

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]

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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:

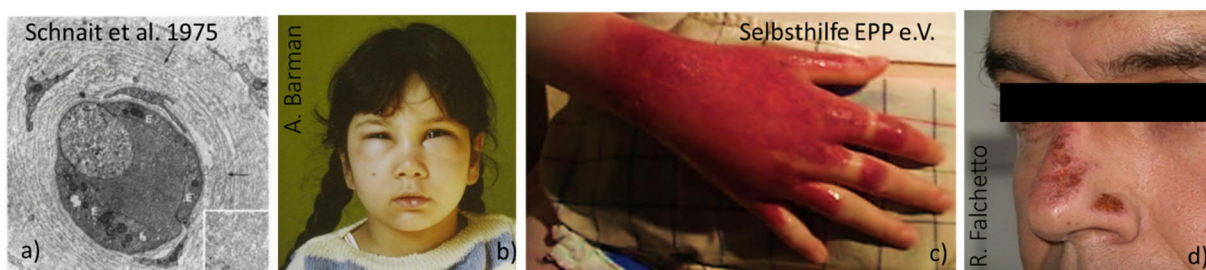


Figure 1: Visible symptoms of EPP: a) Chronic damage to the blood vessels caused by multiple phototoxic reactions in a biopsy from the dorsum of a hand of an EPP patient. Multiple basement membranes, each one resulting from repair process after a preceding phototoxic reaction, surrounding the papillary 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 et 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 12-year-old Savannah who suffers from EPP

Link to access Savannah`s video online: <https://vimeo.com/165356683>

Savannah`s 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 <u>beta-carotene</u> 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 <u>ultraviolet beta (UVB) phototherapy</u> (e.g. 3 x weekly for 4-6 weeks or variations of), which has,	In addition to the stated marginal effectiveness of the UVB phototherapy, some patients do experience severe phototoxic reactions during the sessions

according to clinical experience and a few 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."	(Minder et al. 2009): The UVB sources 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 <u>Dundee cream</u> 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 witness 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: From 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.

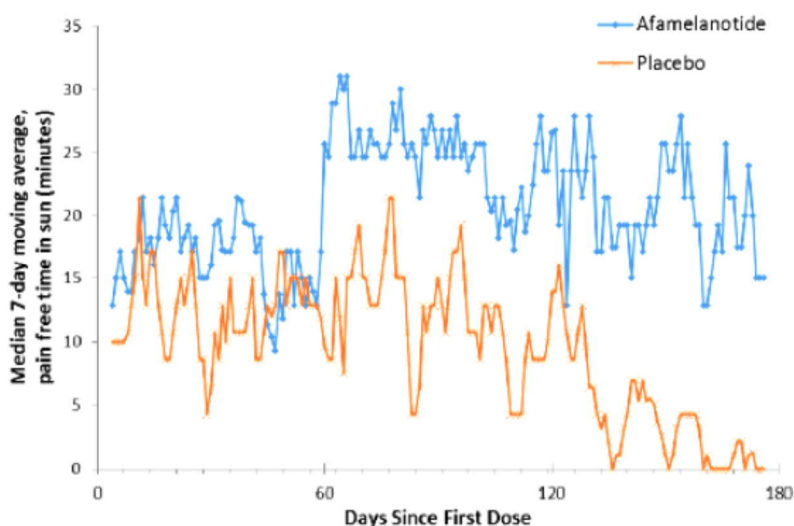


Figure 3: Median of the individual patients' 7 day moving average for pain-free daily exposure to direct sunlight for the CUV039 trial. In the first 60 days of the 180 days study period, no difference in sun exposure times is identifiable between the study groups. After day 60 (2nd dose afamelanotide), 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.

