the evaluation of the tools by the ERG.

3.3.3. Minimal important differences are disease specific

The ERG further refers to significant changes in the quality of life scores obtained using the DLQI estimated for other conditions: “The ERG notes that for general inflammatory skin conditions (e.g. psoriasis, eczema) a change in DLQI score of at least four points is considered clinically important [23]. The largest change observed for afamelanotide was around eight points which is double the recognised minimal clinically important difference for general skin conditions.” (ERG report p. 61)

However, every (skin) condition has it`s individual minimal important differences, for example Shikiar and colleagues established the minimal important difference for chronic idiopathic urticaria between 2.24 points and 3.10 points using DLQI measurements. (Shikiar et al. 2005). This demonstrates that minimal important differences established for a particular skin condition cannot just be applied to other conditions.

Moreover, the ERG even implies that for EPP, higher scores for the minimal important difference should be applied: “It could be that a larger change in score on the DLQI is required to be clinically important (i.e. because the DLQI isn’t necessarily sensitive enough for this condition), though the magnitude of this change cannot be quantified at present.” (Committee papers December 2017, p. 54; slide: DLQI - ERG comments). We want to highlight the inherent unfairness of the suggested approach: The ERG basically argues that higher achievements have to be demonstrated in the case of EPP by a tool knowingly less suitable to also capture them.

3.3.4. Increase in the quality of life in the placebo group by using the EPP-QoL – why did the ERG not report that the same effect was present in the DLQI?

The Committee stated that is was concerned with the EPP-QoL data because an increase in quality of life was observed in the placebo group, too: “Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.” (Appeal Decision p.16; ¶ 94).

However, also in the DLQI, an increase in quality of life was observed in the placebo group: “DLQI scores between the study groups were comparable at baseline at the mid-point in the scale at around 10.4 to 10.7 out of 30 (scores of 6-10 indicate a moderate effect on a patient’s life and scores of 11-20 indicate a very large effect on a patient's life [22]). Scores declined over time in both groups to a nadir of 2.4 to 3.1 for afamelanotide and placebo respectively at day 180 (a score of between 2 to 5 indicates a small effect on a patient’s life [22]). The decline in scores was larger in the afamelanotide group, though differences between the groups in the change from baseline were not statistically significant.” (ERG report p. 60-61).

The EPP-QoL results were statistically significant in both trials:
CUV029: “The differences between the groups were statistically significant at days 120, 180, and 240.” (ERG report p.56)
CUV039: “Differences between the groups in the change from baseline were statistically significant at day 60, day 120, and day 180.” (ERG report p. 58)
In addition, the duration of the quality of life measurements in the long-term observational study was 6 years, and during this time the increase in the measured quality of life was sustained (Biolcati et al. 2015), which indicates a “real effect”.

As the effect on quality of life in the placebo group is observed in both tools, it is not an argument to prefer the DLQI over the EPP-QoL. Again, we are concerned that the mentioned effect in the placebo group was only pointed out for the EPP-QoL and not for the DLQI, which together with the other observed inconsistencies in the evaluation of the tools to measure quality of life in EPP (3.3.1.- 3.3.3) suggests an objectionable bias in the assessment.

## 4. Value for Money

The underlying calculations for quality adjusted life years (QALYs) and incremental cost-effectiveness ratio thresholds (ICERs) and the cost-effectiveness model used by NICE as a basis for their decisions are not accessible to us.
However, NICE published the criteria which inform their cost-effectiveness assessment in their "Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes". We provided new evidence which addresses concerns of the Committee and the Appeal Panel which hopefully clarifies aspects which not have been captured in the committee's previous deliberations. This new evidence on the nature of the condition, the clinical effectiveness and the impact of the technology beyond direct health benefits should to our understanding also modify several of the underlying assumptions which inform the criteria for the cost-effectiveness calculations, amongst others:

- The EPP condition is more severe than previously assumed by the Committee
- The effects measured in the clinical trials are not "small"
- Quality of life as measured with the DLQI is inappropriate to demonstrate the benefits of the afamelanotide treatment
- The testimonies received during the appraisal are reliable, representative and can be used for decision making (as the EMA did)
- It would not be unfair to make reasonable adjustments in the case of the appraisal of afamelanotide, because the HST considered other forms of evidence in other appraisals before (as shown in details for appraisal HST2)

We hope that with the new evidence provided and the findings of the Appeal Hearing the Committee will consider to recommend afamelanotide for reimbursement by the NHS. Following, we address further concerns expressed by the Committee regarding the feasibility of a Managed Access Agreement (MAA) and the cost-effectiveness of afamelanotide.

### 4.1. National value assessments of the afamelanotide treatment

The ORPH-VAL principle 9 recommends, that in order to avoid duplication of efforts and enable faster access to orphan drugs, national value assessments should be coordinated (Annemanns et al. 2017). In the case of afamelanotide, the current pricing was determined during the appraisal process in Germany in 2017 by an independent arbitration board, which on the one hand aimed to achieve cost-effectiveness for the German health care system and on the other hand balanced the interests of the payors against a reasonable return on investment for the manufacturer (https://www.g-ba.de/informationen/nutzenbewertung/217/.; Last accessed 17 Jan 2019). To our knowledge, the pricing asked for afamelanotide by the company in the UK is similar to the price in other countries where afamelanotide is available to EPP patients (Germany, the Netherlands, Italy, Austria and Switzerland).

In addition, we could identify information on pricing and budget impact in other HST appraisals performed and published by NICE so far, and find that afamelanotide has the lowest annual treatment costs per person: For afamelanotide the annual costs per person are between 36.060 GBP (three doses applied) to 48.080 GBP (4 doses applied) and can be as low as 12.020 – 24.040 GBP / year in a minority of patients who only require 1 to 2 doses as seen in the Swiss patient cohort. Most treatments which received a positive recommendation in the HST appraisals so far have annual costs per person approximately between 200.000 to 400.000 GBP (as published by NICE).
With 400- 500 EPP patients in the UK (EPP has a prevalence of 1:150.000) the overall budget impact is also lower than that for the other treatments so far recommended for reimbursement by the HST Committees. (**Side note: The comparison under no circumstances is meant to question the validity of the positive decision for funding for the treatments for those other severe and debilitating conditions**.)

In Ireland, a recent bill aims to reform the reimbursement process for orphan drugs by exempting them from health technology appraisals with heavy emphasis on ICER thresholds and QALYs. The bill also wants to introduce other criteria for considering whether to reimburse such drugs, including budget impact and the availability of the drug elsewhere in Europe. In addition, Scotland just passed new legislation to improve early patient access to 'ultra-orphan' drugs by introducing a system for provisionally funding such medicines while more evidence is gathered on their effectiveness. Ireland and Scotland thereby introduced highly commendable initiatives, recognising the challenges related to orphan drugs.

4.2. Feasibility of a Managed Access Agreement

The Committee during the appraisal process at NICE in agreement with the assessment of the EMA "…noted the possibility that deeply ingrained light avoidance behaviour may have influenced the trial results." (FED p.22). "The committee accepted that data collection in the context of a MAA [Managed Access Agreement] 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) and therefore did not recommend afamelanotide for use in the NHS in England within a MAA. (FED p.23)

However, the NICE Social Value Judgments - Principles for the development of NICE guidance Second edition, section 6.5 and 6.6 (see box 2) states that uncertainty in effectiveness of a treatment caused by behaviour is not a sufficient reason to deny access to a treatment, even if this behaviour impacts on the effectiveness of an intervention and routine quality of life assessments:

**Box 2:**

**Social Value Judgments - Principles for the development of NICE guidance; Second edition: Section 6: Avoiding discrimination and promoting equality:**

"6.5 Conditions associated with stigma
Some conditions, for example, sexually transmitted diseases and drug dependency, are associated with stigma. NICE does not consider that stigma itself is a reason for altering its normal approach to assessing cost effectiveness. However, NICE is aware that stigma may affect people's behaviour in a way that changes the effectiveness of an intervention and that the relief of stigma may not always be captured by routine quality of life assessments. Therefore, NICE expects its advisory bodies to take these considerations into account."