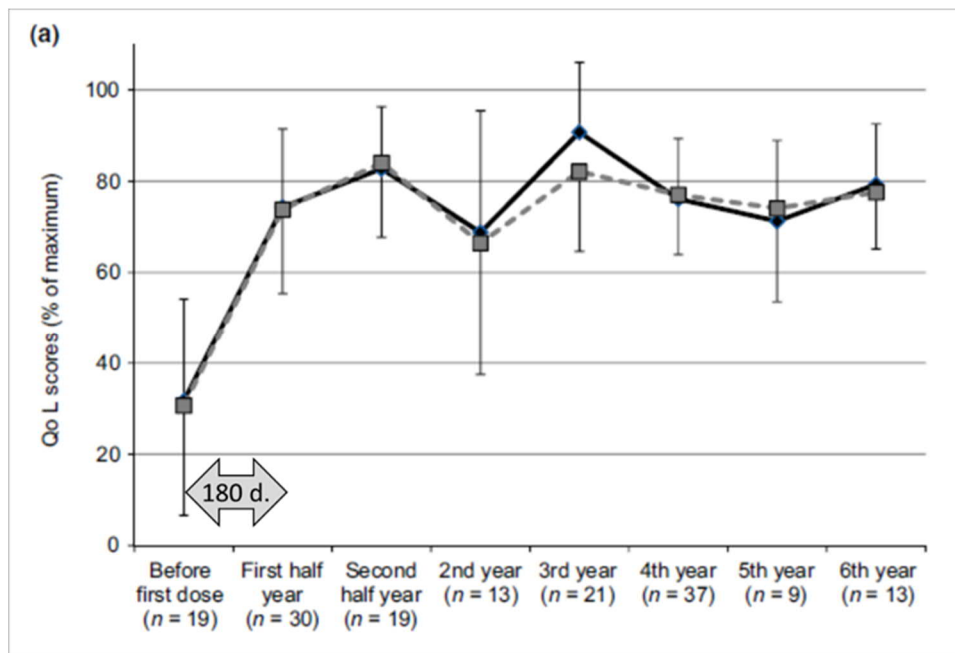


Figure 4: Quality of life as measured with the EPP-QoL in the eight-year observational study by Biolcati et al. (2015). First time point after determination of the baseline (before first dose) is day 180. The stepwise increase in quality of life observed in the clinical trials CUV029 and CUV039 was in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

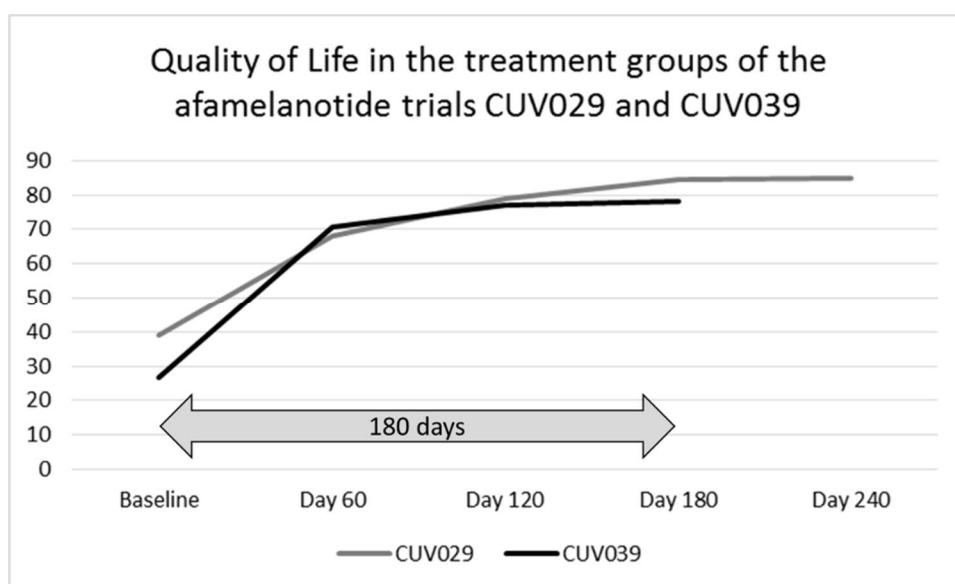


Figure 5: Quality of life as measured with the EPP-QoL in the treatment groups of the afamelanotide trials CUV039 (pivotal trial, duration: 180 days) and CUV029 (European arm, duration: 240 days). A period with stepwise increases in quality of life is visible between baseline and day 180. Quality of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

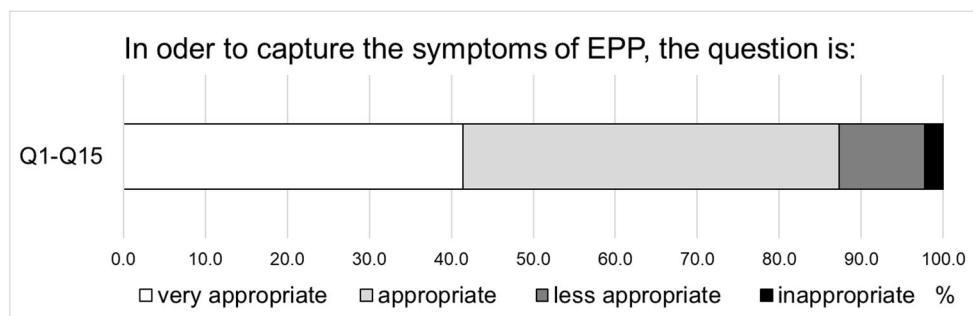
Results

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.

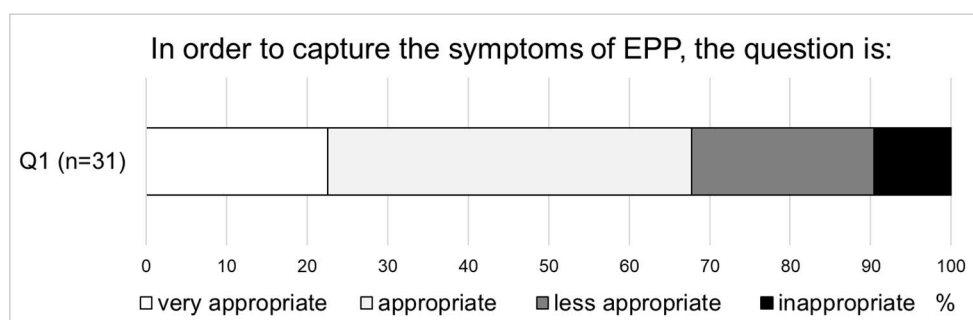


3.1.2. Rating on the appropriateness of single questions in the EPP-QoL (15-items):

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.

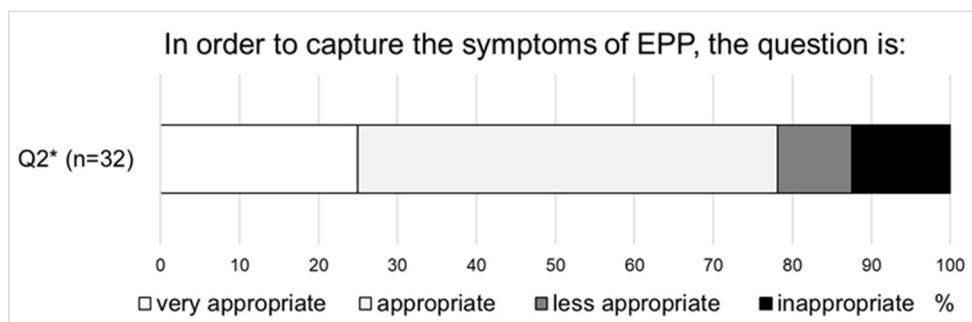
Q1: Over the last two months, how has your well-being been affected by EPP?

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.