"6.6 Behaviour-dependent conditions
The Citizens Council advised that NICE should not take into consideration whether or not a particular condition was self-induced. It was often impossible, in an individual, to decide whether the condition was dependent on their own behaviour or not; and receiving NHS care should not depend on whether people 'deserved' it or not."

Social Value Judgments - Principles for the development of NICE guidance; Second edition: Section 6: Avoiding discrimination and promoting equality; p.24

In EPP, the conditioned light avoidance behaviour changes the effectiveness of interventions and, consequently, the effects of the afamelanotide treatment were not accurately quantifiable in the clinical trials. By making the afamelanotide treatment available to sufferers in the UK, it can be expected that the majority of these patients would also first need to unlearn their conditioned light avoidance behaviour, and would not immediately enjoy the full extent of the benefit. Nevertheless, it has been shown that most EPP patients manage to unlearn their behavioural adaptation (see section 2 and 3). In the case of EPP, it would be irrational to deny access to an effective treatment, only because its quantification is coupled

with uncertainties caused by necessary behavioural adaptations. This consequentially is also recognized in the NICE guidelines on Social Value Judgments.

In addition, the ORPH-VAL principle 5 recommends that “to accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time”. The working group in their publication further states that “Systematically collecting data from registries as well as implementing managed access schemes (where possible) could help mitigate the uncertainties and fill data gaps.” (Annemanns et al. 2017)

The EMA assessed that quantification of efficacy endpoints in the post approval phase are reasonable and feasible in EPP and as a condition of marketing authorization requires a Post-Authorisation Safety Study (PASS) which also includes efficacy endpoints: “The CHMP has recommended approval for Scenesse [afamelanotide] on the condition that the applicant puts in place a robust risk management plan that ensures close surveillance of the safety and efficacy of the medicine. As part of this plan, the company will establish a registry of patients to collect safety and efficacy data.” (Press release EMA/638997/2014; 24 October 2014).

Therefore, as the EMA already collects efficacy data from patients receiving the afamelanotide treatment in Europe it would be unreasonable and irrational for NICE to assume that this is not possible because of the uncertainties connected to evidence generation in EPP.

**Conclusion**

We demonstrated with new evidence and the outcomes of the Appeal hearing that:

a) The EPP condition is more severe than previously captured by the Committee and indeed qualifies as a disability (Appeal Decision p.9; ¶ 53)
b) The effectiveness, although not accurately quantifiable in randomised controlled trials, shall no longer be assessed as “small” (Appeal Decision p.12; ¶ 70) and the full extent of the benefit can be assessed when taking into account patient input as outcome measure
c) The DLQI is an inappropriate tool to capture the benefits of the afamelanotide treatment (section 3) and that
d) The possibility for an MAA should not be denied because of uncertainties caused by disease specific behavioural adaptations which interfere with an accurate determination of the efficacy (section 4.2.), which would also be illogical.

In addition, we are highly concerned by the observed lack of consistency in the evaluation provided by the ERG: In our submission, we report examples in which the ERG applied different assessment standards when they evaluated results by their preferred or alternative tools, ignored the best available evidence and presented analyses which do not stand up to close scrutiny.
As the ERG report informs the Committee on key aspects for their appraisal, we think that a critical evaluation of the ERG report and adaption of the conclusions presented is central for a fair and equitable appraisal process.

Lasty, we urge the Committee and the NHS to enable access to this life-changing treatment: EPP patients suffer second-degree burns in their blood vessels after very short exposure times to sunlight and strong artificial light sources. If during a barbeque someone accidentally suffered second-degree burns on the face and hands, they would be rushed to an emergency unit of a hospital, and everything possible would be done to alleviate the pain and treat the consequences of the burns. Until recently, EPP specialists could not offer their patients anything to either treat or prevent the massively painful phototoxic reactions. Now, with afamelanotide an innovative therapy exists which finally enables EPP suffers to live an almost normal life.

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**British Association of Dermatologists**
**Response to NICE Highly Specialised Technology Appraisal**
**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

On behalf of the British Association of Dermatologists, thank you for inviting us to the NICE meeting in order to address the upheld appeal points in the case of afamelanotide.

1) **Upheld Appeal Ground 1a.1: The committee failed to act fairly by demonstrating consistent discrimination against IPPN as a stakeholder group**
   We look forward to IPPN taking a full part in this NICE meeting. We strongly agree with the Appeal Panel that, given the extensive use, and much greater experience, of afamelanotide in treating EPP patients in other countries outside England (including Italy, Switzerland and several other countries), their long-term experience of treatment with afamelanotide in a real-world setting, their experience and their testimony is crucial to this process. With IPPN represented, NICE will have the opportunity to be provided with additional information about patients' experience from long-term treatment with afamelanotide.

2) **Upheld Appeal Ground 1b.1. (IPPN)**
   **Appeal Ground 1b.1: The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward**
   **And upheld Appeal Ground 1b.1 (CLINUVEL (UK) Ltd): NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities**
   Although these upheld appeal points were presented by IPPN and Clinuvel, the BAD strongly agrees with the Appeal Panel's decision and we have specific criticisms of NICE's qualitative evidence analysis methodology. It is critical that NICE has not followed its own procedure in terms of how it considers evidence in cases, like this, where the disease is rare and where the existing quality of life issues measures do not fully capture the quality of life issues in the disease. Specifically, NICE has been found by the Appeal Panel to have ignored its own 'Interim Process and Methods of the HST Programme' guidance, paragraph 41:

   *"The Evaluation Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Evaluation Committee to consider all of the evidence presented to it, including RCTs, observational studies and 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. In evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions."*

   This is a critical point in this case where the ICER has been used alone in determining the NICE Panel's decision, in a situation where ICER was clearly inadequate and where NICE's own guidance required them to take the qualitative evidence into account in making their decision. In this case, the qualitative evidence from patient (and also physician) testimony was of a striking and dramatically effective therapeutic effect. It is critical that NICE's re-evaluation of afamelanotide, in light of the Appeal Panel's decision, must take a proper account of the qualitative evidence. Formal Qualitative analysis, by methodology including Framework Analysis, is a well-established core set of methodologies in the Social Sciences and in Health Psychology. NICE has previously made no attempt to formally analyse the extensive qualitative interview evidence with which they were presented. NICE has never

indicated that they have sought out any Qualitative Analysis expertise at all, from a Health Psychologist or other relevant expert. NICE was unable to answer the question posed during the Appeal Hearing by Dr Sarkany as to what methodology they had used to objectively assess the qualitative evidence. NICE was also unable to answer the question as to how the analysis of this evidence was incorporated into the NICE Panel's decision. In fact, senior members of the NICE panel and NICE organisation, during the previous meetings, made it clear on several occasions that their decision was made entirely on the basis of the ICER calculation. In the light of the Appeal Panel's decision against NICE on this point, the BAD requests that 1) NICE agree to use a recognised Qualitative Analysis methodology with the expertise of Qualitative Analysis Experts to formally analyse the qualitative evidence presented to them by patients and physicians in the previous hearings, and that these Experts can request further qualitative evidence as required 2) NICE specify, create and use in this case a transparent methodology which enables formally analysed qualitative submitted evidence to be formally incorporated into the process by which the decision is made. This will enable NICE to comply with paragraph 41 of their own guidance.