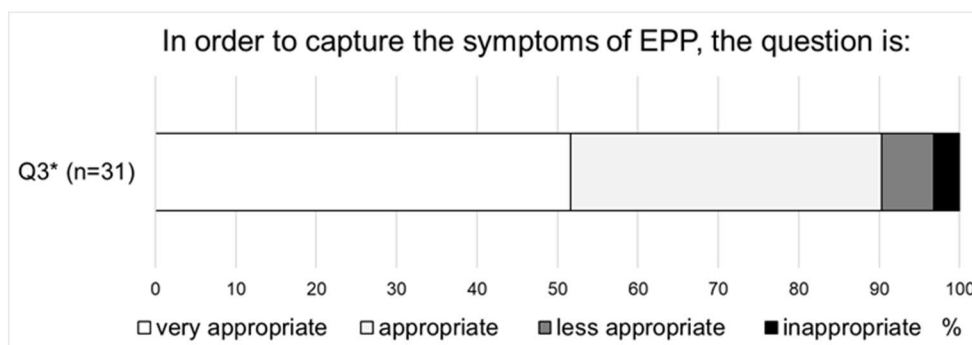
3.1.3. Q2*: Over the last two months, how much has your EPP symptoms influenced your capacity to go to work or school?

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.



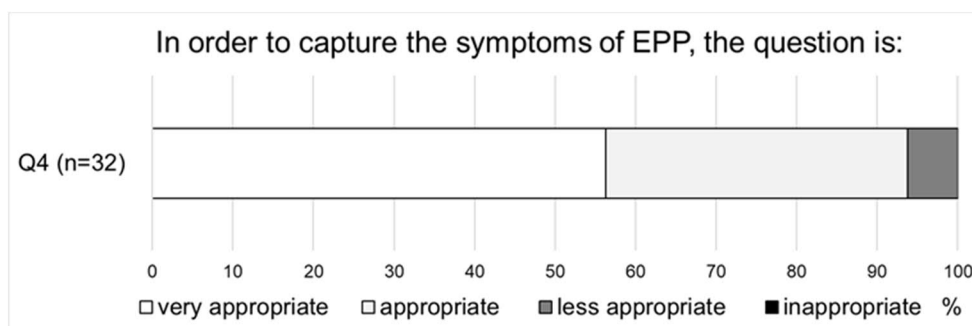
3.1.4. Q3*: Over the last two months, how often did you feel the need to seek out shade?

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



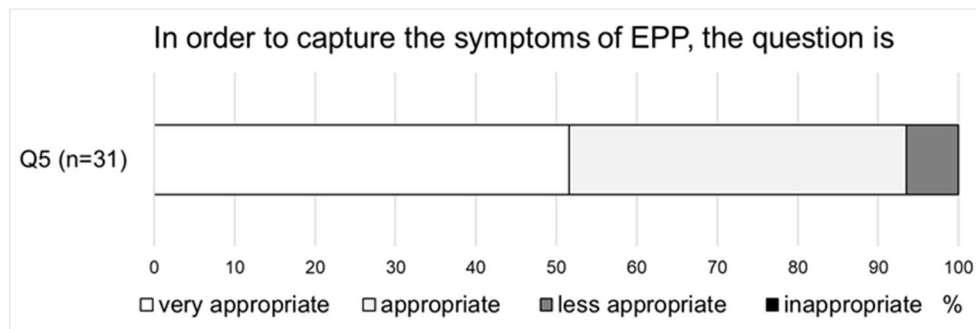
3.1.5. Q4: Over the last two months, how much has EPP influenced the choice of the clothes you wear on a sunny day?

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.



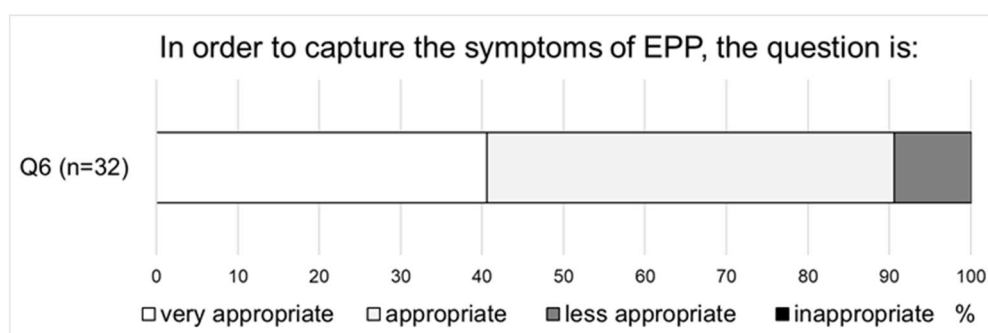
3.1.6. Q5: Over the last two months, how often did you feel you were at risk of developing EPP symptoms?

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.



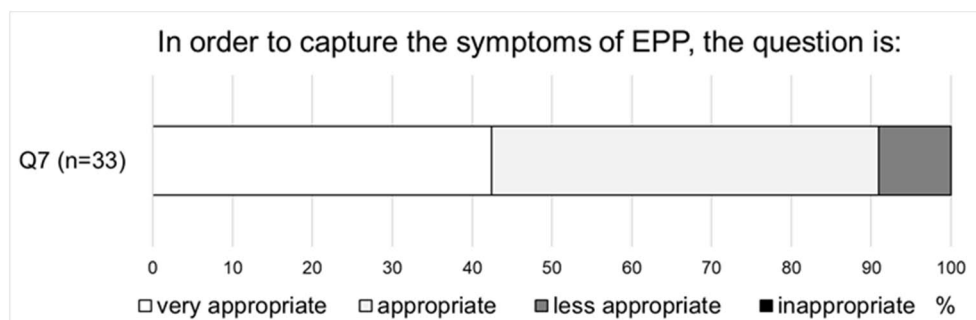
3.1.7. Q6: Over the last two months, how much has EPP affected any social or leisure activities on a sunny day?

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



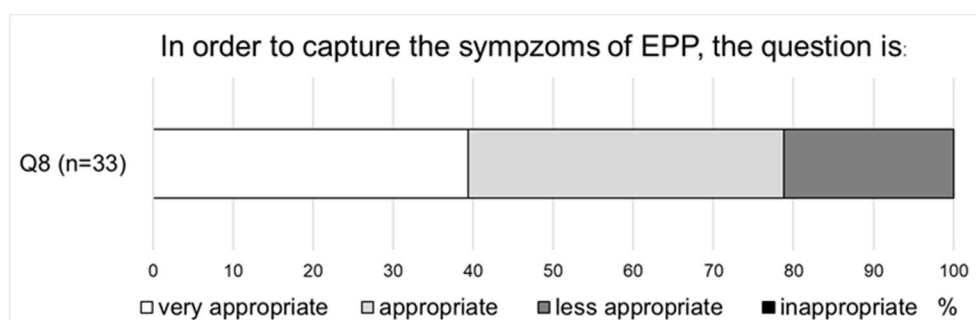
3.1.8. Q7: Over the last two months, how much has EPP influenced your need to plan before leaving your house?

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



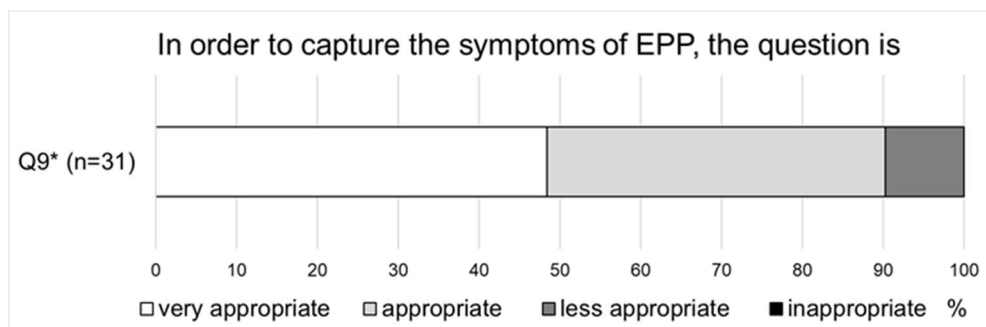
3.1.9. Q8: Over the last two months, has EPP limited your ability to undertake activities in a spontaneous manner?