3) **Upheld Appeal point Ground 2.2: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide (This appeal point was named BAD 2.1 in initial correspondence and during the hearing)**
**And Appeal point Ground 2.3: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide (This appeal point was named BAD 2.5 in initial correspondence and during the hearing)**
**And upheld Appeal point Ground 2.2: The evidence provided shows that the benefit is significant and not small, as assessed by the committee (This appeal point was named IPPN 2.1 in initial correspondence and during the hearing)**
The BAD notes that the Appeal Panel upheld our Appeal on this crucial issue. Specifically, the BAD disputes the committee's view that the clinical trial results suggest "small" benefits with afamelanotide. The average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). This is meaningful as it increases the average time spent by patients with EPP who are on treatment to the expected level for this measure. Data presented by Professor Rhodes has shown that healthy indoor workers spend an average of only 22 minutes outdoors between 10 am and 3 pm on summer weekdays.[1] Several publications also show that time spent outdoors throughout the day (6 am to 8 pm) by the average person is of the order of minutes, not hours, i.e. minutes are of consequence: minutes matter. Moreover, it should be noted that time spent in direct sun may be less that time spent outdoors. The figure of approximately 10 minutes extra per day of sun exposure represents an average daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest. We note the testimony of James Rawnsley, for IPPN, at the Appeal Hearing, who explained that for a patient with EPP, a small absolute change in the number of minutes in the sun could be life-changing. He commented that when he took part in the trial he was able to spend a whole day outside in the sun without any reaction, but that sometimes the feedback in his trial diary about how much time he had actually spent in the sun appeared less positive because of poor weather or his own work commitments. Other patients have made similar observations to us, and to the NICE Committee in the previous meetings. The observational study by Biolcati *et al*. (2015) may have been uncontrolled, but it still found

[1] Webb AR et al. The role of sunlight exposure in determining the vitamin D status of the UK white adult population. Br J Dermatol 2010; 163: 1050-5.

improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first 6 months of treatment.

We will let the Appeal Panel's highly critical judgement of NICE on this point speak for itself, when the Appeal Panel judged this issue of NICE describing the benefits of afamelanotide in EPP patients as 'small'. The Appeal Panel said:

*"Whilst the panel noted Dr Jackson's comment that the term "small benefits" was intended to refer to the randomised trial results rather than the overall benefit of treatment, it also noted that this term was used repeatedly both in the FED and during the hearing. The panel was persuaded by Professor Rhodes' argument that whether an increase of 10 minutes represents a small or a large change can only be interpreted with regard to the normal range for this measure. The panel noted that FED paragraph 4.7 cites differences in the amount of time spent in daylight and decreases in phototoxic reactions that would not necessarily sound small to someone reading the document. The panel judged that describing these differences as small lacks face validity….. Overall, the panel concluded that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide."*

The BAD notes that evaluation of points (2) the qualitative evidence and (3) the size of the benefit would be assisted by participation in the forthcoming NICE meeting of a clinical expert with broad and long-term experience of prescribing afamelanotide for EPP patients, i.e. in a real-world setting, particularly Professor Elisabeth Minder, Zurich, senior author of Biolcati *et al.* (2015) (Elisabeth.Minder@triemli.zurich.ch). Professor Minder would be willing to attend the meeting. This is important and entirely consistent with participation of the international patient group (IPPN) in point (1) above.

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

**Appendix D - professional organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

**About you**

**Your name:** [redacted]

**Name of your organisation: Salford Royal NHS Foundation Trust**
**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:**

I have no links to declare

**Appendix D - professional organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

1. **New or additional evidence not submitted during the original evaluation, particularly regarding anything that supports long term effectiveness of the treatment.**

   - There are no further published trials of clinical effectiveness of Afamelanotide in EPP apart from those considered in the original evaluation
   - The ongoing European Post Authorisation Safety Study (PASS) seems likely to be the only emerging source of additional data in the near future.
   - On 18th March 2018, Clinuvel published a company announcement on its website, giving some "headline" information following analysis of 13 months of data from the PASS study.
   - On 27th October 2018, Dr Debby Wensink (Erasmus Medical Centre, Rotterdam) gave an oral presentation at the General Assembly and Scientific Meeting of the European Porphyria Network, held in Rotterdam. This was an update on their clinical experience of use of Afamelanotide since 2016.
   - The above sources report extremely high rates of long term compliance with afamelanotide treatment (>98%), confirming and strengthening a finding of the observational study Biolcati et al 2015: Br J Dermatol 72:1601

2. **Further evidence that addresses the concerns raised by the committee and/or the appeal panel.**

   **You might also wish to consider how to demonstrate in your submission where some of the benefits of afamelanotide in the 4 categories below may not have been captured in the committee's previous deliberations:**

   I refer in my comments below to paragraphs in the NICE Appeal Hearing document: "Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927] Decision of the panel"

- **Nature of the condition**

**Para 19-26**: It seems entirely appropriate that given the rarity of EPP, information and testimony from the international patients' representative group (IPPN) should be considered alongside that from the British Porphyria Association.

Including this wider pool of patients' testimony will enable a more reliable picture to be gained of the nature of the condition, the resultant disability and its impact on patients' lives.

**Para 43-55:** EPP meets the definition of a disability under the Equality Act 2010. I was surprised to read in the Appeal hearing documentation that this had been a matter of debate.

As a clinician, I regularly provide explanatory letters to support patient requests to schools or employers to implement changes to the learning/working environment, rotas etc. I advise young patients going away to University to register with their student Disability Advisory and Support Services to ensure that they can be offered "reasonable adjustments" and appropriate support to enable them to meet the requirements of their course. In clinical practice, it is obvious that EPP results in disability.

**Appendix D - professional organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology Evaluation**

**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

The equality questions posed by NICE in the original scoping exercise were as follows

*"Please let us know if you think that this evaluation:*
*• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
*• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
*• could lead to recommendations that have any adverse impact on people with a particular disability or disabilities"*

I note that most stakeholders (including me) responded to these questions by identifying sub-groups of the EPP population who might be disadvantaged relative to other EPP patients (eg children, who would not be eligible).

EPP as a cohort sharing the protected characteristic of disability was therefore not highlighted in these answers.

- **Clinical effectiveness**

Appeal ground 2.2 and 2.3:

The appeal panel upheld that it is unreasonable to conclude that clinical trial results suggest "small benefits". This is an extremely important finding.

Professor Rhodes argued in the Appeal Hearing (paragraph 64) that the average absolute benefit gained through afamelanotide treatment (approximately 10 minutes per day of additional time in the sun) puts EPP patients into the normal range for healthy indoor workers.

- **Impact of the technology beyond direct health benefits**

If a person with a disability receives a treatment that enables them to function comparably with a person without that disability, this is a substantial overall benefit. Such a difference may, for example, enable a person with EPP to gain employment they could not otherwise contemplate.

- **Value for money**

I am unable to comment on technical aspects of the cost-effectiveness models under debate.

**Further comments**

- It has been accepted that the available trials show that Afamelanotide is clinically effective and the appeal panel upheld that the benefit was significant and not "small".
- A key area of uncertainty is the magnitude of the clinical effectiveness and how to establish this rigorously. The testimony from patients who have experienced the treatment and expert evidence in the appeal point to the trial results having under-estimated the overall impact and benefit of the treatment.

- Given the above findings, it is a great pity that a Managed Access Agreement (MAA) seems not to be possible at this time (para 27-40). This relatively new mechanism, as I understand it, has been introduced specifically to deal with analogous uncertain situations in the NHS.
- If EPP patients could access Afamelanotide via a suitable MAA, further data would be generated to address the uncertainties identified. English EPP patients would be monitored in accordance with the PASS protocol, thus contributing to the validity of the larger international post-marketing evaluation of afamelanotide, which is ultimately to the benefit of all EPP patients.
- The Evaluation Committee view (outlined in para 102 and 103) that it is implausible that further data gathered during a MAA could resolve uncertainty and result in an acceptable ICER, closes a possible route to progress. It is to be hoped that this is not the case and that further negotiation between Clinuvel and NHS England can take place.
- It otherwise feels implausible that a treatment shown to be clinically effective, perhaps highly beneficial overall, cannot otherwise be offered on the NHS to patients with this rare, lifelong, disabling condition.

NICE National Institute for Health and Care Excellence

## Highly Specialised Technology Evaluation - Patient expert statement

# Afamelanotide for treating erythropoietic protoporphyria [ID927]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

| **About you** | |
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| 1.Your name | **Dr. Jasmin Barman-Aksözen** |
| 2. Are you (please tick all that apply): | ☒ a patient with the condition?<br>☐ a carer of a patient with the condition?<br>☒ a patient organisation employee or volunteer? |

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| | ☒ other (please specify): Molecular biologist with PhD in EPP research and since 5 years responsible for the diagnostic for all forms of porphyrias in the Swiss reference centre |
| 3. Name of your nominating organisation | International Porphyria Patient Network (IPPN) |
| 4. Did your nominating organisation submit a submission? | ☒ yes, they did<br>☐ no, they didn't<br>☐ I don't know |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |

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| 6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☐ yes<br>I contributed to the submission of our organisation as a scientist and expert in the field of porphyrias, however want to also provide my personal experiences with the condition below. |
| 7. How did you gather the information included in your statement? (please tick all that apply) | ☒ I have personal experience of the condition<br>☒ I have personal experience of the technology being appraised<br>☒ I have other relevant personal experience. Please specify what other experience:<br>EPP was the research topic for my PhD in molecular biology at the Swiss porphyria competence centre in Zurich at the municipal hospital Triemli. Since five years, I am Head of the Clinical Chemistry laboratory at the Triemli hospital and in charge of the porphyria diagnostics. I am co-author of 13 peer reviewed articles on porphyrias and actively involved in ongoing national and international research projects concerning all forms of porphyrias.<br>☒ I am drawing on others' experiences. Please specify how this information was gathered:<br>As the Vice-President of the IPPN, the Scientific Advisor of the Swiss Society of Porphyria and former Scientific Advisor of the German EPP patient organisation I am in contact with around 400 EPP patients worldwide, many of them having experience with the afamelanotide treatment and other remedies to try to address the disease. |
| **Living with the condition** | |
| 8. Did you have any difficulty or delays in receiving a | Despite considerable efforts to obtain a correct diagnosis by my parents and later also myself, I diagnosed myself with EPP after reading a Wikipedia description of the condition not until during my master's thesis. After contacting specialist physicians, I received helpful information and since the early access scheme for |

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| diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family? | afamelanotide started in Switzerland in 2012 also the appropriate therapy. From my own unsuccessful literature search I know that textbook descriptions of EPP are often misleading and incorrect. |
| 9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to | I grew up with the knowledge that "rain is wet and sun is pain". Spring and summer were hell on earth, because every ray of sunlight immediately induced massively painful burns, the so called "phototoxic reaction", in all parts of the body which were exposed to light. The feeling can only be described as being burnt alive. The pain is so intense, that every second in the sunlight has to be avoided as best as possible – but I had to go to school and take part in outdoor sports events etc. The problem was that the burns in the beginning of the reaction did not lead to visible alterations on the skin, and therefore teachers and physicians did not believe me although sometimes I already was in severe pain and only wanted to immediately get out of this terrible sunlight.<br><br>When I was forced to stay in the sunlight, often for several hours, the exposed body parts – mainly hands and the face because one cannot cover them consistently - developed visible signs: The day after the exposure they became swollen and deeply red, because the blood vessels were burnt and damaged, and the blood leaked out into the tissue. In this condition, words are not sufficient to describe the pain. No pain medication helped, my own body heat was unbearable, the body heat of my parents who wanted to comfort me was unbearable to a degree that I had to push them away from me, and I could not sleep for several nights. I remember that at the age of six or seven I started to consider suicide, because I figured that there is no place for me to exist in a world in which even physicians did not believe me, and people forced me into extremely painful situations again and again. Often, there was no hope left in me.<br><br>My parents did understand that and protected me. They tried – without a confirmed diagnosis – to explain the situation to school teachers and all the expert physicians we visited in order to obtain an answer. My parents were labelled as being hysterical and I was sent to a psychotherapist. This is when we stopped seeing physicians for my EPP symptoms altogether. After that, we only tried to somehow adjust my life around the condition more consequently: I did not join my friends for outdoor activities but stayed at home |

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| school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings? | alone with some excuse, I ignored the strangers making fun of me when in bright sunlight I used an umbrella as protection and I stopped telling anybody when I was in distress or pain, because nobody would believe me anyway.<br><br>At university, I was deeply intrigued about the new prospects of genetically modified plants, and I trained to become a plant scientist. However, although modifying plants basically is lab work, I was required to take outdoor excursions in order to complete my training. I tried to participate with all the protective measures possible but could not stay outdoors for long enough. That forced me to give up this career path, and I lost two years at the university because not only I had to lay the foundations for a new subject but I also was depressed that again those unexplained symptoms interfered with my life choices.<br><br>At the end of my biology studies, I however found a Wikipedia article authored by another EPP patient. She described the symptoms with an accuracy I had not encountered before and this was the day I obtained my diagnosis. I convinced the dermatologists at my university hospital to confirm my “Dr. Google” diagnosis in a specialist lab in Germany and thereafter was invited to give a talk at a conference on porphyrias. This resulted in a research position at the reference centre for EPP and related diseases in Zurich, Switzerland where I successfully conducted research on gene expression and iron metabolism in EPP.<br><br>In 2012, the early access scheme for afamelanotide started in Switzerland and I could access the treatment for the first time. Since then, I have completed my PhD, became Head of the clinical chemistry laboratory, started teaching at the university of Zurich, been invited to Keystone and other important international science meetings, have co-founded the International Porphyria Patient Network and had so many other magnificent moments. My life did not only turn to the better and more normal, but became exceptional. I now can use my full potential, I am no longer restricted to the dark spaces, but feel confident to be in the spotlight.<br><br>I can and I will not accept that EPP patients are not taken seriously any longer and that treatments which enable them to live an almost normal life, to even enjoy sunlight, will be withheld based on unreasonable grounds. |