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



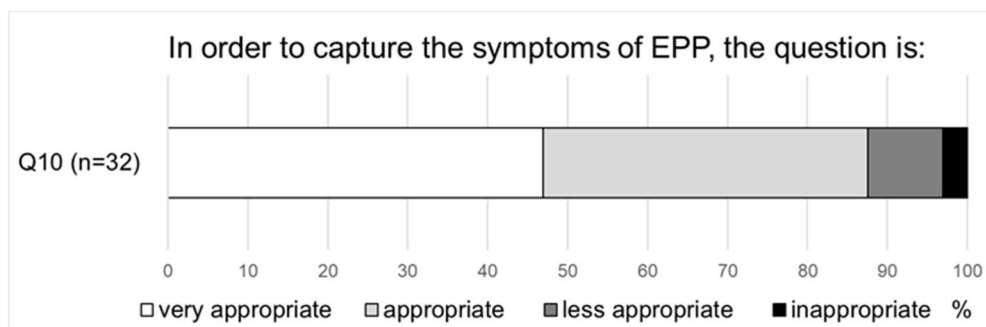
3.1.10. Q9*: Over the last two months, how often have you not worn protective clothing on a sunny day?

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



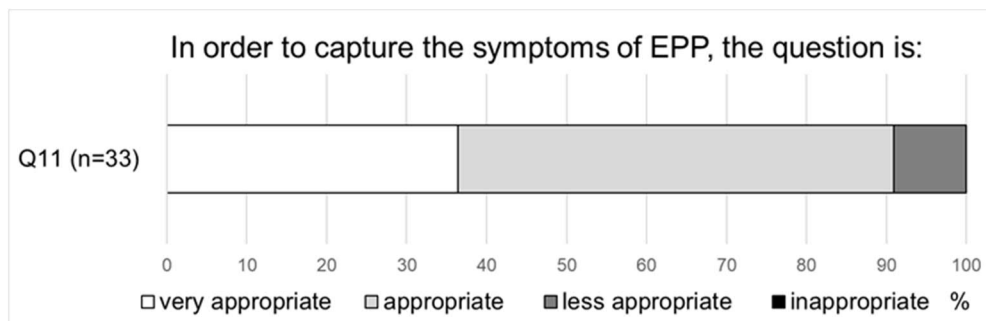
3.1.11. Q10: Over the last two months, how much has EPP interfered with your going shopping or looking after your home (indoors and outdoors) or garden on a sunny day?

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



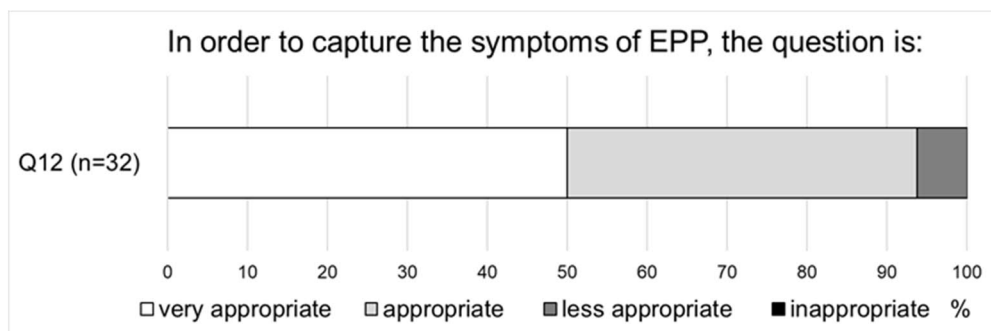
3.1.12. Q11: Over the last two months, how much has EPP prevented you from attending outdoor social activities with family and friends?

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



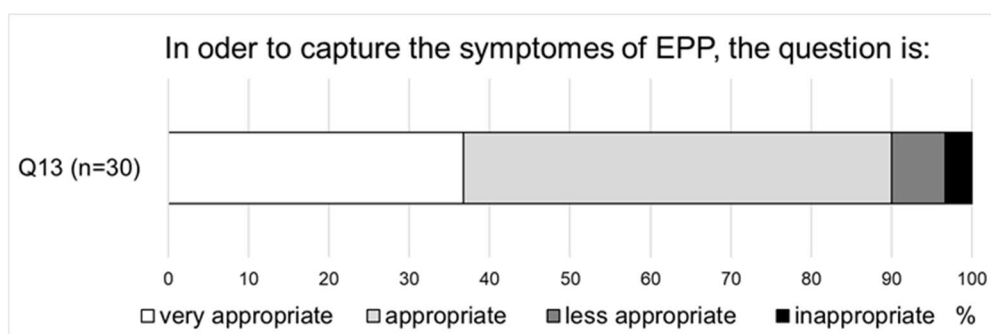
3.1.13. Q12: Over the last two months, how much has EPP limited your amount of outdoor activities?