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| **Current treatment of the condition in the NHS** | |
| 10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough? | Currently, there is only one approved treatment for EPP with proven efficacy and safety, afamelanotide. Under treatment with afamelanotide, I am able to live an almost normal life with considerably less pain (reduced number and severity of phototoxic reactions) and can expose myself for several hours to direct and strong lights.<br>I unsuccessfully tried several remedies including beta-carotene, a variety of sunscreens (some with pigments) and UV-B therapy. Many of the treatment attempts I tried for years like beta-carotene and sunscreens, and I did not care that they made me look strange (orange hue) or were inconvenient to apply, I stopped because they did not help me at all. |
| 11. Is there an unmet need for patients with this condition? | EPP is a severely painful and underestimated ultra-rare condition which urgently needs to be treated. |
| **Advantages of the technology (treatment)** | |
| 12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also | I have access to the afamelanotide treatment since 2012, and since then have a normal life:<br>Under treatment, I can be outdoors in the sunlight for hours as opposed to only a few minutes without treatment. Phototoxic reactions might also be triggered under treatment when staying outdoors for a very long time, however they are much less severe than without the treatment and they resolve the next day. In the beginning I was cautious, because I did not yet know if the treatment would both work for me, and if so, what my new limits, the new tolerance would be. Therefore, I extended my exposure to sunlight successively, every day daring a few more minutes – until one day I stayed outdoors with my husband the entire day. This was the moment I knew that a new life had begun for me, but also for my husband, my parents and friends – everybody who had to forgo outdoor activities and plans because of my condition.<br>Previously, on sunny days, I often felt anxious and I also had fears about my future. I felt as a burden to my family and friends, and often found excuses to not join an outdoor activity to not hinder their plans. This all has normalised now, I am a full member of society, have a job and career options, can travel to conferences even if they are in the summer. |

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| include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life. | |
| 13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment? | The treatment is a slow release implant formulation which provides almost complete protection against phototoxic reactions for about 8 weeks. The implant is applied with a thick needle to the fat tissue just above the hip. Besides the unproblematic medical procedure, there is the data collection for the ongoing Post-Authorisation Safety (and Efficacy) Study implemented by the EMA as a condition of approval. This takes some time, too.<br>Since I work at the Swiss reference centre I do not have to travel, however I know Swiss patients travelling 2-3 h one way for an appointment. Others even fly in from Germany or the USA. |
| **Disadvantages of the technology (treatment)** | |
| 14. What do patients or carers think are the disadvantages of the technology?<br>Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they | Disadvantages of the technology (slow release implant formulation) are the fixed dosage in terms of fixed concentration and treatment intervals. Adaptable doses would be preferable, especially also for the treatment of children, the most severely affected group of EPP patients.<br>The few mild side effects like a slight nausea after the injection (which was also present in the placebo group during the trials) and one to two days of a little bit fatigue are in my opinion clearly outweighed by the considerable benefits the treatment provides. |

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| long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially? | |
| **Patient population** | |
| 15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why. | Patients more daring to expose themselves to sunlight and strong artificial light under treatment experience a bigger benefit or might benefit faster.<br>I am aware of two patients in Switzerland, two patients in Germany and one in Austria who did not experience a sufficient treatment effect and stopped with the treatment, however the reasons are not entirely clear. These non-responders are significantly outnumbered by approximately 180 patients I am in contact with who experience a massive benefit which they describe as life-changing.<br>Currently, children cannot benefit from the afamelanotide treatment because there is not yet a marketing approval for paediatric use. However, to my knowledge, trials are in preparation. |
| **Equality** | |
| 16. Are there any potential equality issues that should be taken into account when | EPP is connected to behavioural adaptations, e.g. avoidance of all daytime outdoor activities including social and work-related activities and a massive stigmatisation due to the necessity for protection against visible light, e.g. thick long clothes, hats, umbrellas etc. in bright sunshine and even indoors (light coming through window glass, light from energy saving bulbs). Due to the massive pain of the |

| | |
|---|---|
| considering this condition and the treatment? | phototoxic reactions which cause secondary burns in the blood vessels, the patients have to protect themselves from all forms of light exposure. However, because the symptoms mostly remain invisible and/or patients completely cover up, usually the environment does not believe the necessity of the behavioural adaptions and bully and harass the patients, which leads to further social withdrawal, lower self-esteem, less supportive networks and so on.<br>The behavioural adaptations very likely also led to issues during the clinical trials, as the patients first had to unlearn their light avoidance and had to dare to expose themselves to sunlight during the trials (time in sunlight was the main outcome measured for the studies). |
| **Other issues** | |
| 17. Are there any other issues that you would like the committee to consider? | As EPP is an ultra-rare condition with a limited research history (less than 1000 peer reviewed publications) many uncertainties might remain for the appraisal process. We urge NICE to keep in mind the “ultra-orphan” nature and the great unmet need of the EPP condition but also the consistency in the more that 35 testimonies submitted during the appraisal process and consultation phase by EPP patients, carers and / or experts who describe the treatment effects of afamelanotide as truly life changing. |
| **Key messages** | |
| 18. In up to 5 bullet points, please summarise the key messages of your statement:<br>• EPP is an inborn error of metabolism associated with severely painful reactions to the visible light range.<br>• EPP is connected with a massive behavioural adaptation which stigmatises the patients and leads to social withdrawal and isolation.<br>• No effective treatment option exists for EPP besides the approved afamelanotide therapy.<br>• The afamelanotide treatment enables the patients to live an almost normal life and makes them full members of society.<br>• As an ultra-rare condition with limited research history and, accordingly, still many uncertainties, we appeal to NICE to listen to the patients voice. | |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

**Your privacy**

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# CONFIDENTIAL UNTIL PUBLISHED

## Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

## Afamelanotide for treating erythropoietic protoporphyria

## ADDENDUM 2 (post appeal)

## CONFIDENTIAL


**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

**Authors** Joanne Lord, Professorial Fellow in Health Economics
Jonathan Shepherd, Principal Research Fellow

**Correspondence to** Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute, Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac



**Date completed** **15 February 2019**

# 1. Introduction

Following the NICE Appeal Panel decision of 9 October 2018, the company submitted a proposal for a Managed Access Agreement (MAA) to NICE (Clinuvel letter of 21/1/19). This letter included a copy of a revised Budget Impact Assessment (BIA) document, dated October 2017 and previously submitted to NICE in a letter dated 6/11/17. As the Evidence Review Group (ERG) assigned to this evaluation, NICE have asked us to comment on the revised BIA and proposed MAA.

In this document, we summarise and comment on the assumptions and calculations in the company's budget impact assessments:

- The original BIA from the Company Submission (CS) and economic model
- The company's revised BIA of October 2017

We developed an Excel model to check the company's original and revised BIA calculations and enable further sensitivity analysis if required. These were adapted from the 'BIM' and 'Costs and Resources' sheets of the company's economic model, and replicate their calculations.

We also summarise the provisions of the company's proposed MAA and comment on how they relate to the assumptions in the company's budget impact calculations.

# 2. Original Budget Impact Assessment (August 2017)

The company estimated the budget impact for the NHS in England to be [redacted] in the first year of uptake and [redacted] for each of the subsequent 4 years (CS section 13).

The company state that these estimates reflect a '*maximum* budget impact to NHS England', based on the following assumptions:

- [redacted] EPP patients 'eligible for treatment in England'
- [redacted] of eligible patients treated in year 1 and [redacted] from years 2 to 5
- [redacted] implants per treated patient per year
- An acquisition cost of [redacted] per implant

Assumptions about the costs of administration were not explicit in the CS, but we note that an additional cost of [redacted] per patient per year was included on top of the drug acquisition cost (see calculations in Table 1 below).

Based on the cost and resource use calculations in the company's economic model, we infer that this administration cost comprises:

- [redacted] for dermatological screening (1 extra visit at £170 plus laboratory tests)
- [redacted] for [redacted] implant injection visits (£203.75 per visit)
- [redacted] for a final visit after the last implant of the year

**Table 1 Estimated budget impact from company submission**

| | Uptake [a] | Patients treated [b] | Implants used [c] | Acquisition cost [d] | Administration cost [e] | Budget impact NHS England [f] |
|---|---|---|---|---|---|---|
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Percentage of eligible patient population. Company submission section 13.2

b Calculated by multiplying % uptake by the company's assumed eligible population ([redacted])

c Calculated by multiplying the number of patients treated by [redacted] implants per patient per year

d Calculated by multiplying the number of implants by the cost per implant ([redacted])

e Calculated by subtracting the drug acquisition cost from the total budget impact.

f Company submission section 13.7

In the ERG report, we noted the inconsistency between the assumed number of implants and the number of implant injection visits in the company's calculations (ERG report section 5.1). With [redacted] per patient per year, the estimated budget impact rises slightly to [redacted] in year 1 and [redacted] in years 2 to 5 (CS Table 36).

We also presented sensitivity analysis to illustrate the impact of varying assumptions about the number of patients eligible for treatment (from 300 to 600 each year) and the mean number of implants per patient, per year (2 or 3) (ERG report Table 37).

## 3. Revised Budget Impact Assessment (October 2017)

The company presented revised estimates of budget impact in Appendix 1 of their report dated October 2017.

The calculations differed from those in the original company submission in four respects:

- The number of people eligible for treatment was reduced by excluding children under the age of 18 ([redacted]), to reflect the marketing authorisation.
- The numbers of patients treated per year were reduced, based on assumptions about constraints on current and projected service capacity in England. The company identified 2 current expert centres for EPP treatment and 6 other centres with expertise in rare metabolic disorders who could provide afamelanotide with training, and [redacted]. The company defined three scenarios of treatment numbers over the five-year period (see Table 2 and Table 3 below).
- The mean number of implants per patient varied from [redacted] per year in the 'most probable' scenario, up to [redacted] in the 'maximum' scenario. This is the key driver of cost per patient; hence, the assumption of fewer implants gives a lower predicted budget impact.
- Additional administration costs were fixed at [redacted] per patient per year in all scenarios. This matches the cost reported in CS Table D6, but the assumptions underlying this estimate were not specified.

The company's revised budget impact predictions are lower than those reported in the CS under all scenarios.

We note an apparent error in application of the administration cost in the company's revised budget impact calculations: the additional cost of [redacted] per patient per annum was actually only added once per year for the whole population, and not multiplied by the number of patients treated. We correct this error in Table 3. This causes a small increase in the revised budget impact estimates across all scenarios.

**Table 2 Company scenarios in revised budget impact assessment**

| | Most probable | Possible | Maximum |
|---|---|---|---|
| Number of centres | [redacted] | [redacted] | [redacted] |
| Patients treated per centre per year | [redacted] | [redacted] | [redacted] |
| Mean implants per patient per year | [redacted] | [redacted] | [redacted] |

***Source:*** Table 1 Clinuvel Budget Impact Assessment for England, October 2017

**Table 3 Company's revised budget impact assessment (with ERG correction)**

| | Uptake [a] | Patients treated [a] | Implants used [a] | Acquisition cost [a] | Administration cost [b] | Budget impact NHS England [c] |
|---|---|---|---|---|---|---|
| **Most probable scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Possible scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Maximum scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 [d] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Table 1 Clinuvel Budget Impact Assessment for England, October 2017

b ERG correction: [redacted] per patient treated

c ERG correction: acquisition cost + administration cost

d Company states that scenario is impossible in year 5, as patients treated exceeds estimated prevalence

## 4. ERG critique of revised BIA

**Number of people eligible for treatment**

The company's revised estimate of the number of patients in England who would be eligible for treatment is reasonable. The restriction to people aged 18 years and older reflects the marketing authorisation and the calculation is accurate based on the Elder et al. prevalence of 9.2 per million and population of 43,752,473 adults in England (ONS mid-year 2017).[1] [2]

We note that there is uncertainty over the Elder et al. prevalence estimate: reported 95% confidence interval 7.7 to 11.6 per million, which translates to between 337 and 508 adults diagnosed with EPP in England. There are also other uncertainties that are difficult to quantify. Elder et al. found variations in incidence between countries: with a higher incidence in the UK than in most other countries. Their prevalence estimates are also higher than reported numbers of cases in retrospective studies: e.g. only 389 cases of all ages were identified in the UK by Holme et al (2006).[3] Elder et al. argue that this disparity may be due their own assumption of constant incidence, whereas rates of diagnosis had actually been increasing.

Uncertainty over prevalence does not cast doubt on the company's revised budget impact estimates, because these are driven by the capacity constraints. However, it does suggest that the upper limit of treatment capacity ([redacted] treated patients in year 5 in the company's maximum scenario) might not be 'impossible'.

**Number of patients to be treated**

The company's revised method of estimating treatment numbers based on capacity is an improvement, as it reflects information about real-world constraints. Whether the assumed number of treatment centres and the limits on how many patients each centre could treat are realistic is a matter of judgement for NHS England and clinical experts. But we consider that the company has explored a fair range of scenarios from [redacted] patients treated in year 1 up to between [redacted] in year 5.

**Mean number of implants per patient**

There is uncertainty over the mean number of implants that patients will receive per year. In their cost-effectiveness analysis, the company assumed a mean of [redacted] per year, based on experience with expanded access and commercial distribution in other countries (CS Table D5). The evaluation committee uncertainty over whether this number is generalisable to

England, and concluded that they should take into account that people may have up to 4 implants per year (FED 4.18).

**Administration costs**

There is a lack of clarity over what costs the NHS will incur in addition to the drug acquisition cost. The company assumes a fixed additional annual cost of [redacted] per patient in their revised budget impact calculations. This is equal to the estimated annual cost for members of the placebo group in the company's economic model: which comprises one dematological screen, one photoprovocation test, one set of laboratory tests and prescription of calcium and vitamin D (see Table 4 below).

The company's economic model assumes that patients treated with afamelantotide will require one extra dermatological screen and one extra set of laboratory tests each year, in addition to specialist outpatient visits for implant injections and an extra final visit of the year. We summarise the total additional administration cost for each treated patient in Table 5 below. If these total administration costs are included, there is a small increase in the estimated budget impact (up to [redacted] in year 5 under the company's maximum scenario).

**Table 4 Resource use and unit cost assumptions from the economic model**

| Resources | Unit cost | Afamelantotide | Placebo |
|---|---|---|---|
| Implant injection | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| Photoprovocation test | [redacted] | [redacted] | [redacted] |
| Calcium + Vit D | [redacted] | [redacted] | [redacted] |

Source: Extracted by ERG from "Costs and Resources" sheet in company economic model

**Table 5 Additional administration costs per patient treated with afamelanotide**

| Resources | Most probable [redacted] implants | Possible [redacted] implants | Maximum [redacted] implants |
|---|---|---|---|
| Implant injections | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| **Total administration cost** | [redacted] | [redacted] | [redacted] |
| **Drug** | | | |

Source: Calculated by ERG from assumptions in "Costs and Resources" sheet in company economic model

## 5. Proposed MAA (January 2019)

| Proposed Managed Access Agreement | ERG comments |
|---|---|
| i) [redacted] | |
| ii) [redacted] | [redacted] |
| iii) [redacted] | Prevalence estimates support an estimate of [redacted] adults with diagnosed EPP in England (95% confidence interval 337 to 508).[1 2] There is additional uncertainty around these figures due to methodological issues. |
| iv) [redacted] | |
| v) [redacted] | [redacted] |
| vi) [redacted] | [redacted] |
| vii) [redacted] | |
| viii) [redacted] | |

| | | |
|---|---|---|
| ix) | [redacted] | [redacted] |

**References**


1. Elder G, Harper P, Badminton M, et al. The incidence of inherited porphyrias in Europe. *Journal of inherited metabolic disease* 2013;36(5):849-57. doi: 10.1007/s10545-012-9544-4 [published Online First: 2012/11/02]
2. Office for National Statistics (ONS). Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2017, 2018.
3. Holme S, Anstey A, Finlay A, et al. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. *Br J Dermatol* 2006;155:574-81.

# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## Pro-forma Response

## ERG report

## Afamelanotide for treating erythropoietic protoporphyria [ID927]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm**, **Friday 1 March 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

## Issue 1 Confidentiality marking

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 4, bullet 2: This information has never been made public, and is proposed for redaction by NICE below | [redacted] | Information is confidential | This information was included in the Scenesse Budget Impact Assessment (October 2017). The entire document is marked as confidential, thus we have marked it as CIC. |
| Page 8, row 3, prevalence estimate: Redacted elsewhere in this document; presented above as [redacted] | "Prevalence estimates support an estimate of [redacted] adults" | Correction of error; information is confidential | Error corrected. Data is marked as CIC in recognition of its confidential status. |

# CONFIDENTIAL UNTIL PUBLISHED

## Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

## Afamelanotide for treating erythropoietic protoporphyria

## ADDENDUM 2 (post appeal)

## CONFIDENTIAL

## ERRATUM


**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

**Authors** Joanne Lord, Professorial Fellow in Health Economics
Jonathan Shepherd, Principal Research Fellow

**Correspondence to** Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute, Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac



**Date completed** **15 February 2019**

# 1. Introduction

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In this document, we summarise and comment on the assumptions and calculations in the company's budget impact assessments:

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|---|---|---|---|---|---|---|
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| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Percentage of eligible patient population. Company submission section 13.2

b Calculated by multiplying % uptake by the company's assumed eligible population ([redacted])

c Calculated by multiplying the number of patients treated by [redacted] implants per patient per year

d Calculated by multiplying the number of implants by the cost per implant ([redacted])

e Calculated by subtracting the drug acquisition cost from the total budget impact.

f Company submission section 13.7

In the ERG report, we noted the inconsistency between the assumed number of implants and the number of implant injection visits in the company's calculations (ERG report section 5.1). With [redacted] per patient per year, the estimated budget impact rises slightly to [redacted] in year 1 and [redacted] in years 2 to 5 (CS Table 36).

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**Table 2 Company scenarios in revised budget impact assessment**

| | Most probable | Possible | Maximum |
|---|---|---|---|
| Number of centres | [redacted] | [redacted] | [redacted] |
| Patients treated per centre per year | [redacted] | [redacted] | [redacted] |
| Mean implants per patient per year | [redacted] | [redacted] | [redacted] |

***Source:*** Table 1 Clinuvel Budget Impact Assessment for England, October 2017

**Table 3 Company's revised budget impact assessment (with ERG correction)**

| | Uptake [a] | Patients treated [a] | Implants used [a] | Acquisition cost [a] | Administration cost [b] | Budget impact NHS England [c] |
|---|---|---|---|---|---|---|
| **Most probable scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Possible scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Maximum scenario** | | | | | | |
| Year 1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Year 5 [d] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

***Sources and calculations***

a Table 1 Clinuvel Budget Impact Assessment for England, October 2017

b ERG correction: [redacted] per patient treated

c ERG correction: acquisition cost + administration cost

d Company states that scenario is impossible in year 5, as patients treated exceeds estimated prevalence

## 4. ERG critique of revised BIA

**Number of people eligible for treatment**

The company's revised estimate of the number of patients in England who would be eligible for treatment is reasonable. The restriction to people aged 18 years and older reflects the marketing authorisation and the calculation is accurate based on the Elder et al. prevalence of 9.2 per million and population of 43,752,473 adults in England (ONS mid-year 2017).[1] [2]

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**Number of patients to be treated**

The company's revised method of estimating treatment numbers based on capacity is an improvement, as it reflects information about real-world constraints. Whether the assumed number of treatment centres and the limits on how many patients each centre could treat are realistic is a matter of judgement for NHS England and clinical experts. But we consider that the company has explored a fair range of scenarios from [redacted] patients treated in year 1 up to between [redacted] in year 5.

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England, and concluded that they should take into account that people may have up to 4 implants per year (FED 4.18).

**Administration costs**

There is a lack of clarity over what costs the NHS will incur in addition to the drug acquisition cost. The company assumes a fixed additional annual cost of [redacted] per patient in their revised budget impact calculations. This is equal to the estimated annual cost for members of the placebo group in the company's economic model: which comprises one dematological screen, one photoprovocation test, one set of laboratory tests and prescription of calcium and vitamin D (see Table 4 below).

The company's economic model assumes that patients treated with afamelantotide will require one extra dermatological screen and one extra set of laboratory tests each year, in addition to specialist outpatient visits for implant injections and an extra final visit of the year. We summarise the total additional administration cost for each treated patient in Table 5 below. If these total administration costs are included, there is a small increase in the estimated budget impact (up to [redacted] in year 5 under the company's maximum scenario).

**Table 4 Resource use and unit cost assumptions from the economic model**

| Resources | Unit cost | Afamelantotide | Placebo |
|---|---|---|---|
| Implant injection | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| Photoprovocation test | [redacted] | [redacted] | [redacted] |
| Calcium + Vit D | [redacted] | [redacted] | [redacted] |

Source: Extracted by ERG from "Costs and Resources" sheet in company economic model

**Table 5 Additional administration costs per patient treated with afamelanotide**

| Resources | Most probable [redacted] implants | Possible [redacted] implants | Maximum [redacted] implants |
|---|---|---|---|
| Implant injections | [redacted] | [redacted] | [redacted] |
| Final visit of year | [redacted] | [redacted] | [redacted] |
| Dermatological screening | [redacted] | [redacted] | [redacted] |
| Laboratory tests | [redacted] | [redacted] | [redacted] |
| **Total administration cost** | [redacted] | [redacted] | [redacted] |
| **Drug** | | | |

Source: Calculated by ERG from assumptions in "Costs and Resources" sheet in company economic model

## 5. Proposed MAA (January 2019)

| Proposed Managed Access Agreement | ERG comments |
|---|---|
| i) [redacted] | |
| ii) [redacted] | [redacted] |
| iii) [redacted] | Prevalence estimates support an estimate of [redacted] adults with diagnosed EPP in England (95% confidence interval 337 to 508).[1 2] There is additional uncertainty around these figures due to methodological issues. |
| iv) [redacted] | |
| v) [redacted] | [redacted] |
| vi) [redacted] | [redacted] |
| vii) [redacted] | |
| viii) [redacted] | |

| | | |
|---|---|---|
| ix) | [redacted] | [redacted] |

**References**


1. Elder G, Harper P, Badminton M, et al. The incidence of inherited porphyrias in Europe. *Journal of inherited metabolic disease* 2013;36(5):849-57. doi: 10.1007/s10545-012-9544-4 [published Online First: 2012/11/02]
2. Office for National Statistics (ONS). Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2017, 2018.
3. Holme S, Anstey A, Finlay A, et al. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. *Br J Dermatol* 2006;155:574-81.