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.



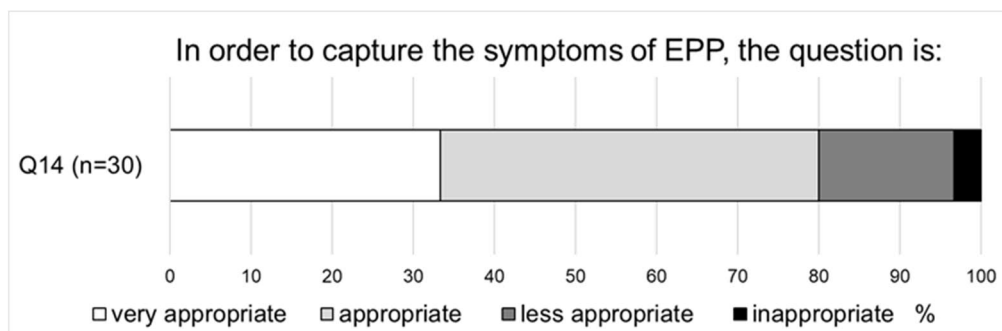
3.1.14. Q13: Over the last two months, how often did you experience typical EPP skin complaints?

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



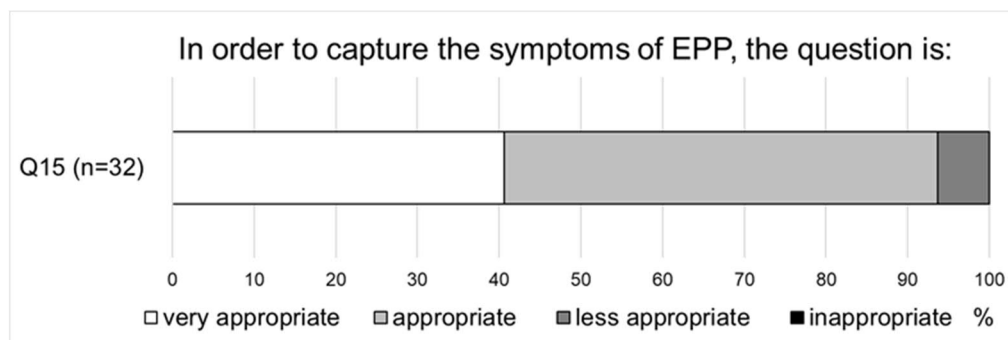
3.1.15. Q14: Over the last two months, how much has your quality of life improved?

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 content 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	EPP-QoL questions ^c
	<u>Over the last week</u> , how much has <u>skin affected</u> ...	<u>Over the last two months</u> , how much has <u>EPP affected</u> ...

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
		Q13. Frequency of typical EPP skin complaints
		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	
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"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	Q10. Going shopping, looking after home or garden on sunny day
	Q4. Clothes you wear	Q4. Choice of clothes on sunny day
		Q9. Frequency not wearing protective clothing on sunny day^d
		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 activites	Q6. Social or leisure activities on sunny day
	Q6. Sport	Q11. Outdoor social activities with family and friends
		Q12. Amount of outdoor activities
		Q7. Need to plan before leaving house
		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
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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	
	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	
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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
		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 content 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 content 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)	<u>87.5 % loss in sensitivity</u> 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	<u>Approx. 20 % loss in sensitivity</u> 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	<u>50 % noise</u> 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). 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	<u>20 % - 25 % relevant outcomes missed in the DLQI</u> : 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 content 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 important²³. 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 its individual minimal important differences, for example Shikier and colleagues established the minimal important difference for chronic idiopathic urticaria between 2.24 points and 3.10 points using DLQI measurements. (Shikier 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 it 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.

Lastly, 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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