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Dr Peter Jackson, Chairman, Highly Specialised Technologies Committee
Ms Sheela Upadhyaya, Associate Director Highly Specialised Technologies
National Institute of Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT
Sent via HST@nice.org.uk

CC: Marie Manley, Sidley Austin LLP (mmanley@sidley.com)
Martin Chamberlain QC, Brick Court Chambers (martin.chamberlain@brickcourt.co.uk)
Sarah Love, Brick Court Chambers (sarah.love@brickcourt.co.uk)

08 March 2019

**Re: SCENESSE® for the treatment of erythropoietic protoporphyria [EPP]**

Dear Dr Jackson, Ms Upadhyaya,

We have duly noted the ERG report dated 15 February 2019.

ERG provided commentary to NICE around uncertain outcomes. We address the commentary and identify certain inaccuracies for the purpose of eliminating doubt in our discussion and your assessment.

The ERG failed to recognise in its report that the product is made available only to trained and accredited academic expert centres in the European Union, which would also be applicable to the UK. Further, the ERG failed to acknowledge that the distribution of SCENESSE® takes place through a closed supply chain, and that the pharmaceutical product is not made available to any other prescribers, general pharmacies or other wholesale channels. The 'closed distribution' provides each European nation with a guarantee on limited prescription of the product, and therefore poses a limited burden and no financial risk to the respective European healthcare systems.

**Budget Impact Assessment [BIA]**
CLINUVEL has consistently disclosed to the HST Committee the number of EPP patients in England who would be eligible for treatment with SCENESSE®. Since CLINUVEL has specialist knowledge of the patient population, the number of eligible adult patients is estimated to be 404. The maximum recommended dose is four implants per annum, with the discretion for expert physicians to prescribe up to six per calendar year. However, the ERG incorrectly uses a range of 300 to 600 eligible EPP patients in its sensitivity analysis. Since there could only be a maximum conceivable 404 eligible EPP patients eligible, the number of 600 is inappropriate, incorrect and misleading. This figure should not be factored into any further analysis or discussion.

Three scenarios have been provided by CLINUVEL and the ERG, a) most probable, b) possible, and c) maximum. In none of these scenarios would CLINUVEL exceed the maximum annual budget under the NHS of £20 million.

Under the most probable scenario the impact on the NHS budget would range from £3.3M to £6.4M, in a possible scenario from £7.8M to £14M, and in a maximum scenario £12.M to £19.4M per annum.

The sensitivity of BIA lies in the number of centres prepared to provide clinical care, while the HST has been all too aware of the limited number of university centres in the country willing to provide the multidisciplinary care required for EPP patients, and hence the limited willingness from academic clinical experts to prescribe the drug. Further compounding the BIA model, the HST has been equally aware that British university centres have proven reluctant to register more than 50 EPP patients for clinical care due to the administrative time expended under the PASS protocol. Therefore, it will be challenging for CLINUVEL to commit eight academic expert centres by year 4 and 5 to provide treatment, though we will undertake the best efforts to make the treatment available to all EPP patients.

**PASS Expenditures and associated administration cost**
The European Porphyria Network demanded from the Company in 2014 – upon receiving marketing authorisation and post-marketing commitments – unconditional financial support for up to 12.5 hours per patient per annum to enable treatment under the EMA's imposed PASS protocol. This reflects the time required to facilitate treatment under the PASS. In full transparency and in the principle of fairness CLINUVEL had agreed to reimburse each European EPP expert centre under the PASS protocol – through a Clinical Trial Agreement – a net amount of €1,400 maximum per annum per patient for the additional administrative time spent on each EPP patient, and for entering data onto the European EPP Disease Registry. As stated and part of CLINUVEL's international policies and governance, CLINUVEL does not provide discounts, rebates or other payments to hospitals, physicians, intermediaries or third parties, nor does it promote or advertise the sale of the product.

**Price of SCENESSE®**
CLINUVEL has lowered the price of SCENESSE® on two occasions in the course of the availability of treatment since 2014, from €21,971 to €16,842 and in 2017 from €16,842 to the current €14,100.95, 64% of the original price of the treatment. As of 19 April 2019, the price will be adjusted by CPI (1.6%) to €14,327 for all countries, including Switzerland. In the coming two years there will be an increase according to CPI, before CLINUVEL increases its drug price in 2021. The remainder of the ERG commentary on pricing is correct.

**Proposed Managed Access Agreement [MAA]**
CLINUVEL fully understands that each European country is working within the budgets to each treatment allocation, and the Company would commit to:

(i) the European pricing of SCENESSE® - £12,020 net per injection – to be fixed for 24 months except for annual CPI adjustments - with no further rebates discounts or cashbacks under any scheme. A price increase is foreseen to conform to market rates and the increase in cost of goods in 2021.

(ii) treat all eligible adult EPP patients in England by 2022 to 2024, depending on the centres willing to participate and prescribe the product. The number of 404 EPP patients is correct and serves as the basis for this MAA and Budget Impact Assessment.

(iii) NHS obtaining annual reports from the disease registry (EEDR) relating to British patients on treatment, whereby an evaluation would be made with the Company after 24 months.

(iv) a maximum midpoint between the most probable (a) and possible scenario (b) of £10.2 million maximum implant expenditures per annum for the first two years (24 months from start in 2019 to 2021) with a total of £20.4 M, after which a formal evaluation would be made but with the intention to continue the supply of treatment.
Since CLINUVEL has intimately known the patient populations it focuses on, and since it has never exceeded these volume agreements in any other European country, it is confident it will be able to meet and stay within the proposed threshold for England. It would agree to reimburse 35% of each

individual implant cost upon exceeding the overall threshold; ex aequo tam if the Company underbids the threshold by more than 10% (less than £9 million product expenditures per annum under the NHS), the NHS would publicly acknowledge the accuracy of the Company's commitment under the agreed MAA, in view of the delays NICE has incurred and errors made during the review process at the detriment of EPP patients.

(v) reimbursement of 50% of the last administered product's net costs to the NHS in the event the treatment has proven ineffective.
Inefficacy of treatment is defined as an independent written assessment and declaration by the expert physician, together with the patient's declaration, that the patient wishes to indefinitely cease treatment with SCENESSE® due to the lack of improvement or effectiveness during daily life. An interruption of treatment due to inability to travel, work commitments or pregnancy does not constitute lack of efficacy.

(vi) further develop and fund the "Inventory of Daily Activities" to enable assessment of impact of treatment.

(vii) continue the financial support to the British EPP expert centres trained and accredited by CLINUVEL for the administrative resources used under the PASS protocol.

In the ERG report a comment is made on prioritising EPP patients. CLINUVEL will not accept the responsibility of preselecting EPP patients since all patients annually and periodically are affected by phototoxicity and anaphylactoid reactions, and the Company does not see making these decisions included in its remit. This decision to treat is exclusively made by the treating physicians in consultation with their patients.

CLINUVEL has exhausted its efforts to demonstrate that zero financial risk would be posed by SCENESSE® for the treatment of EPP, congruent with other European countries, and therefore we have fulfilled the essential criteria. In light of the undisputed benefit of the treatment and all proposed cost minimisation measures, CLINUVEL anticipates that NICE will work the Company to ensure patient access to this life-changing treatment.

I look forward to discussing the proposed MAA with the HST Committee. We reserve all our rights.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD