NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Afamelanotide for treating erythropoietic protoporphyria [ID927]

Contents:

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

Pre-meeting briefing

Afamelanotide for treating erythropoietic protoporphyria

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues (1)

Clinical effectiveness

- Are the clinical trials generalisable to clinical practice in England?
- How and in which seasons will afamelanotide be used in clinical practice?
- Does evidence from trials suggest that afamelanotide is effective in treating EPP?
  - Is the estimated efficacy of afamelanotide measured in clinical trials affected by the conditioned behaviour of light avoidance in EPP?
  - Is there any evidence that the conditioned behaviour of light avoidance in EPP could be reversed?
  - What support may be required to reverse conditioned light avoidance?
- Do the trial outcomes reflect the anticipated real life benefits of afamelanotide?
- What is the impact for patients of
  - more hours in light without pain?
  - fewer phototoxic reactions?
  - What is the minimally important difference for these outcomes from patients'/clinicians' perspective?

Key issues (2)

Quality of life

- What is the most appropriate measure to capture the quality of life of people with EPP? Generic dermatology DLQI or non-validated condition specific EPP-QoL?
- Are there any aspects of EPP impacting on quality of life that are not captured by generic quality of life measures?
- Are the proxy conditions suggested by the company to have similar quality of life to EPP appropriate?
- Does afamelanotide improve quality of life?
- Are patient experiences of EPP and afamelanotide in England similar to those reported in other European porphyria centres?

Key issues (3)

Cost effectiveness

- What are the strengths and limitations of using the following approach to model benefits:
  - Using EPP-QoL data from trials to stratify patients and using a proxy condition to derive the weighting of each strata in the model (company model)
  - DLQI values from a clinical trial mapped to EQ-5D to model the benefits over time with afamelanotide (ERG preferred approach)
  - What is the committee's preferred approach?
- What is the most appropriate measure of benefits for the purpose of evaluating whether afamelanotide is a value for money use of NHS resources?
  - Incremental cost per disability adjusted life year (DALY) averted?
  - Incremental cost per quality adjusted life year (QALY) gained?
- Are there any groups of people for whom afamelanotide would be expected to be more or less cost effective?
- What are the anticipated stopping rules for afamelanotide?

Key issues (4)

Cost effectiveness – issues related to scenario analyses

- What is the expected average number of implants per year?
- Afamelanotide is taken for part of the year (up to 4 implants~8 months)
  - How quickly does afamelanotide have a treatment effect? Immediately after the first implant or does protection against phototoxicity build up over time?
  - What would happen to treatment effect after the last implant of the year? How long does treatment effect persist?

Contents

Disease background

- Erythropoietic protoporphyria (EPP) is a genetic disorder of ferrochelatase enzyme deficiency; approximate prevalence of 513 patients in England (company estimate)
- Results in accumulation of protoporphyrin IX (PPIX) in skin and liver.
- Protophyrin IX reacts to visible light (sunlight and some artificial light) and can cause anaphylactoid and phototoxic reactions in people with EPP
- Phototoxic reactions cause damage to subdermal capillary walls resulting in erythema (redness of skin), oedema (swelling) and intense burning sensation, which can last weeks until damage heals. Symptoms are exacerbated or prolonged by further exposure to light, heat variation, pressure and air movement.
- Patients report severe anxiety during reactions and suicidal ideations have been reported
- Cumulative exposure to light has a 'priming' effect. An exposure to a few minutes of daily light will eventually trigger phototoxic reactions
- There is no effective treatment and patients avoid light. The consequences of long term light avoidance on physical and psychological wellbeing is not fully understood, but is linked to anxiety, social isolation and very poor quality of life.
- 2 -5% patients experience liver failure, but for the majority of patients with EPP life expectancy is normal
- The long term prognosis is uniform but the severity of the condition can vary from patient to patient (clinical expert statement)

Current best supportive care for EPP

- There is currently no effective treatment available on the NHS
- No painkillers are beneficial
- Patients need regular monitoring (including full blood count, iron stores, liver function, vitamin D and red cell protoporphyrin). This is done annually. Patient groups report that some EPP patients are not receiving any regular follow up

Current options	Issues for patients
Light avoidance + sun protection (complete light blocking creams like Dundee cream) + clothing	Patients also need to take vit D supplements to correct deficiency. Creams conspicuous, ruin clothing. Social isolation.
Oral beta carotene* Typically taken April- Oct. 50- 100 mg daily children; I50-300 mg adults. 15 mg or 25 mg capsules available	Large number of daily capsules. Can cause orange tinge to skin which can be unacceptable to patients
Narrow band UVB therapy* 12 visits (visits may be 2-3 times a week) patients need to “top up” treatment by going out in sunlight	Not often suitable (suitability assessed by photodermatologist, only at specialist centres) Top up cannot always be achieved May experience redness or soreness.

* these have not been shown to be effective and are decreasingly used

Patient experience: symptoms (1)

Severe pain on exposure to light

- Often rapid, unbearable pain can develop within less than 5 minutes in the light
- Even on total retreat from light into a darkened room, it can take days, in some cases weeks for body and skin to return to the point where light can once again be tolerated

Patients describe the pain:

- "*The skin which has been affected during an attack cannot be touched by even a sheet, as that feels like a knife on your body – even opiates are ineffective for the pain.*"
- The pain is accurately described [by American patient with EPP] as like *"lava being poured [over skin]… burning from the inside out…"*.

Patient experience: symptoms (2)

All encompassing tiredness

- All encompassing tiredness is common to all EPP sufferers and results from having a body (more specifically a blood supply) that is constantly trying to heal from the damage the EPP reaction causes in the haem formation process.
- Patient description of the tiredness accompanying an EPP reaction:

"*EPP reactions just lay me flat. When I'm not suffering an EPP reaction I'm a very energetic person. But when the EPP hits I'm absolutely useless to myself, my employers and everyone around me. All I can do is retreat to bed and wait for my body to repair itself. This can take days. Until then every little thing is a huge effort. The frustration with not being able to function is intense. I become grumpy, unsociable and hit out at even the simplest request. Were my family not so understanding I'd be living a very lonely life by now!*"

Patient experience: diagnosis delays

- The condition is normally diagnosed clinically by dermatologists and can only be confirmed by specialised laboratory testing.
- There may be a delay to diagnosis because of the complicated nature of the condition
  - Median diagnosis age reported to be 22 years although for most symptoms exist from birth or soon after.
- The main challenge in diagnosing EPP is that for some people skin symptoms are not visible, despite severe and unrelenting pain following exposure to visible light.
- Public awareness of the condition is extremely low - approaching zero apart from people who are extremely close to those who have actually achieved a successful diagnosis. Detailed awareness and understanding of EPP in general medical practice is also low.
- Delayed diagnosis can mean that patients are incorrectly assumed to have allergies, or are simply thought to be overly dramatic. Patients are often left alone with their burning and painful skin and suffer isolation and incomprehension from those in their immediate surroundings, e.g. family, work, or when seeking help from medical professionals.

Patient experience: impact of phototoxic reactions

- A patient's daily life is primarily driven by the need to remain safe and secure from the light that triggers phototoxic reactions. Even patients amongst the least severely affected have reported suicidal feelings during the periods they are suffering a reaction
- The debilitating pain and tiredness impacts on social and family life, where establishing and maintaining relationships can be extremely difficult, leading to isolation and depression
- *"I would hide my pain from friends or even family which adds another layer of suffering… ."*
- Study opportunities, job security and career development are negatively affected by days lost to EPP symptoms, which has a subsequent effect on career progression, earnings potential and lifetime earnings.
- Compensating for the effects of and preventing phototoxic reactions adds significantly to the costs of carrying out normal daily life. Restricted options and preventative measures required to take part in other normal activities often adds hundreds, if not thousands of pounds sterling to the cost of living for both patients and their families. Lifetime costs can easily extend into hundreds of thousands of pounds.

Patient experience: impact of light avoidance

- Patients suffer stress and anxiety associated with the expectation of pain from EPP symptoms and are frustrated by being unable to participate in 'normal' day-to-day life.
- Compromises made by patients include: only going outside after dark and working night jobs; minimising travel; needing help from others for everyday tasks (such as school run, shopping); adapting houses/ vehicles with light filters; choice of clothes to minimise light exposure
- Physical and mental health can be affected due to the lack of opportunity to participate in sport and exercise.
- *"I am forced to isolate myself from friendships groups and lack the shared experiences and bonding with them. I often feel down, low and frustrated due to the limitations of my condition."*
- *"I have no freedom, I am ruled by the light! I cannot plan ahead, I cannot just go for a walk or mow my lawn. I cannot pop to the shop, or take my kids to the park! I have to assess how I feel on that day, can I cope with the light? Is it going to get sunnier? What is the UV rating? So .. life becomes a muddled ball of anxiousness!"*
- "*I cannot wear what I want to! This leads to issues with not feeling at your best! It is tough to wear layers in the heat when you are burning already!*"

Patient perspectives: impact of EPP on work

The British Porphyria Association reported the results of a survey carried out by an EPP patient organisation in the Netherlands:

- 91% patients changed careers because of EPP
- 40% patients reported losing a job because of EPP
- 46% patients took several [multiple consecutive] sick-days after an EPP-attack in the last 5 years
- 35% patients can only work with adjustments

The British Porphyria Association noted that is not aware of a similar study in the UK, but engagement with its members suggests these figures are likely indicative for the UK too.

Patient experience: impact on family and carers

- Sometimes family members have the burden of responsibility of caring for or supporting a parent with EPP. This can have an impact on the social, educational and career potential for children and other family members.
- EPP has also been known to be the cause of relationship breakdowns. Family tensions often run high as a result of the direct and indirect impact of phototoxic reactions with detrimental effects on family life.
- Children of parents with EPP are often unable to take part in events due to being unable to have parental supervision – even when simply playing outside. This can impact on their physical well-being. Furthermore, family members can also experience psychological isolation due to being unable to take part in events, even though they don't have the condition.
- Family experiences are limited or undertaken without the EPP patient. When important life experiences are not shared, subtle disconnects emerge. Life paths diverge.
- EPP can limit normal interactions. For example a person with EPP may be unable to hug a child or hold their hand when sore from a reaction *"That is hard for a child who just needs comforting, they do not always understand, this make it hard for us as sufferers too!"*

Patient experience of afamelanotide

- British Porphyria Association: members who were involved in trials suggest that the reduction in severity of attacks and reduction in recovery times will greatly reduce and even eliminate some of the factors that presently impinge on quality of life
- Selected patient experiences from other European countries
  - Ten minutes passed, the 20,30, 40 minutes and more in the sun without the typical painful symptoms! After over 40 years… I finally have something against EPP… this treatment changed my life!"
  - "For the first time I have experienced how pleasantly warm the sun can feel"
  - "For the first time in over 50 years, I was able to venture to the store without the threat of enduring 2 days of excruciating pain"
  - …."Two years ago we feared for our son's life as he was in such a dark place due to the cruel and painful effects of EPP. At that time he was on academic probation and had to go on meds to control his anxiety. Today, he is a happy, healthy and vibrant member of the student body at his college…"
  - "For the first time in my life I could accompany my daughter to an athletic competition"..
  - "Both my sister and I were in the Phase III trial for this drug and my sister received the 'real thing' and it positively changed her life during those 6 months… she was finally able to participate"

Afamelanotide

- Marketing authorisation granted by EMA (2014)
- indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).
- Afamelanotide is a chemical analogue of alpha-melanocyte stimulating hormone. It increases the melanin content of the skin. It does not need exposure to light in order to be effective in stimulating melanin
- Melanin protects against phototoxicity by:
  - absorbing UV and visible light
  - antioxidant activity
- The marketing authorisation stipulates it should be administered at a specialist porphyria centres. In England these are:
  - Salford Royal (Salford)
  - St James' University Hospital (Leeds)
  - Kings College Hospital (London)

Afamelanotide dose and administration

Formulation	Controlled release injectable implant
Administration	Subcutaneous injection
Doses	16mg
Dosing frequency	One implant is administered every 2 months prior to expected and during increased sunlight exposure, e.g. from spring to early autumn. Three implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year. The overall duration of treatment is at the specialist physician's discretion
Average course of treatment	Up to four implants per year (lifelong treatment). Average dose of *** implants per year seen in treatment to date.
Price	£12,020 per injectable implants

Decision problem (1)

Intervention(s)	Afamelanotide
Population(s)	Adults with erythropoietic protoporphyria
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • duration of tolerance to sunlight and other forms of visible light • phototoxic reactions • change in melanin density • adverse effects of treatment • health-related quality of life (for patients and carers) • mortality

Decision problem (2)

- The final scope issued by NICE stated that value for money should include a cost effectiveness assessment using incremental cost per quality-adjusted life year (QALY). The company have not presented a cost effectiveness assessment using QALYs.
- The company has stated that it does not consider the QALY framework to be appropriate, instead measuring treatment benefit in DALYs – disability adjusted life years and presenting ICERs per DALY averted (rather than ICERs per QALY gained).
- This is outside of the NICE reference case and the company were encouraged to presented QALY-based analyses as the base case, supplemented by DALY analyses as appropriate. However the company maintain that this approach would not be suited to this condition.
- The Evidence Review Group (ERG) considers that measuring QALYs is feasible and have presented these results.

Clinical effectiveness

- The data presented is from the company submission (section C).
- This has been supplemented with published data from the European Public Assessment Report (EPAR) and a trial publication reporting on 2 of the trials (Langendonk et al 2015). The data from the EPAR and Langendonk et al 2015 was extracted by the Evidence Review Group.
- For background, the considerations of the European Medicines Agency on granting a license for afamelanotide under exceptional circumstances have been summarised from the EPAR (by the NICE technical team). These are presented in the appendix slides.

Double blind, placebo controlled RCTs

Source	Trial name	Location, duration and numbers enrolled	Primary outcome(s)
Langendonk 2015	CUV029	Europe 9 months (5 doses) N=76 (16 from UK)	Time (hours) in light with no pain between 10:00 to 15:00/person/study period
Langendonk 2015	CUV039*	USA 6 months (3 doses) N=94 (93 treated)	Time (hours) in light with no pain between 10:00 and 18:00/person/study period
Clinuvel unpublished	CUV030	USA 6 months (3 doses) N=77	Time (hours) in light between 10:00 and 15:00 and 10:00 and 20:00 on pain free days
Clinuvel 2010 unpublished	CUV017	Australia/Europe 12 months (Crossover study 3 doses of afamelanotide and placebo) N=100	Frequency of phototoxicity "pain"

* Considered by EMA to be pivotal trial for its regulatory decision

Observational studies

Source	Study name	description
Biolcati 2015a	N/A	Long term observational study of 146 patients with EPP treated with afamelanotide in Switzerland + Italy (Biolcati reports on 115). Incorporates data from single arm Phase II study (CUV010) and CUV017 as well as ongoing use of afamelanotide in compassionate use and expanded access programmes. Data reported from patient with follow up from 2006 to 2014 (patients treated for up to 8 years)
Langendonk 2017	CUV-PASS-001	Ongoing post authorisation disease registry safety study. N=104 European EPP expert centres Data reported from June 2016-31 May 2017
Harms 2009b	CUV010	Single arm study, n=5 of afamelanotide (20mg). Primary outcome was photoprovocation response time

CUV039 was the pivotal trial in the regulatory decision making

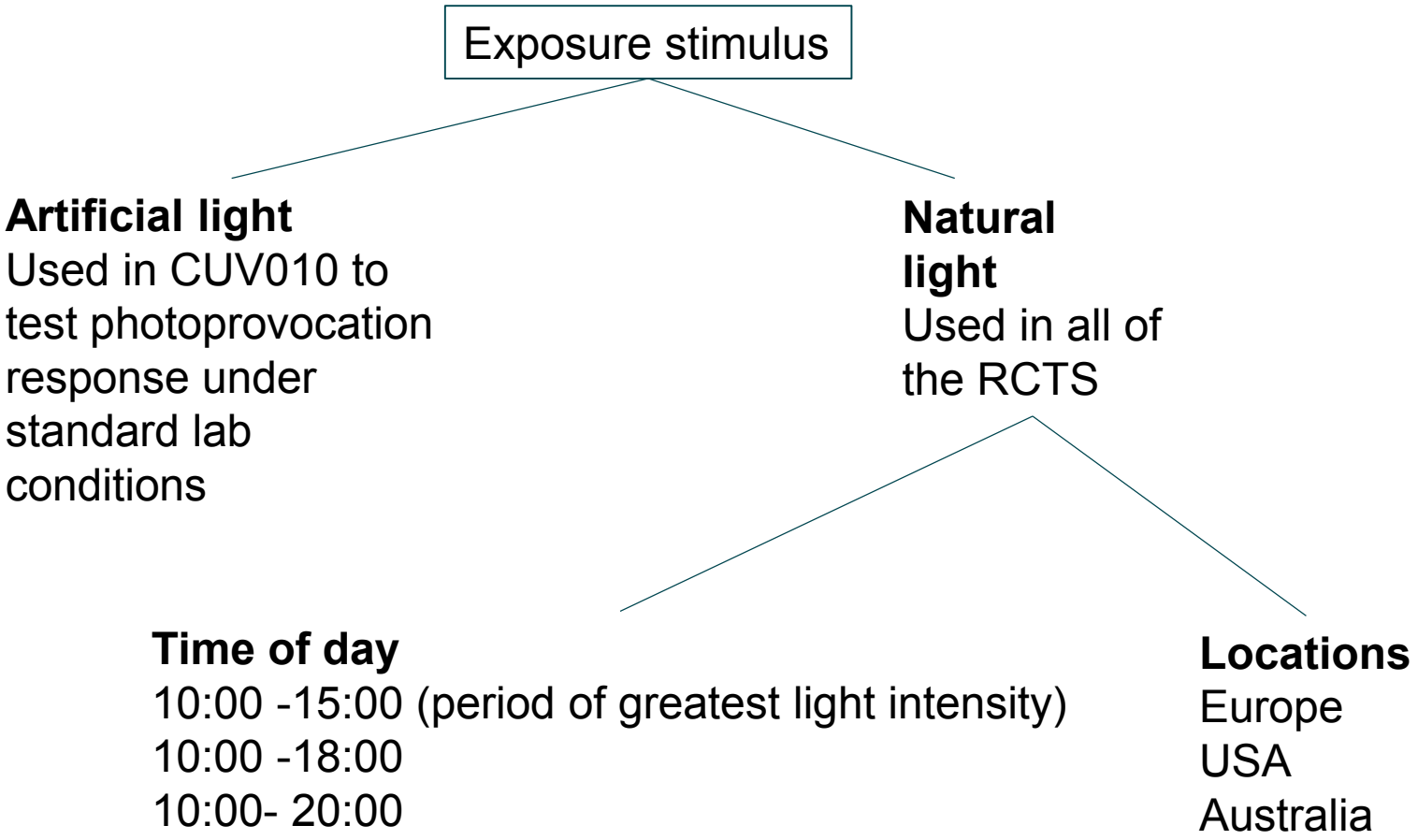
The EPAR reports that a Good Clinical Practice (GCP) inspection was conducted on studies CUV029 and CUV030 as a result of changes to their analysis plans and the lack of clarity regarding sample size. The conclusion of the inspection was that the main efficacy data from these two studies were not considered robust and they could not be used to inform the marketing authorisation of afamelanotide.

The key criticisms were:

- that the design of the patient diary for capturing the data as needed for the analysis of endpoints related to duration of sun exposure was not suitable;
- the change to the statistical analysis plan of study CUV030 after data had been analysed;
- Improper statistical planning and data handling for both trials and
- Verification of the databases and of relevant events such as database lock / unlock was not possible.

The inspection of study CUV039 concluded that it was compliant with the GCP hence its status as the sole pivotal study informing marketing authorisation.

Light stimuli used in the clinical trials



In trial programmes spring and summer period was defined as 15th March to 1st October in Europe

Reporting of outcomes

Outcomes in clinical trials (1/4)

Outcome	Description	Trial in which measured	Data reported (source)*
Duration of tolerance to sunlight and other sources of visible light			
Hours with no pain	Patients with no pain (or mild pain) kept a diary of how many hours they voluntarily exposed themselves to light (between set time periods within a day over the course of the study). The results are the cumulative values over the course of the study.	All RCTs	CS ERG (EPAR, Langendonk)
Hours with no pain or mild pain			

*The company submission is inconsistent in terms of whether it reports effect size, baseline and follow up values, p values and it does not include all published results for the CUV clinical trials. For background, this pre-meeting briefing also includes data reported in the EPAR or a publication from the clinical trials of afamelanotide (Langendonk et al 2015), which has been extracted by the ERG, in addition to data presented in the company submission.

Outcomes in clinical trials (2/4)

Outcome	Description	Trial in which measured	Data reported (source)
Phototoxic reactions (measured pain aspects of phototoxicity using Likert scale [0= no pain; mild 1-3/4*; moderate 4 to 6; severe 7 to 9; 10= worst imaginable])			
Number	Number of episodes with Likert score ≥4 on 1 or more consecutive days	CUV010, CUV017 CUV029 CUV030 CUV039 Ongoing CUV-PASS-001	ERG (Langendonk CUV039; EPAR)
Total severity of individual phototoxic reaction	Sum of Likert scores over all days of individual reaction		
Maximum severity	Highest daily Likert score during reaction		

* See notes

Outcomes in clinical trials (3/4)

Outcome	Description	Trial in which measured	Data reported (source)
Health related quality of life			
SF-36	The company stated that it does not consider the SF-36 and DLQI suitable to quantify the humanistic burden of EPP	CUV010 CUV017	None
DLQI		CUV029 CUV030 CUV039	ERG reported DLQI outcomes from CUV039 from EPAR
EPP-QoL	12 and 15 question versions have been produced. This is a new disease specific questionnaire designed by expert porphyria physicians with company	CUV029 CUV030 CUV039 (+ Biolcati)	Company reported statistical significance and difference magnitude from CUV trials. ERG reported mean values at each time point for CUV029 and CUV039

Outcomes in clinical trials (4/4)

Outcome	Trial in which measured	Data reported (source)
Change in melanin density	CUV010 Secondary outcome in CUV029	Company submission (CUV010)
Adverse events	All RCTs	Company submission
Mortality	Survival was not an outcome in the trials.	Not applicable

Outcomes - results

Hours in direct sunlight with no pain

Outcome	Study CUV029 (Europe)		Study CUV030 (USA)		Study CUV039 (USA)	
	AFA N=38	PLA N=36	AFA N=39	PLA N=38	AFA N=46	PLA N=43
Time period of light exposure 1 :10:00-15:00 (5h)						
Mean hours (SD)	20.4 (± 40.5)	5.6 (± 9.3)	Not reported		71.2 ± 89.2	41.6 ± 45.3
Median (range)	5.63 (0-194)*	0.75 (0-36)*	8.88 (0-48.3)*	0.75 (0-70.3)*	39.6 (0-419)	31.8 (0-199)
P value	p=0.006*		P=0.011*		p=0.092 [a]	
Time period of light exposure 2: 10:00-20:00 (10h)					**10:00 -18:00 (8h)**	
Mean (SD)	Not reported		Not reported		115.6 ± 140.6	60.6 ± 60.6
Median (range)	***	***	16.0 (0-126.3)*	1.25 (0-106.3)*	69.4 (0-651)	40.8 (0-224)
P value	Median difference between groups p=0.007*		Median difference between groups p=0.06*		Median difference between groups p=0.044	

* Reported in company submission, other results reported in ERG report tables 6 + 7,
[a]extracted from EPAR by ERG (not in company submission or Langendonk 2015)

Hours in direct sunlight with mild or no pain

Outcome	Study CUV029 (Europe)		Study CUV039 (USA)	
	AFA N=38	PLA N=36	AFA N=46	PLA N=43
Time period 1 :10:00-15:00 (5h)			**10:00-18:00 (8h)**	
Mean hours (SD)	Not reported		141.1 ± 165.1	74.6 ± 67.5
Median (range)	***	***	80.0 (0.5-825)	51.0 (1.25-251)
P value	P=0.043*		P=0.053*	
Time period 2: 10:00-20:00 (10h)				
Mean (SD)	Not reported			
Median (range)	***	***		
P value	P=0.026*			

* Reported in company submission pages 32-33, other results reported in ERG report table 6

Hours in sunlight per day

- The previous slides show the cumulative hours over the course of each study.
- There are limited published data on the number of hours per day a person may be able to be in sunlight with afamelanotide and whether this varies day by day
- ERG: EPAR states that there were 15 people in trial CUV039, who experienced more than 60 minutes of direct sunlight exposure per day. 12 (26%) in the afamelanotide group and 3 (7%) in the placebo group.
- The minimally important clinical difference for duration of exposure to light has not been determined.

Phototoxic reactions: number per person

Outcome	Study CUV029 (Europe)		Study CUV039 (USA)	
	Afamelanotide N=38	Placebo N=36	Afamelanotide N=46	Placebo N=43
Number of phototoxic episodes per subject, mean ± SD; median (range)	2.0 ± 2.8;* 1.0 (0-11)*	4.1 ± 5.1;* 2.0 (0-20)*	2.0 ± 3.3; 1.0 (0-15)	3.3 ± 6.8; 1.0 (0-35)
	Difference p=0.04		Difference p=0.602	
Phototoxic reactions during study - no	77	146	Not reported	Not reported
	Difference p=0.04			

* Reported in company submission page 33, other results reported in ERG report table 8

Phototoxic reactions: duration (days)

Outcome		Study CUV029 (Europe)		Study CUV039 (USA)	
		AFA N=38	PLA N=36	AFA N=46	PLA N=43
Duration of photo-toxic reactions	Mean (SD)	Not reported		3.2 (± 6.0)	6.6 (± 16.8)
	Median (range)			1.0 (0-34)	1.0 (0-98)
				Difference p=0.50	
Duration of longest phototoxic reactions	Mean (SD)	1.5 (± 1.8)	3.8 (± 7.4)	1.3 (± 1.9)	1.7 (± 2.1)
	Median (range)	1.0 (0-7)	2.0 (0-37)	1.0 (0-12) [a]	1.0 (0-10) [a]
		Difference p=0.08		Difference p=0.519 [a]	
Duration of photo-toxicity, per patient,	Mean (SD)	3.7 (± 5.6)	10.0 (± 18.3)	Not reported	
	Median (range)	1.0 (0-23)	3.0 (0-90)		
		Difference p=0.04			

Results reported in ERG report table 8. [a] these data were not reported in the company submission or Langendonk et al 2015 and were extracted from the EPAR by the ERG

Phototoxic reactions: severity (Likert score)

Outcome		Study CUV029 (Europe)		Study CUV039 (USA)	
		AFA N=38	PLA N=36	AFA N=46	PLA N=43
Sum of Likert score for severity of phototoxic reactions during study	Mean (SD)	***	***	16.3 ± 33.2	34.1 ± 86.7
	Median (range)	***	***	4.0 (0-196)	6.0 (0-507)
		Difference p=0.025*		Difference p=0.44	
Overall maximum Likert score per patient	Mean (SD)	***	***	3.5 ± 3.1	3.9 ± 3.3
	Median (range)	***	***	4.0 (0-8)	5.0 (0-9)
		Difference p=0.010*		Difference p=0.544	
Patients with severe phototoxic reactions, n (%)		25 (66)	28 (78)	Not reported	

* Reported in company submission page 33, other results reported in ERG report table 8

Melanin density

- Measured in CUV010 (single arm study n=5)
- Company submission (page 26): melanin density (MD), quantified by spectrophotometry, increased during the first 30 days after administration at all tested sites with one exception in one patient. The change in MD as measured on days 30, 60, 90 and 120 (measured at 6 anatomical sites) was significantly different to baseline (p=0.0043). The increase in pigmentation induced darkening of the dermis with a natural appearance.
- ERG report (page 55) [Biolcati et al] reported an increase in melanin density that was maintained over the six year treatment assessment period. The increase was around 1 unit (1 unit corresponds to roughly the difference in skin colour between two skin types in the 6-point Fitzpatrick scale of skin types)
- ERG report (page 38): melanin density is cited in the afamelanotide EPAR as an indicator of pharmacodynamics, rather an effectiveness outcome (EPAR section 2.4.3).

Mortality

No mortality data was presented in the company submission. However, the company stated that EPP is not associated with a shorter life expectancy for the majority of people without liver complications. The company noted 2 -5% patients experience liver failure.

Conditioned light avoidance in EPP

- Company: clinical trial outcomes may not reflect full benefits of afamelanotide because of conditioned light avoidance
- EPP patients report phototoxicity as the main symptom, consisting of second degree burns, and inexplicable internal “pain” due to endothelial damage (there is no medical nomenclature, hence “pain”; NSAIDs and opioids do not alleviate or treat the internal ordeal).
- Patients have learned to cope with, manage, and accept their disorder since birth and are conditioned to avoid light sources.
- The median delay in diagnosis is 12 years in the UK, but 16 and 18 years respectively in Sweden and Switzerland.
- Patients have learned that there is no treatment and the environment does not recognise the disorder since symptoms are invisible unless a second degree burn occurs.
- Uniquely, EPP patients experience a prodromal phase, signifying that the seconds/minutes of insulting emitted light cause afferent nerve stimulation, which compels patients to withdraw from light sources and avoid further exposure.

ERG comments on clinical effectiveness

- **There is a lack of detail about the trials in the company submission.** Clinical study reports and study protocols for all studies have not been made available to the ERG. Therefore a full independent assessment of the methodological characteristics and results of the studies not possible.
- Unclear if true ITT analysis was used in all trials (which would require all randomised patients to be analysed)
- **Similarity of baseline characteristics between trial arms is unclear**. Full baseline data for trials were requested but not provided by company. Some baseline characteristics presented in the journal article for CUV029 and CUV039. In CUV039 fewer people with Fitzpatrick type 1 skin (never tans, always burns) in afamelanotide arm (16%) than placebo arm (33%). Company commented that there is no evidence that ********** have any impact on the safety or efficacy of afamelanotide.
- **Risk of unblinding by tanning effect of afamelanotide acknowledged by company** (response to clarification question A8). Company stated that this issue had been addressed by the [European Medicine Agency's CHMP, who considered patients may have known their treatment because of tanning, but did not consider this knowledge would have affected patients' behaviour (see notes).

ERG comments on clinical effectiveness

- There were no unexpected differences in people dropping out of each arm of the trials
- Criticisms by the EMA of studies CUV029 and CUV030 need to be taken into account because EPP-QoI data from CUV029/30 is used (pooled with data from CUV039) in the company's assessment of cost-effectiveness
- The clinical effectiveness evidence base comprises four multi-centre double-blind RCTs including approximately 340 patients in total, plus a long-term retrospective observational study of 115 patients providing data on safety and efficacy up to eight years of afamelanotide use. Two of the RCTs included a small number patients from UK expert porphyria treatment centres (amongst other countries). The ERG believes that all relevant clinical effectiveness studies have been included in the company submission.
- The clinical effectiveness studies measured a range of outcome measures of relevance to patients and clinicians, including: time patients are able to spend in sunlight without experiencing pain or with only mild pain; phototoxic reactions; adverse events and HRQoL (though not HRQoL of carers and family members). There do not appear to be any clinically important outcome measures that have not been included in the study programme.

Adverse events

- No serious treatment related adverse events were reported in the placebo controlled EPP studies (CUV017, CUV029, CUV030 and CUV039)
- Headache and nausea were the most commonly reported adverse events related to study drug.
- The most frequent adverse events in Biolcati et al. 2015 (115 patients treated for up to 8 years): nausea, headache, administration site conditions and fatigue.
  - "Afamelanotide caused only mild adverse effects" (Biolcati et al 2015a)
- A risk management plan has been agreed between the EMA and the company. As part of this the company has established the European EPP Disease Registry (EEDR), hosted by the Erasmus Medical Center (Rotterdam, Netherlands). The EEDR captures safety and effectiveness data from European EPP Expert Centres involved in the post authorisation safety study (PASS)
- For the period 23rd June 2016 -31st May 2017, 96 patients in the PASS study experienced adverse events, four serious adverse events (three unrelated to treatment). No unexpected adverse reactions reported.1 report of lack of effect resulting in discontinuation.
- ERG report page 64 The EPAR (p 93) states "Four deaths were reported during clinical studies with the afamelanotide implant, all of which were regarded as definitely not related to study treatment by the investigators.

Adherence to afamelanotide

Biolcati et al 2015

- The company stated that the discontinuation rates were low despite the long duration of treatment and the considerable sacrifice of time and costs for patients.
- British Association of Dermatologists commented: [there is a] very high adherence rate of 74% of patients who continue with afamelanotide, even where their patients have to travel very long distances for treatment (the majority of those that discontinued, i.e. 23%, did so for reasons such as finance and pregnancy)
- The company stated that only three of the 115 patients indicated that afamelanotide did not improve their condition. Most others who left did so for compelling reasons, such as intended pregnancy or intolerable financial burden.

Quality of life

QoL- SF-36

- Used in in CUV017 but no quantitative results provided by company
- The company does not consider the SF-36 captures the humanistic burden of EPP
- The company stated that baseline SF-36 values were higher than expected:
  - mean across all patients of the eight quality of life scales and the physical and mental component scores being above the population average score of 50
  - probably because patients have developed strategies to be able to live with their disease and adapt their daily life to the limits of their disease symptoms without compromising their perceived quality of life
  - may also reflect the reluctance of some EPP patients to admit that they have a disease which can alter their lifestyle
  - there were no marked trends over time between the two groups associated with the dose administered per period
- EPAR states that in study CUV017 results “showed no improvement in QoL during and after treatment with Scenesse” (company submission p 85) but no further detail is presented

EPP-QoL

- The EPP-Qol instrument has been designed specifically to measure the impact on EPP
- Company stated that trials CUV029, CUV030 and CUV039 demonstrated improvements in QOL with afamelanotide treatment.
  - CUV029: at each time point (Days 60, 120, 180, 240 and 270), the mean EPP-QoL score was lower for the afamelanotide group than for the placebo group ($p=0.011$ at Day 270) (page 33 Company submission)
  - CUV030: at each time point (Days 60, 120 and 180), mean change from baseline for the afamelanotide group was approximately twice that of the placebo group ($P<0.05$) (page 35 company submission)
  - CUV 039: median change from baseline for the afamelanotide group was between 1.6 and 1.9 times that of the placebo group using the original scoring algorithm. The differences between the treatment groups at Days 60, 120 and 180 were statistically significantly in favour of the afamelanotide group (page 38 company submission)
- Biolcati et al. 2015: 'The [EPP-QoL] scores being only 32% of maximum before initiation of afamelanotide treatment rose strongly after initiation of treatment to 74% and remained stable at this level during the whole 6 years of observation'

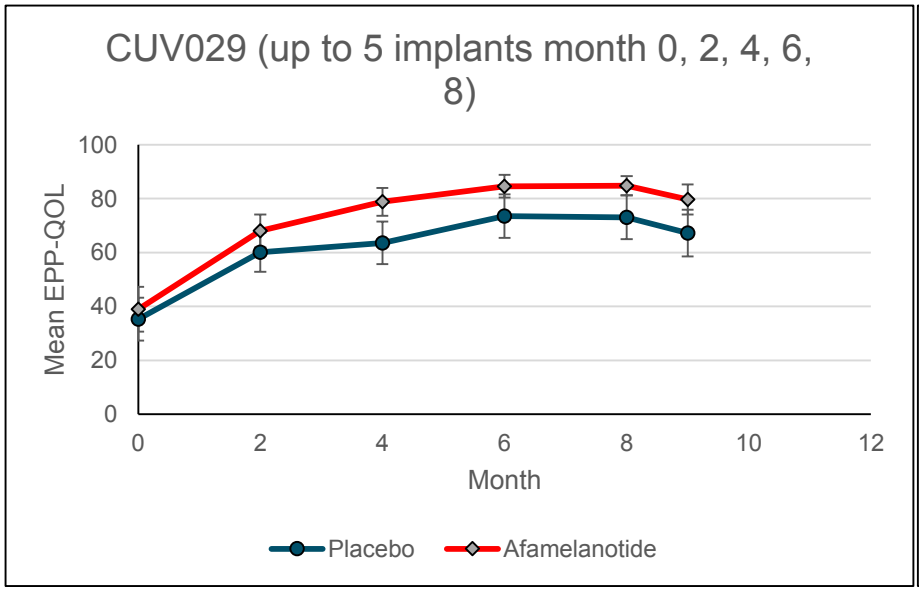
EPP-QoL scores over time

Trial and questionnaire score	Afamelanotide			Placebo		
Study CUV029 (Europe)	Mean	sd	n	Mean	sd	n
Baseline score at day 0, before dose 1	39.00	25.80	37	35.30	23.70	34
Score at day 60, before dose 2	68.00	19.10	37	60.10	22.00	35
Score at day 120, before dose 3	78.80	16.20	37	63.60	23.90	35
Score at day 180, before dose 4	84.60	12.60	35	73.50	24.30	35
Score at day 240, before dose 5	84.80	10.70	34	73.10	24.10	34
Score at day 270, final visit	79.70	16.10	32	67.20	25.70	34
Study CUV039 (USA)						n
Baseline score at day 0, before dose 1	26.6	19.9	47	26.2	19.4	43
Score at day 60, before dose 2	70.6	24.2	47	49.6	29.8	43
Score at day 120, before dose 3	76.9	22.0	46	55.8	30.2	42
Score at day 180	78.1	24.9	46	63.0	26.2	43
Scores at day 360, 240 days after last dose	38.4	27.0	44	45.4	29.6	40

ERG report table 10. These data were extracted from Langendonk et al by the ERG

EPP QoL – ERG comments

The ERG plotted the mean EPP-QoL scores reported in Langendonk for CUV029 and CUV039. The final EPP-QoL measure was on day 270 in CUV029 (a month after the last implant) and at 1 year in CUV039 (8 months after last implant)



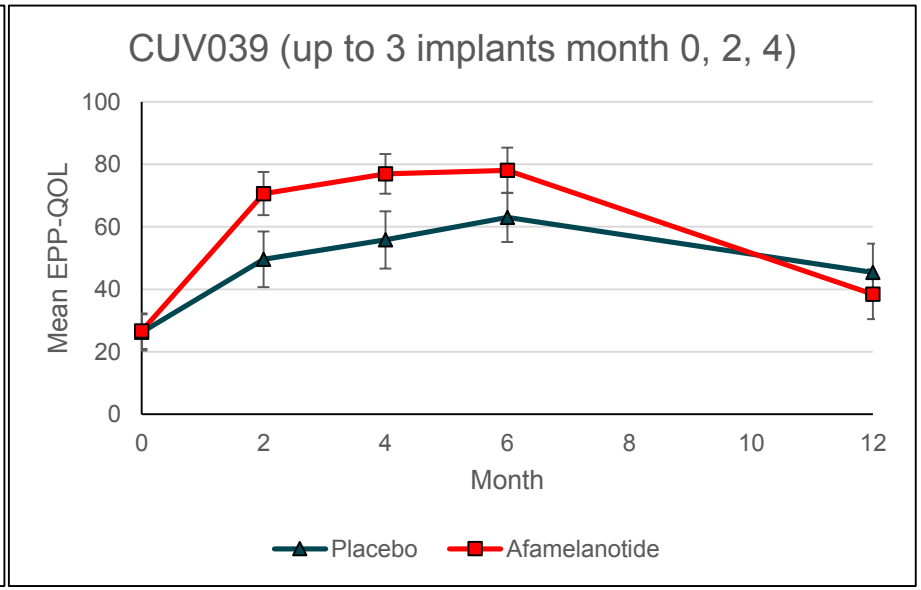


Figure 1 ERG report page 80 (data plotted from Langendonk et al 2015)

EPP-QOL – ERG comments

- The instrument contains highly specific questions about impact of the condition on ability to undertake daily activities, choice of clothing but no questions on pain (one of the most debilitating aspects of the condition).
- Overall the results from studies CUV029 and CUV039 show that HRQoL increases following implant and is maintained over time as implants are replaced every 60 days. However, the clinical significance of the increases observed is unclear no clinically justified interpretation of changes in EPP-QoL scores is available.
- Has not been fully validated and minimal important clinical difference in EPP-QoL not known; important because EPP-QoL results are the only outcome from the clinical effectiveness studies that directly inform the company's cost-effectiveness analysis.
- EPP-QoL score thresholds have not been clinically justified by the company

Dermatology Life Quality Index (DLQI)

- Administered to patients in the CUV029, CUV030, and CUV039 studies but no results presented by the company citing inappropriateness of the DLQI for assessing quality of life in EPP since this questionnaire was not developed to capture the impact of light on skin and its influence on the lives of patients.
- ERG extracted data from the EPAR for study CUV039 (table 11 ERG report)

Visit (day)		afamelanotide	placebo	P- value
1 (0)	N	47	43	
	Mean (SD)	10.7 (6.3)	10.4 (5.7)	
2 (60)	N	47	43	
	Mean (SD)	4.7 (5.7)	6.4 (6.0)	
	Change from baseline (SD)	-6 (5.9)	-4 (5.5)	0.214
3 (120)	N	46	42	
	Mean (SD)	2.8 (4.2)	4.1 (4.8)	
	Change from baseline (SD)	-7.8 (6)	-6.5 (6.2)	0.589
4 (180)	N	46	43	
	Mean (SD)	2.4 (4.2)	3.1 (4.1)	
	Change from baseline (SD)	-8.1 (6.2)	-7.3 (5.6)	0.799

DLQI – ERG comments

Appropriateness of DLQI as a measure for EPP

- Company did not consider DLQI to be an appropriate measure for EPP but it has been used in other studies to assess quality of life with EPP (e.g. Holme et al 2006 a UK survey of people with EPP). The wording of the DLQI pain question is "over the last week how itchy, sore, painful or stinging has your skin been?" which is pertinent to the nature of EPP
- The Holme et al survey is the largest survey conducted with people with EPP. It demonstrated that DLQI scores in people with EPP are higher than other skin conditions and is indicative that EPP has a substantial impact on patients' quality of life.

Results from CUV039 and minimal clinically important difference

- No statistically significant difference between afamelanotide and placebo in the change from baseline DLQI score in CUV039.
- For general inflammatory skin conditions (e.g. psoriasis, eczema) a change in DLQI score of at least four points is considered clinically important.
- 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.
- The largest change observed for afamelanotide was around eight points which is double the recognised minimal clinically important difference for general skin conditions.

Cost-effectiveness

Overview of modelling approach

- The company model uses a proxy condition to estimate the disability associated with EPP.
- The proxy condition is associated with different levels of disability dependent on its severity (mild, moderate and severe)
- The company have used pooled EPP-QoL data from the CUV029, CUV030 and CUV039 trials to determine the proportion of people with mild, moderate and severe EPP before and after treatment with afamelanotide
- The results are presented as incremental costs per disability adjusted life year (DALY) averted

Company's economic model: structure and assumptions

Model structure	• ***
	***
Parameters	***
	***
Benefits	Modelled disability adjusted life years (DALYs) averted using a proxy condition (*** to derive disability weights
	***

Background to DALYs

- WHO Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has quantified health losses from a wide range of diseases and injuries. This was a large international survey to elicit judgements from the general public about health losses associated with multiple causes of disease and injury
- Disability weights have been published; the most recent are Salomon et al 2012 (used by the company)
- The weights are between 0 and 1 (the higher the number the greater the disability)
- The weights are applied to the survival estimates for each treatment to produce a disability adjusted life year (DALY)
- The model estimates DALYs as sum of years of life lost and years lived with disability. So, for each year in the model, one year of health life is lost (1 DALY) for each member of the cohort who is dead, and a proportion of a year of healthy life is lost (less than 1 DALY) for each member of the cohort who is alive.

Company's rationale for using DALYs rather than QALYs

Company

- A cost per DALY averted framework provides a better fit for the condition
  - the ability to lead a 'normal' life in the community is severely impacted
  - People adapt to the condition (conditioned behavioural response to avoid light)
- Extreme paucity of robust utility data on which to inform a cost utility analysis.

ERG

- QALYs are a conceptually appropriate metric for quantifying the value of health effects of afamelanotide for patients with EPP, as for other lifelong and chronic disabling conditions
- Satisfactory methods for estimating QALY gain are available and these methods, though not perfect, are superior to the methods used by the company to estimate DALYs averted.

ERG comments: DALY approach and NICE reference case

The ERG assessed the company's DALY approach against the NICE reference case for measuring benefit in order to assess value for money

	Requirements in reference case	ERG comments
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	**Not met.** The outcome measure used in model (12 item version of EPP-QOL) does not include all direct health effects for patients (no questions on pain, distress, anxiety or impact on work).
Measuring and valuing health effects	Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	**Not met**. DALYs the primary measure of benefit.
Source of data for measurement HRQoL	Reported directly by patients and/or carers.	**Met.** EPP-QOL used in the submission to define severity of disease was derived from patients
Source of preference data	Representative sample of the UK population	**Not met**. DALY weights not derived from a representative UK sample.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	**Met.** No QALYs, but the DALYs are the same weight regardless of other characteristics.

Summarised from table 15, page 69 ERG report

Proxy conditions to model EPP

- There are no disability weights specific for EPP
- The company therefore used disability weights for proxy conditions it considered similar to EPP
- The company's first choice of proxy condition for EPP was hereditary angioedema (HAE) because "the acute or subacute reaction seen in HAE resembles best the anaphylactoid reaction observed in EPP at the start of phototoxic episode, whereby oedema, distress and untreatable pain dominate the clinical course". Disability weights were not available for HAE so the company considered alternative proxy conditions for EPP.
- The company used ********** as the proxy condition in its base case. It stated: although the reasons are different, behaviour adopted by individuals with EPP can be likened to that of individuals who suffer from ***** due to a fear of certain environmental factors. ***** is clinically considered as a DSM-IV **********
- ***** was used as a proxy in a sensitivity analysis. The company stated: "In research conducted by CLINUVEL, people with EPP were likened to people suffering with **** (data on file)". No further rationale was presented.

.

Estimation of proportion of people with mild, moderate and severe EPP

- The disability weights for the company's proxy condition were stratified by condition severity: mild, moderate and severe.
- The company transformed the EPP-QoL to a 100 point scale and stratified disease severity as:
  - 'severe' 0 to 33.3
  - 'moderate' 33.4 to 66.6
  - 'mild' 66.7 to 100
- It used pooled EPP-QoL data from CUV029/30/39 to determine the proportion of people in these groups at baseline and at 120 days (the longest follow up interval available in all 3 trials)

	Baseline		120 days	
EPP-QoL Score	AFA (%)	SoC (%)	AFA (%)	SoC (%)
66.7 to 100 [mild]	***	***	***	***
33.4 to 66.6 [moderate]	***	***	***	***
0 to 33.3 [severe]	***	***	***	***

AFA= afamelanotide; SoC = historical standard of care.
Company submission table C12 page 59

Application of disability weights in the model

- The company produced a weighted average (using the disability weights for each level of disease severity multiplied by the proportion of people in each severity group)
- The weighted average disability weights at 120 days were:

	Disability weight used in the model depending on proxy	
	***	***
Afamelanotide	***	***
Standard of care	***	***

- The company applied these weights for the full year (i.e the benefit of afamelanotide was assumed to start immediately after treatment and be sustained after the last implant of the year)

Company submission table C13 page 59

Number of implants

The company estimated the number of implants per person per year as *** in the base case. Based on current averages and predicted future use (NB. The company submission did not give detail on how these data were derived)

Injections per annum per patient	Proportion of patients	Source
*	***	CLINUVEL data on file
*	***	CLINUVEL data on file
*	***	CLINUVEL data on file
*	***	CLINUVEL data on file
*	***	CLINUVEL data on file
***	**********	

Company submission table D5 page 76

Resource use: drug and test costs

Type of cost		Cost per admin/ visit	Source
Treatment	Afamelanotide implant	£12,020	CLINUVEL
	β-carotene (vitamin A)	£0.05	Over the counter pharmacy
	Vitamin D + Calcium	£0.04	
Laboratory tests	Erythrocyte total protoporphyrin	£2.00	NHSSRC; Integrated blood services [DAPS03]
	Plasma porphyrin	£2.00	
	Complete blood count	£2.00	
	Ferritin	£2.00	
	Liver functioning	£1.00	NHSSRC; Clinical biochemistry [DAPS04]

Company submission table D3 page 74.

Resource use: administration and consultation costs

In addition to drug administration costs, afamelanotide requires an appointment to inject each implant and a final visit after the last implant of the year

	Cost per admin/ visit	Source
Principal physician	£135.00	PSSRU 2016; Consultant: medical
Consultant	£135.00	
Nurse	£35.00	PSSRU 2016; Nurse, Band 5
Total annual administration cost of afamelanotide including monitoring and tests: £328.61 (N.B. ERG reported total modelled annual admin cost of afamelanotide as ****)		

Resource use component	Implant injection	Final visit
- Principal physician	30 mins	15 mins
- Consultant	30 mins	15 mins
- Consultant	15 mins	15 mins
- Nurse	1 hour	1 hour

Company submission tables D3 and D4 pages 74 and 75. Annual admin. Costs from table D6 page 77 and ERG report table 19 page 81

Company base case

Intervention	Costs	DALYs
Afamelanotide	***	***
Placebo	***	***
Difference (Δ)	***	***
ICER		£278,471 per DALY averted

Company submission table D9 page 82

Company scenario analyses (1)

The company applied alternative multiplying factors to the disability weights for its proxy condition (**********). The source of these multiplying factors was not stated. In a 3rd scenario the company used an alternative proxy condition (********)

	Mild	Moderate	Severe	AFA	SoC
Base case	***	***	***	***	***
Scenario 1	***	***	***	***	***
Scenario 2	***	***	***	***	***
**********	***	***	***	***	***

Scenario	Analysis	Incremental costs	Incremental DALYs	ICER
	Base case	**********	****	£278,471
DALY proxy change	Scenario 1	**********	****	£208,854
	Scenario 2	**********	****	£417,707
	**********	**********	****	£727,143

AFA afamelanotide; SoC standard of care
Company submission tables D7 page 80 and D15 page 87

Company scenario analyses (2)

- The company tested a scenario in which all people started taking afamelanotide at age 18, with a time horizon of 60 years (lifetime). This had no impact on the incremental costs per DALYs avoided.
- The company tested scenarios in which people received the number of implants recommended per year in the marketing authorisation for afamelanotide (3 implants) or the maximum number permitted per year (4 implants)

Scenario	Analysis	Incremental costs	Incremental DALYs	ICER
Base case		******	*****	£278,471
Age of cohort	18	******	*****	£278,471
Number of implants per year	N=3	******	*****	£378,561
	N=4	******	*****	£503,672

Company submission Table D15 page 87

Company scenario analyses (3)

The company made a series of assumptions on the proportion of the average weekly wage people receiving afamelanotide or standard of care would earn. Assumptions included†

- Mean weekly wage £518 (source cited as a website that was not available)
- Retirement age 62
- Proportion of mean wage with treatment increased from 50 % to 100% at 3 years

Scenario	Analysis	Incremental costs	Incremental DALYs	ICER
Inclusion of societal impact	Afa: Increase from 50% to 100% of mean wage over 3 years	**********	*****	£172,302
	Afa: 50%, SoC: 0%	**********	*****	£165,442
	Afa: 50%, SoC: 20%	**********	*****	£210,654
	Afa: 50%, SoC: 10%	**********	*****	£188,048
	Afa: 90%, SoC: 10%	**********	*****	£97,624

Company submission table D15 page 87; † from ERG report page 87

ERG's critique of company's model

- Structure of model appropriate but uses strong simplifying assumptions (only mortality rate changes with age or duration of treatment)
- Assumptions that afamelanotide does not have any impact on life expectancy, and that adverse effects are minor and transient, with negligible effects on healthcare cost or quality of life are reasonable given current evidence
- Does not capture potential changes with age or duration of treatment in
  - Quality of life without treatment
  - Improvement in quality of life with treatment
  - Rates of compliance and continuation of treatment
  - Costs of monitoring and other treatments for EPP
- No sensitivity analyses over the parameters that reflect treatment effectiveness in the model or the methods and assumptions used to derive them
- Cost estimates used are largely by an assumption about the mean number of implants per person per year. This figure was estimated from 'real world' data, and it is not clear whether this was consistent with use in the clinical trials.
  - CUV030 and CUV039 up to 3 implants could be used, in CUV029 up to 5 implants

ERG's critique of company's model

Use of EPP-QOL to define level of disease severity

- There is insufficient information about the development and validation process of the EPP-QOL scale. It appears that the scoring system was revised after initial analysis of trial results, which introduces risk of bias.
- The definition of mild, moderate and severe disease by division of the EPP-QOL scale into thirds is arbitrary and the ERG cannot assess if it is consistent with the disability weights attached to these levels of severity in the DALY calculations.
- There were more people in the severe state at baseline in the best supportive care modelled population *** than afamelanotide ***.The ERG cannot assess whether difference is statistically significant, but note that a small imbalance in disability can be amplified as DALYs are extrapolated over a long time horizon. As there is no correction for baseline severity in the model, this may have introduced bias in favour of afamelanotide
- There is insufficient information about how the results of the three trials, CUV029, CUV030 and CUV039 were analysed and pooled. There is a lack of clarity over whether ITT datasets were used, the number of patients included from each trial, and whether the method of pooling accounted for clustering. This is potentially important given heterogeneity in study location and possibly in patient characteristics.

ERG's critique of company's model

Snapshot of 120 days may not be representative of quality of life over the whole year

- Company stated that they used day 120 as the follow up point because this was the longest follow-up interval in all trials. Appears 180 day data may have been collected for all 3 trials (company submission 33, 35 and 38). Do not have [pooled] 180 day results. Note for CUV029 and CUV039 the largest between-arm difference in mean EPP-QOL was at 120 days.
- Improvements in disease severity were also observed in the control group. There may be a placebo effect (although some degree of unblinding was likely in these studies) and other factors that impact on quality of life estimates. These include improved monitoring and standard treatments for all trial participants; seasonal effects; and/or 'regression to the mean effect' (if patients were more likely to consult a specialist, and hence be recruited to a trial, at times when their quality of life was worse than usual)

How well proxy conditions reflect quality of life/disability associated with EPP unclear

- We do not know if ********** is an appropriate proxy for EPP. There are similarities in some of the psychological and functional impacts, but it is not clear if the magnitude and levels of severity are comparable. **********.

ERG comments: external validity of model - published economic evaluation

- ERG's systematic search of economic evaluations identified a published abstract (Thompson et al., 2016) for the ISPOR 21st Annual International Meeting, Washington 2016. Authors from ICON (UK consultancy) and company.
- The abstract reported on an economic model that appears to be very similar to the model submitted to NICE, with both sharing the following characteristics: a lifetime time horizon, a discount rate of 3.5%; levels of EPP symptoms categorised as mild, moderate or severe; proportions of patients by level of severity based on trial data and DALYs the primary measure of benefit

	Base case	Lower limit for DALYs	Upper limit for DALYs
DALYs averted	1.87	0.72	2.50
ICER: £/DALY averted	£373,000	£968,764 *	£279,004 *

- This abstract also presented a sensitivity analysis from QALYs from 'preliminary SF-36 data from early clinical trials' and from other 'similar' conditions
- ICER of £401,000 per QALY gained from a sensitivity analysis using hereditary angioedema as a proxy, and a range from £208,000 to £1.1 million per QALY in sensitivity analyses using alternative sources for utility weights
- Company's response to clarification

"**********."

ERG's exploratory analyses

ERG's exploratory analyses

The ERG produced a:

- Simple QALY version of the company model: applied utility estimates for mild, moderate and severe disease for the company's proxy of ********** from the literature
  - i) Assumed utility value = 1 – disability weight (using the disability weights identified by the company)
  - ii) Identified published EQ-5D data for mild, moderate and severe disease for the company's proxy and applied these in the company model
- ERG exploratory base case: used same health states as company base case, but estimated QALYs from mean DLQI results at 0, 60, 120 and 180 days from study CUV039 mapped to EQ-5D scores

ERG exploratory analyses: summary

A comparison of the parameters used in the company base case, the ERG's simple QALY version and exploratory base case presented below:

	Company base case	Simple QALY version	ERG exploratory base case
Value for money	Incremental cost per DALY averted	Incremental cost per QALY gained	Incremental cost per QALY gained
Source of clinical data	CUV029, CUV030 and CUV039 (method of pooling not specified)	No change	CUV039 only
Outcome measure	EPP-QOL 12 item	No change	DLQI
Effectiveness statistics	Proportion of sample by thirds of EPP-QOL scale at 120 days: intervention and control groups	No change	Between-group difference in mean change from baseline DLQI at 60, 120 and 180 days

Table 26 page 91 ERG report

ERG exploratory analyses: summary

	Company base case	Simple QALY version	ERG exploratory base case
Method of extrapolation	Assumed fixed within year and between years	No change	For afamelanotide: assumes linear onset of benefit over 2 months after 1st implant; loss of benefit over 2 months after last implant of year. Both arms, assumes return to baseline by end of year
Valuation	Disability weights from GBD 2010 for proxy of **********	Utilities 1)inverse of disability weights 2) EQ-5D for same proxy **********	Utilities mapped from DLQI to EQ-5D from registry data for moderate to severe psoriasis
Mean implant use	*** per person per year (not related to effectiveness)	No change	No change for costing but effectiveness data based on max 3 implants/year

Table 26 page 91 ERG report

ERG simple QALY adaption methods

Summary of the utility values derived from company's disability weights

Scenario		Utility value
1.0) Utility value = 1-disability weight (*** afamelanotide; *** standard of care)	Afamelanotide	***
	Standard of care	***
1.1) Afamelanotide utility value adjusted for higher EPP-QoL scores at baseline than placebo. (the corresponding disability weights at baseline) were **** (afamelanotide) and **** (standard at care)) (see notes)	Afamelanotide	***
	Standard of care	***
1.2) afamelanotide adjusted for baseline as above + assumed that utility value for afamelanotide would attenuate to equal placebo 2 months after last implant	Afamelanotide	0-6 months **** 8-12 months ***
	Standard of care	0-12 months ***

These data are reported in figures 2,3,4 on pages 103 and 104 ERG report

ERG simple QALY adaption methods

In a separate scenario, rather than calculating utility from the company's disability weights the ERG used published EQ-5D estimates for company proxy condition for EPP (ERG scenario 1.3)

- Utility for mild, moderate and severe
  ****
  ****
- The survey included the SF-6D and EQ-5D questionnaires and regression modelling was used to estimate mean utility values and additional decrements for moderate and severe symptoms.
- Used same proportions of people with mild/moderate/severe EPP based on pooled data from CUV029/030/39 as company base case.
- Assumed that the weighted average EQ-5D at baseline for the placebo group is the same as that of the afamelanotide group. The ERG then estimated an EQ-5D change from baseline which is applied evenly throughout the year for the afamelanotide group.
- The utility values were 0.618 with standard of care and 0.634 with afamelanotide

ERG's rationale for using the DLQI rather than the EPP-QoL in its exploratory base case

- It has been shown to detect a relatively severe impact of EPP, compared with other skin conditions, and differences between patients
- DLQI contains direct questions about the impact of the condition on pain and discomfort, feelings of self-consciousness or embarrassment as well as functional effects
- Company states that anxiety, depression and pain are significant features of EPP but the EPP-QoL does not directly ask about these
- EPP-QoL focusses more on the ability to perform outdoor activities but does not measure the importance of these activities to the individual
- There is a 1 week recall period in the DLQI, and a 2 month period in the EPP-QoL. A longer recall period reduces the risk of missing periods of time when EPP has less effect on patients' lives. But it increases the risk of recall bias
- The framing of the question about quality of life in EPP-QOL is biased, as it does not include the possibility that quality of life might have reduced: "over the last two months, how much has your quality of life improved: very much; a lot; a little; not at all"
- Questions were removed from EPP-QoL after initial analyses of trial data. This poses a risk of bias.

ERG exploratory base case methods

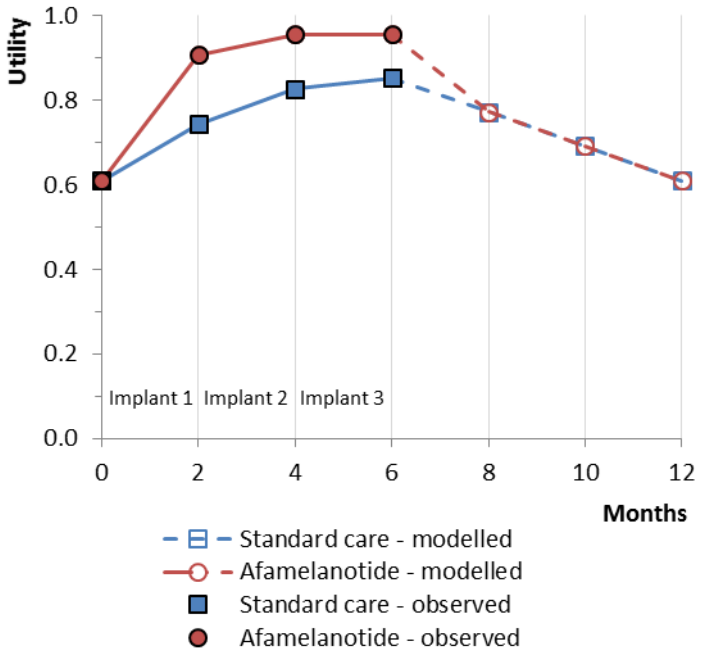
- Baseline values were from control arm of CUV039 both modelled arms were assumed to start with same utility
- Used mean DLQI results from CUV039 (at 0, 60,120 and 180 days) to model treatment effect on quality of life
- Estimated utility values were mapped from the estimated mean DLQI at each time point using the mapping algorithm reported by Currie and Conway 2007
- Assumed that the benefits of treatment would decline linearly over a 2 month period after the last implant of the year (from day 180-240)
- Assumed that utility would return to the same baseline value at the end of the year, with no persistence of effect between years (based on EPP-QoL at 360 days in CUV039)
- Assumed no treatment persistence between years, and the same number of QALYs each year
- Assumed a mean of 3 implants per person (the maximum for the intervention group in study CUV039, and as recommended by the Summary of Product Characteristics)

Observed and modelled utility over time

ERG simple QALY adaption

Figure redacted

ERG exploratory base case



Figures 2 and 6 pages 103 and 108 of ERG report

Scenario analyses around ERG exploratory base case

- The ERG carried out the following scenario analyses around its exploratory base case assumptions
- **Fast onset of effect (scenario 2.1).**
  - Assumed the treatment effect of afamelanotide would be immediate
  - Applied the observed mean difference in DLQI for afamelanotide vs. control at day 60 throughout 1st 2 months.
  - Rationale was that the pharmacodynamics of afamelanotide (reported in EPAR) show peak increase at melanin density at day 15, suggesting protective effect may start before 2 months (when DLQI was measured). ERG noted that exact relationship between melanin levels and physical protection and between physical protection, behaviour change and utility was unclear
- **Slower attenuation of treatment effect (scenario 2.2)**
  - Treatment benefit after last implant declines over 6 months rather than 2
- **Fast onset and slower attenuation (scenario 2.3 [combination of 2.1 & 2.2])**
- **Maximum of 2 implants per year (scenario 2.4)**
- **Maximum of 4 implants per year (scenario 2.5)**

Simple QALY model results

Treatment	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SCENARIO 1.0: company base case					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£278,386
SCENARIO 1.1: adjustment for baseline					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£454,800
SCENARIO 1.2: adjustment for baseline and attenuation of effect					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£779,657
SCENARIO 1.3: utilities for proxy condition					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£1,726,802

The ERG does not believe that any of these scenarios are plausible because they rely on an analysis of trial data that was post hoc and not transparent, the definitions of mild, moderate and severe disease were arbitrary and not related to the levels of severity in the disability weights/ utilities, which were also derived for a non-EPP population

ERG report table 32 page 113

ERG exploratory base case results

Treatment	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SCENARIO 2.0: ERG base case					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£1,605,478
SCENARIO 2.1: fast onset					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£1,290,678
SCENARIO 2.2: slow attenuation					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£1,343,359
SCENARIO 2.3: fast onset and slow attenuation					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£1,115,671
SCENARIO 2.4: maximum 2 implants per year					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£1,337,494
SCENARIO 2.5: maximum 4 implants per year					
Standard care	***	***	-	-	-
Afamelanotide	***	***	***	***	£1,785,957

Deterministic sensitivity analyses around simple QALY adaption

scenario	1.0	1.1	1.2	1.3
Effects proportion of people treated with afamelanotide with mild disease at day 120 **********				
Lower 60%	£221,520	£320,421	£549,293	£1,299,022
Upper 90%	£405,664	£933,075	£1,599,556	£2,889,993
GBD disability weight for mild disease **********				
Lower ****	£208,790	£341,100	£584,743	-
Upper ****	£417,579	£682,200	£1,169,486	-
Disutility (mild vs. moderate or severe estimates from publication)				
Moderate	-	-	-	£1,249,637
Severe	-	-	-	£2,542,183
Mean implants per year				
Lower 2	£253,371	£413,934	£709,600	£1,571,639
Upper 3	£378,444	£618,266	£1,059,884	£2,347,455

Data from table 34 ERG report page 116

Deterministic sensitivity analyses around ERG exploratory base case

Upper and lower parameter ranges		ICER
Effects (mean difference afamelanotide vs. placebo DLQI change day 60; 120; 180). Base case: -2.0; -1.3; -0.8		
Lower	-0.4; -0.0; -0.0	£17,543,596
upper	-4.9; -4.8; -4.5	£552,284
Utility loss per unit increase in DLQI. Base case: 0.020		
lower	0.018	£2,263,826
upper	0.033	£1,198,119
Mean implants per year. Base case: *** (on average patients would use ***** of the maximum number implants per year		
lower	2	£1,461,217
upper	3	£2,182,524

Data from table 35 ERG report page 116 and table 31 page 106

ERG's most optimistic analysis for afamelanotide

The ERG carried out a most optimistic analysis which combined the most favourable scenarios it had tested. This included:

- Simple QALY adaption modelling approach
- The assumptions that resulted in lower ICERs in the deterministic analyses including fewer people with mild disease at day 120 with afamelanotide; , lower disability weights for mild disease and lower mean number of implants (from deterministic sensitivity analyses).

This resulted in an ICER of £151, 212 per QALY gained

However the ERG did not believe that this or any of the other ICER estimates based on its simple adaption of the company model were plausible

The ERG's preferred set of analyses were based on mean DLQI data from the pivotal study CUV039 mapped to EQ-5D utility values using a published algorithm. Results from this modelling approach were less favourable, and did not fall below £1.1 in any of the scenarios that the ERG tested

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains
- In the company base case incremental undiscounted DALYs:***
- ERG simple QALY adaption incremental undiscounted QALYs: ***
- ERG exploratory base case incremental undiscounted QALYs: ***
- ERG exploratory most optimistic scenario incremental undiscounted QALYS: ***

Lifetime incr QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr)
Greater than or equal to 30	3

Budget impact over 5 years

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Year 1*	Year 2*	Year 3*	Year 4*	Year 5*
***	***	***	***	***

Authors

- **Mary Hughes**
  Technical Lead
- **Raisa Sidhu**
  Technical Adviser
- with input from the Lead Team (Jeremy Manuel, Glenda Sobey and Francis Pang)

Appendix (1) supplementary information from EPAR

- **Response from ad-hoc expert group on clinical effectiveness** "The experts stated that the magnitude of effects observed in the clinical trials were minimal and in a way disappointing but the expert panel argued that the totality of evidence was perceived convincing. Relative small changes were observed in a minority of individuals with small increase in sun light exposure observed and might be an underestimation of the true beneficial effect due to the patient behaviour. At the same time the experts noted that a translation of the small effect in terms of exposure to direct sunlight can translate into a significant time in the shade [see response to question 1]. The so-called super responders' were noted with interest even if no response to this response could be given. Important for the expert panel was that the data were pointing to the same positive direction. Overall the experts, clinicians and patients, were reasonably convinced of the trial data showing an effect of afamelanotide. The expert panel considered to explore a behavioural psychology test sub-analysis on the super-responders. This test would help to better understand how the results were strikingly different from other patients in the clinical trials. (EPAR page 88 response to question 5)
- **Real world data**: data from 73 patients of the Swiss and Italian Expanded Access / Compassionate Use programs have been presented, purporting to show long-term adherence to treatment with few withdrawals based on lack of efficacy or tolerability. Although efficacy data were not collected in these programmes it was observed the relatively high long-term adherence rates of patients might suggest some effectiveness of the treatment. (EPAR page 91)

Appendix (2) supplementary information from EPAR

Divergent position expressed by CHMP members: It is agreed that the strength of evidence of efficacy from the single pivotal trial is not strong enough to grant a Marketing Authorisation not subject to Specific Obligations. It is agreed that there are limitations in the statistical methodology employed and that the clinical relevance of the effects estimated in the clinical trials is not unequivocal. In addition, whilst the trials submitted in the dossier report effects in favour of afamelanotide, it remains unclear to what extent the functional unblinding of patients treated with Scenesse has impacted on the estimated effects. The ad-hoc expert group reported clinically impressive results that are inconsistent with the findings from the clinical trials. By way of explanation, and in support of an approval under Exceptional Circumstances, the applicant presents a rationale for why a randomised placebo-controlled trial is likely to be a less effective tool for determining treatment effects in this setting, primarily concerning the patient's 'learnt' behaviour. Whilst this rationale was shared by the ad-hoc expert group, it has not been established in an objective and verifiable manner and the extent to which this phenomenon impacts the clinical trial data cannot be estimated. Importantly, other tools to capture data on efficacy have not been explored exhaustively, for example, historical / external controlled clinical trials of longer duration such that the learnt behaviour has time to change, or series of case-reports that also systematically captured patient benefit in terms of exposure to light without phototoxicity, or quality of life. Furthermore, whilst there are no objections based on the observed safety data, in light of the lower than usual standards of evidence for efficacy, it is concerning that long-term safety data have not been systematically collected in the clinical trial programme.

EPAR page 107

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria

Final scope

Remit

To evaluate the benefits and costs of afamelanotide within its licensed indication for treating erythropoietic protoporphyria for national commissioning by NHS England.

Background

The porphyrias are a group of 8 disorders in which chemical substances called porphyrins accumulate. Erythropoietic protoporphyria (EPP) is a genetic storage disorder which is usually caused by the impaired activity of the enzyme, ferrochelatase. EPP results in excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma, and red blood cells.[1]

EPP is a cutaneous porphyria, and therefore the major symptom is hypersensitivity of the skin to sunlight and some types of artificial light, such as fluorescent lights, resulting in phototoxicity (a painful chemical reaction under the skin). After a person with EPP is exposed to sunlight, the skin may become swollen, itchy and red and the person may experience an intense burning sensation. The symptoms in response to sunlight typically last for between 2 and 3 days, but can last up to 10 days or longer, leading to severe pain and loss of sleep. The pain is unresponsive to non-opiate analgesics. These symptoms, along with anxiety and social isolation because of sunlight avoidance, can have a profound impact on quality of life. Over time, light exposure can cause thickening of skin on the knuckles and scarring on the face. Some people with EPP may have complications related to liver and gallbladder function.[2]

A study in 2006 suggests there are around 390 patients with EPP in England.[3] Experts suggest that accounting for underdiagnoses may increase the estimates to between 500 to 600 patients in England.

There are no specific pharmacological treatments for EPP. Non-pharmacological options include sunlight avoidance strategies, for example staying indoors, seeking shade during sunny periods, or wearing sunlight blocking clothing. The photosensitivity results from light in the visible spectrum, meaning that most sunscreens (with the exception of light-reflecting substances such as zinc oxide) are of little use. Other treatments for EPP include beta-carotene, activated charcoal and cholestyramine; these treatments are taken orally and are used to stop the porphyrins from being reabsorbed in the body but they are thought to be of limited benefit. Narrow

band UVB therapy is sometimes given in order to build up the skin's resistance to the effects of the sun but again is thought to be of limited use.

The technology

Afamelanotide (Scenesse, Clinuvel UK) activates the synthesis of eumelanin mediated by the MC1R receptor. Eumelanin contributes to photoprotection through strong broad band absorption of UV and visible light, where eumelanin acts as a filter; antioxidant activity; and inactivation of the superoxide anion and increased availability of superoxide dismutase to reduce oxidative stress..

Afamelanotide has a UK marketing authorisation under exceptional circumstances for 'prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)'. It is administered through a subcutaneous dissolving implant.

Intervention(s)	Afamelanotide
Population(s)	Adults with erythropoietic protoporphyria
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • duration of tolerance to sunlight and other forms of visible light • phototoxic reactions • change in melanin density • adverse effects of treatment • health-related quality of life (for patients and carers) • mortality
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options

Impact of the new technology	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. Guidance will take into account any Managed Access Arrangements.
Related NICE recommendations and NICE Pathways	None
Related National Policy	**NHS England** NHS England (2013) 2013/14 NHS STANDARD

	CONTRACT FOR METABOLIC DISORDERS (ADULT): PARTICULARS, SCHEDULE 2 – THE SERVICES A. SERVICE SPECIFICATIONS/E06/S/a NHS England (2013) 2013/14 NHS STANDARD CONTRACT FOR SPECIALISED DERMATOLOGY SERVICES (ALL AGES) PARTICULARS, SCHEDULE 2- THE SERVICES, A- SERVICE SPECIFICATIONS A12/S/a **Other policies** Department of Health (2014) NHS outcomes framework 2015-2016 Department of Health (2013) The UK strategy for rare diseases

References

1. Erythropoietic Protoporphyria (EPP) (2008) European Porphyria Network
2. Porphyrias (2015) PatientUK
3. Holme SA, Anstey AV, Finlay AY et al. Erythropoietic protoporphyria in the UK: Clinical features and effect on quality of life. British Journal of Dermatology 2006; 155: 574-581.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Clinuvel UK (afamelanotide) Patient/carer groups • British Porphyria Association • Genetic Alliance UK • Muslim Council of Britain • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Genetic Nurses and Counsellors • British Association of Dermatologists • British Dermatological Nursing Group • British Inherited Metabolic Disease Group • British and Irish Porphyria Network • British Skin Foundation • British Society for Genetic Medicine • Primary Care Dermatology Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Mark Holland Metabolic Unit • UK Genetic Testing Network • UK Clinical Pharmacy Association Others • Department of Health • Kings College Hospital NHS Foundation Trust • NHS Ealing CCG • NHS England • NHS South Cheshire CCG • Welsh Government	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Cardiff porphyria service • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Welsh Health Specialised Services Committee Comparator manufacturers • None Relevant research groups • Cochrane Cystic Fibrosis and Genetic Disorders Group • European Porphyria Network • MRC Clinical Trials Unit • National Institute for Health Research • Society for the Study of Inborn Errors of Metabolism Associated Public Health Groups • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the evaluation; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the recommendations.

All non-company/sponsor consultees are invited to make an evidence submission or submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the recommendations.

Commentators

Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the final evaluation documentation for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary*)*.

All non-company/sponsor commentators are invited to nominate clinical specialists or patient experts.

[1] Non-companyconsultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

INTERIM

Specification for company submission of evidence

May 2017

Contents

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows companies what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the company to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme'. After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested

in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with ‘see appendix X’. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes ‘commercial in confidence’ information and data that are awaiting publication (‘academic in confidence’). When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document ‘Related procedures for evidence submission’.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Glossary of terms and abbreviations

Term	Definition
AP	Actinic prurigo
BIPNET	British and Irish Porphyria Network
CAD	Chronic actinic dermatitis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CUV1647	Drug designation prior to approval of the international non-proprietary name (INN) 'afamelanotide'
DALY	Disability Adjusted Life Year
DLE	Discoid lupus erythematosus
DLQI	Dermatology Life Quality Index
EEEC	European EPP Expert Centre
EEDR	European EPP Disease Registry
EMA	European Medicines Agency
EPP	Erythropoietic protoporphyria
EPP-QoL	EPP quality of life questionnaire
EPNET	European Porphyria Network
EU	European Union
EudraCT	European Clinical Trials Database
GBD	WHO Global Burden of Diseases, Injuries, and Risk Factors Study
HAE	Hereditary angioedema
HIV/AIDS	Human immunodeficiency virus infection/ acquired immune deficiency syndrome
HRQoL	Health-Related Quality of Life
MAA	Managed Access Arrangement
NIH	US National Institutes of Health
PASS	Post authorisation safety study (CUV-PASS-001/CUV-PASS-002 unless indicated otherwise)
PLE	Polymorphic light eruption
Protoporphyrin IX	Tetrapyrrole containing 4 methyl, 2 propionic and 2 vinyl side chains. Metabolic precursor for haem compounds
Phototoxicity (phototoxic reaction)	Non-immune chemically induced exacerbation expressed by the skin triggered by a light source. Anaphylactoid reactions and general malaise frequently seen.
PRAC	Pharmacovigilance Risk Assessment Committee
PRT	Photoprovocation Response Time
PSUR	Periodic Safety Update Report
PubMed	PubMed (pubmed.gov) is a free resource developed and maintained by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine® (NLM)
SmPC	Summary of Product Characteristics
SU	Solar urticaria
SoC	Standard of Care
WHO	World Health Organization

Executive Summary

EPP is a poorly characterised ultra-orphan disorder with [redacted]an estimated current total of 513 patients in England based on disease prevalence. The disease severely impacts upon quality of life and ability to function normally, inhibiting social participation, education and employment. EPP patients are uniquely prone to second degree burns following exposure to light sources. SCENESSE® (afamelanotide 16 mg) is the first treatment developed to mitigate and attenuate anaphylactoid and phototoxic reactions in EPP patients. SCENESSE® is administered as a prophylactic treatment. [redacted]

Target indication – 'ultra-orphan' genetic disorder EPP

EPP is a genetic disorder of Ferrochelatase (FECH) enzyme deficiency that causes a disturbance in the haem pathway, resulting in the accumulation and storage of protoporphyrin IX (PPIX), predominantly in patients' skin and liver. PPIX is a phototoxic molecule, which reacts after brief exposure to visible light (peaking at 408 nm, blue spectrum). Both environmental and artificial light sources (particularly modern 'energy saving' globes) can cause anaphylactoid and phototoxic reactions in EPP patients. Cumulative exposure to light has a 'priming' effect and after only a few minutes of daily light exposure will, eventually, trigger severe phototoxicity. Owing to the lack of treatment, the few porphyria expert physicians in the EU and US were historically never urged to investigate or quantify the impact on the quality of life of EPP patients, as it was known and accepted that these patients lived in the dark.

The impact of light deprivation to man is currently only partially understood. A large cohort study of EPP patients in the UK found EPP to be "a persistent, severely painful, socially disabling disease with a marked impact on Quality of Life (QoL)" (Holme et al. 2006). However it was noted that the current QoL questionnaires, and in particular Health Related Quality of Life (HRQoL) questionnaires commonly used in dermatology (i.e. the Dermatology Life Quality Index (DLQI) and Short-Form [SF-36]), are not suitable for the quantification of the humanistic burden of EPP. Hence, the expert porphyria physicians globally together with the sponsor designed a new disease-specific "EPP-QoL questionnaire". Other studies have shown that EPP patients live severely restricted lives, and develop lifelong psychological and physical coping mechanisms (Rufener 1987; Langendonk et al. 2015) in order to have at least some normalised existence in the dark.

Patients report that their immediate environment (family, social, school, work) and most medical professionals do not understand their lifelong handicap (FDA, 2016).

A published prevalence figure of 25.4 per 1,000,000 in the UK may, due to methodology, significantly overestimate the patient population, with the largest UK prevalence study identifying 394 EPP patients across the UK (Elder et al. 2013; Holme et al. 2006). Leading UK EPP experts suggest the European-wide prevalence figure of 9.2:1,000,000 is more appropriate (see correspondence in Appendix 7).

Prior to approval of SCENESSE® there were no other treatments for EPP patients.

Clinical trials and special access schemes

SCENESSE® has been evaluated for the prevention of phototoxicity in adult patients with EPP in five clinical trials over 9 years. A total of 352 EPP patients received SCENESSE® during trials lasting 6–12 months. Clinical trials focused on the safety of the product and the clinical benefit of treatment. All studies were designed in conjunction with academic EPP expert physicians. At the conclusion of each study there was strong and persistent patient and physician demand for ongoing compassionate access to the product, which was facilitated in seven countries.

[redacted]

Afamelanotide has maintained a positive safety profile throughout clinical trials (n=352), special access schemes ([redacted]) and post authorisation access ([redacted]) to date. Common side effects include nausea, headaches and facial flushing, all of which are transient in nature and occur within 24–72 hours after implant administration. CLINUVEL continues to monitor all adverse events from the use of SCENESSE® under its post authorisation risk management plan and maintains a pharmacovigilance system. For more information on the safety profile of afamelanotide in EPP, see Kim & Garnock-Jones (2016) and Lane et al. (2016).

There are no alternative treatments or comparators used at present, nor in development. A systematic review of treatments has previously been published indicating the paucity of efficacy of any other therapy studied in EPP (Minder et al. 2016).

Distribution following European MA

SCENESSE® was approved by the EMA in October 2014. The agency noted that currently there are no scientific tools by which to measure or quantify the impact of EPP or the benefit of treatment. A strict risk management plan was agreed with the EMA for the use of the product. SCENESSE® will be available only through expert porphyria centres in England. Academic expert physicians will be trained and accredited to treat EPP patients according to a specific European post-authorisation safety study.

Pharmacoeconomics

A simple economic model was designed to quantify lifetime costs and benefits of treatment compared to standard of care (SoC). Benefit was quantified using Disability Adjusted Life Years (DALYs) rather than Quality Adjusted Life Years (QALYs) due to the nature of the underlying condition. Extensive scenario analyses were undertaken.

[redacted]

Section A – Decision problem

1 Statement of the decision problem

Table A1 Statement of the decision problem

CLINUVEL proposes no variations to the final scope.

	Final scope issued by NICE
Population	Adults with erythropoietic protoporphyria
Intervention	Afamelanotide
Comparator(s)	Best supportive care
Outcomes	The outcome measures to be considered include: • duration of tolerance to sunlight and other forms of visible light • phototoxic reactions • change in melanin density • adverse effects of treatment • health-related quality of life (for patients and carers) • mortality
Subgroups to be considered	N/A
Nature of the condition	• disease morbidity and patient clinical disability • with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Cost to the NHS and PSS, and Value for Money	Not addressed in scope. Demonstrated using a cost per DALY model.
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Special considerations, including issues related to equality	N/A

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

SCENESSE® (afamelanotide 16mg)

2.2 What is the principal mechanism of action of the technology?

Melanocortin-1 Receptor (MC1R) agonist

2.3 Please complete the table below.

Table A2 Dosing Information of technology being evaluated

Pharmaceutical formulation	Controlled release injectable implant
Method of administration	Subcutaneous injection
Doses	16mg
Dosing frequency	One implant is administered every 2 months prior to expected and during increased sunlight exposure, e.g. from spring to early autumn. Three implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year. The overall duration of treatment is at the specialist physician's discretion
Average length of a course of treatment	Up to four implants per year (lifelong treatment). [redacted]
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	N/A

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

SCENESSE® was centrally approved by the European Medicines Agency for the proposed indication on 23 October 2014, ratified by the European Commission on 22 December 2014.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

[redacted]

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

[redacted]

3.4 If the technology has been launched in the UK provide information on the use in England.

Not applicable

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

As part of the European Risk Management Plan, the European EPP Disease Registry (EEDR) has been established and patients are encouraged to enrol in the post authorisation safety study (PASS) for which data are captured. SCENESSE® is also subject to additional monitoring (▼ product), with solicited and spontaneous safety reports handled by CLINUVEL's pharmacovigilance team.

During the review further data on the safety profile of the product from its commercial use in other countries will be available as reported to EMA, with the PASS annual report due in December 2017.

[redacted]

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

[redacted]

5 Equality

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Not applicable

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

EPP is a poorly understood disorder that has not been well characterised due to the lack of any previously available treatment. EPP is a genetic disorder of Ferrochelatase (FECH) enzyme deficiency that causes a disturbance in the haem pathway, resulting in the accumulation and storage of protoporphyrin IX (PPIX), predominantly in patients' skin and liver. PPIX is a phototoxic molecule, which reacts after brief exposure to visible light (peaking at 408 nm, blue spectrum). Both environmental and artificial light sources (particularly modern 'energy saving' globes) can cause anaphylactoid and phototoxic reactions in EPP patients. Cumulative exposure to light has a 'priming' effect and after only a few minutes of daily light exposure will, eventually, trigger severe phototoxicity.

Subdermally, PPIX reacts in capillaries creating oxygen radicals which attack capillary walls, causing onset of erythema, oedema, and an intense burning sensation which can last for days or weeks (Minder et al. 2016). These phototoxic reactions are unresponsive to regular analgesics or any other medication and require the recovery of damaged tissue (i.e. time) prior to their subsidence (Balwani et al. 2014).

During a reaction any subsequent exposure to light, as well as heat variation, pressure and air movement, can exacerbate and prolong symptoms. Patients also report severe anxiety during reactions, with recent reports of suicidal ideations (FDA, 2016).

Due to the rarity of the disease and the delay in diagnosis patient's condition they modify their behaviour to avoid all forms of light exposure. This typically leads to an indoors existence, shunning any form of light exposure, which causes lifelong isolation deprivation of social participations or contacts. Long-term scarring, particularly of the face, lips and hands, is a common feature (Holme et al. 2006).

Owing to the lack of treatment, the few porphyria expert physicians in the EU and US were never urged to investigate or quantify the impact on the quality of life of EPP patients, as it was known that these patients lived in the dark.

The impact of light deprivation to man is currently understood only partially. A large cohort study of EPP patients in the UK found EPP to be "a persistent, severely painful, socially disabling disease with a marked impact on Quality of Life (QoL)" (Holme et al. 2006). However it was noted that the current QoL questionnaires, and in particular Health Related Quality of Life (HRQoL)

questionnaires commonly used in dermatology (i.e. the Dermatology Life Quality Index (DLQI) and Short-Form [SF-36]) are suboptimal for the quantification of the humanistic burden of EPP. Hence, the sponsor designed a new disease-specific “EPP-QoL questionnaire”. Other studies have shown that EPP patients live severely restricted lives, and develop lifelong psychological and physical coping mechanisms (Rufener, 1987; Langendonk et al. 2015) in order to have at least some normalised existence in the dark.

It has long been recognised in the literature that the disease severely restricts patients’ lives, and the distress caused by EPP is compounded by a lack of understanding of the condition from the patient’s immediate environment (i.e. family, colleagues, family doctors; see Rufener, 1987; FDA, 2016). This distress is often compounded by the ‘invisible’ nature of symptoms, with phototoxicity occurring *under* the skin.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

The Company believes there to be a maximum of 513 EPP patients in England. Correspondence provided previously to NICE from UK experts has confirmed the ultra-orphan nature of this indication (see correspondence in Appendix 7).

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

With the exception of the 2-5% of EPP patients who experience liver failure (Balwani et al. 2014), EPP patients have a normal life expectancy. In the modelling provided ONS statistics have been relied upon (ONS, 2016).

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

EPP severely impacts upon quality of life and ability to function normally, inhibiting social participation and development, education (both access and opportunities) and employment.

A large cohort study of EPP patients in the UK found EPP to be “a persistent, severely painful, socially disabling disease with a marked impact on Quality of Life (QoL)” (Holme et al. 2006). However it was noted that the current QoL questionnaires, and in particular Health Related Quality of Life (HRQoL) questionnaires commonly used in dermatology (i.e. the Dermatology Life Quality Index (DLQI) and Short-Form [SF-36]) are suboptimal for the quantification of the humanistic burden of EPP. Hence, the company, along

with global experts, designed the new disease-specific “EPP-QoL questionnaire”. Other studies have shown that EPP patients live severely restricted lives, and develop lifelong psychological and physical coping mechanisms (Rufener 1987; Langendonk et al. 2015) in order to have at least some normalised existence in the dark.

Rufener (1987) emphasises that the severity of the disease is only realised when patients discuss their ordeal.

Holme et al. (2006) emphasised the impact of EPP on choice of profession, while Stafford et al. (2010) showed that patients with photodermatoses (including EPP) experienced significantly higher rates of unemployment compared to the healthy population. Anecdotal statements indicate that whilst some people have learned to live around a condition which provides a lifelong ‘invisible’ handicap by adapting working hours and conditions, others are unable to work due to their condition.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Clinical development – SCENESSE®

SCENESSE® (afamelanotide 16 mg) is the first treatment developed to mitigate and attenuate anaphylactoid and phototoxic reactions in EPP patients. SCENESSE® is administered as a prophylactic treatment. SCENESSE® has been evaluated in five clinical trials over nine years for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP). In total 352 EPP patients received SCENESSE® during trials lasting 6–12 months. Clinical trials focused on the safety of the product and the clinical benefit of treatment. All studies were designed in conjunction with academic expert EPP physicians. At the conclusion of each study there was strong and persistent patient and physician demand for ongoing compassionate access to the product, which was facilitated in seven countries.

Clinical trials of SCENESSE® showed that the drug could reduce the incidence and severity of phototoxic reactions experienced by EPP patients compared to placebo (Langendonk et al. 2015). These results should be understood in the context of the disorder, where patients are lifelong conditioned to avoid light exposure which can trigger reactions. Those patients who chose to challenge their condition in trials generally saw the greatest benefit in terms of increased direct sunlight exposure (a proxy measure used in clinical trials to approximate overall exposure).

Quality of life impact

CLINUVEL studies of SCENESSE® used an EPP-specific QoL tool (EPP-QoL) to measure disease impact and the effects of therapy. These data have

been published in the NEJM (Langendonk et al. 2015) and BJD (Biolcati et al. 2015a). Anecdotal evidence in these papers points to a significant benefit to patient QoL beyond the tools provided, a reflection of the EMA's acknowledgement that there are currently no scientific tools to truly measure EPP or an effective treatment.

Longer term and post-authorisation use

Longer term use of the product has shown ongoing benefit of treatment to patients (Biolcati et al. 2015a; Langendonk, 2017). The overall safety profile of the product continues to be maintained.

[redacted]

Societal impact

Patients receiving treatment reporting being able to participate in 'normal' activities for the first time ever (Biolcati et al. 2015a). This impact ranges from being able to undertake day-to-day tasks (such as household chores and shopping) without fear of anaphylactoid reactions and burns, through to expanded opportunities for study and employment, and an increased ability to participate in family activities (collecting children from school and sports, outdoor social activities). Due to the relatively small number of patients receiving treatment longer term, evidence of these impacts has yet to be published in a larger cohort of patients.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

No NHS guidance has ever been issued for EPP. The lack of available effective therapies for EPP means no formal treatment recommendations exist. The European Porphyria Network (EPNET) of expert physicians and researchers is expected to develop treatment guidelines.

SCENESSE® is currently considered standard of care for the approved indication in the Netherlands and Germany.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

SCENESSE® is intended to be prescribed in line with the approved SmPC and used in accordance with the PRAC approved post-authorisation safety study (CUV-PASS-001, protocol appended).

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Not applicable

Currently, CLINUVEL has instigated that all EPP patients need to be treated in a multidisciplinary team, most preferably in an academic or university medical centre. These guidelines have been imposed by the Company.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

The expert centres administering SCENESSE® will be encouraged to provide treatment only under the approved PASS protocol. This non-interventional study may include the entry and upload of pseudonymised patient data into the European EPP Disease Registry (EEDR) as well as intensive patient monitoring for defined subpopulations (i.e. patients over 70 years of age).

Clinical practice for EPP has not been defined in the UK, however periodic dermatological and gastroenterological examinations are included in the PASS, which proposes to set a standard of care for EPP.

Exclusion criteria (as outlined in the PASS protocol) and contra-indications (as outlined in the SmPC) are strictly monitored by CLINUVEL as part of its ongoing pharmacovigilance programme across Europe.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

SCENESSE® is the first systemic hormone pharmaceutical to mitigate, treat and prevent anaphylactoid reactions to light exposure. The treatment addresses the self-limiting requirement of lifelong light deprivation and starvation of EPP patients. SCENESSE® is a first-in-class drug and the first melanocortin approved for endogenous and systemic use. The novel molecule, formulation, and clinical application clearly designate it as a most innovative product.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Not applicable

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Not applicable

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

CLINUVEL is required by the EMA to implement the PASS incorporating the EEDR. This protocol requires local ethics approvals and patient consent prior to commencement. CLINUVEL must train and accredit all UK expert centres prior to use of the product, regardless of whether patients are treated under the PASS protocol.

SCENESSE® is subject to additional monitoring (black triangle product). Expert centres are required to report adverse events experienced by patients during the use of the product to CLINUVEL and/or local authorities. Patients over the age of 70 are subject to additional monitoring.

[redacted]

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Not applicable

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A search was conducted of PubMed seeking to identify published literature related to the use of SCENESSE® in EPP. This search was also cross-referenced with CLINUVEL's internal literature library, which found no discrepancies.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

As CLINUVEL is the only supplier of afamelanotide in any dosage form for human use (SCENESSE®), the Company is aware of all clinical research undertaken using the product. The Company does not engage in 'ghost writing' of peer-reviewed papers and thus some clinical results remain unpublished. Results from these studies, however, have been presented at international medical conferences, and released by CLINUVEL as part of its Australian Securities Exchange disclosure requirements. Where possible, CLINUVEL seeks to obtain copies of all presentations given on the use of SCENESSE® in EPP. Where available, abstracts of presentations have been provided in references.

To ensure all possible unpublished studies could be identified, a search of both the NIH ClinicalTrials.gov and Eudract (https://www.clinicaltrialsregister.eu/ctr-search/search) websites was

conducted utilising the identical search terms as the PubMed search described in 9.1.1.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for published studies

Inclusion criteria	
Population	Adult patients with erythropoietic protoporphyria
Interventions	Afamelanotide subcutaneous implant
Outcomes	Any
Study design	All
Language restrictions	English
Search dates	10 June 2017, 15 July 2017
Exclusion criteria – N/A	

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Three studies were included, CUV010, CUV029 and CUV039. No studies were excluded.

Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Adults with erythropoietic protoporphyria
Interventions	Afamelanotide injectable implant
Outcomes	Any
Study design	Any
Language restrictions	English
Search dates	10 June 2017, 15 July 2017
Exclusion criteria – N/A	

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Data from two clinical trials, one observational study and the PASS protocol were included. No studies were excluded.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

In total 18 peer-reviewed journal articles were identified. Of these, four articles were original publications of study data, two of which (Harms et al. 2009a and Harms et al. 2009b) reported on the same study, the Phase II CUV010 clinical trial. One article (Langendonk et al. 2015) reported data from the two late stage Phase III clinical trials (CUV029 and CUV039), while the final article (Biolcati et al. 2015a) reported long-term observational data from the use of SCENESSE® in EPP patients in Italy and Switzerland.

Data from two unpublished clinical trials were available from conference presentations and company stock exchange announcements, along with an update on the long-term observational study published in Biolcati et al (2015a) and data from the PASS protocol.

The CUV017 Phase III cross-over study data were presented on behalf of the investigators in 2010 (Minder et al. 2010) and with commentary on the use of the product in ongoing compassionate use programmes in 2011 (Minder, 2011). The CUV030 Phase II double-blind placebo-controlled study were presented on behalf of the investigators in 2013 (Balwani, 2013). As study

sponsor, CLINUVEL also released results from these studies to the Australian Securities Exchange (CLINUVEL PHARMACEUTICALS LTD, 2010; CLINUVEL PHARMACEUTICALS LTD, 2011).

Further observational data from the use of SCENESSE® in EPP patients have been presented (Biolcati et al. 2015b) along with the first observations from the PASS protocol (Langendonk, 2017).

Table C3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Harms et al. (2009b)	CUV010	Adults with EPP	Afamelanotide 20mg	None, Phase II
Langendonk et al. (2015)	CUV029	Adults with EPP	Afamelanotide 16mg	Placebo (double blind)[1]
Langendonk et al. (2015)	CUV039	Adults with EPP	Afamelanotide 16mg	Placebo (double blind)[1]
Biolcati et al. (2015a)	N/A	Adults with EPP	Afamelanotide 16mg	None, observational

[1] Placebo is considered equivalent to standard of care as described in the decision problem.

Table C4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
CLINUVEL (2010)	CUV017	Adults with EPP	Afamelanotide 16mg	Placebo (double blind)[1]
CLINUVEL (2011)	CUV030	Adults with EPP	Afamelanotide 16mg	Placebo (double blind)[1]
Langendonk (2017)	CUV-PASS-001	Adults with EPP	Afamelanotide 16mg	Non-interventional

[1] Placebo is considered equivalent to standard of care as described in the decision problem.

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

Not applicable

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

Table C5 Summary of methodology for randomised controlled trials

Study name	CUV010 A Multicentre, Phase II, Open Label Study to Evaluate the Safety and Efficacy of Subcutaneous Implants of CUV1647 (afamelanotide) in Patients with Erythropoietic Protoporphyria (EPP)
Objectives	Primary objectives: Determine whether afamelanotide implants can reduce the

	susceptibility of patients with EPP to provocation with a standardized light source (time to appearance of provoked symptoms). Determine the effect of afamelanotide on the amount of rescue medication used.
Location	National Porphyria Center, Triemli Hospital, Zurich, Switzerland
Design	Open label study
Duration of study	In the protocol, it was planned that study participation for each subject would be for a period of approximately one year, with 6 implants at intervals of 60 days. However, following highly encouraging results for interim data to Day 120 (after 2 implants), the study was terminated prematurely, to progress the investigation of this product in a multi-centre study (CUV017).
Sample size	5 adult EPP patients
Inclusion criteria	• Male or female subjects with a diagnosis of EPP (confirmed by elevated free protoporphyrin in peripheral erythrocytes and/or ferrochelatase mutation) of sufficient severity that they have requested treatment to alleviate symptoms • Aged 18-70 years • Fitzpatrick Skin Type I- IV • Written informed consent prior to the performance of any study-specific procedure.
Exclusion criteria	• Any allergy to afamelanotide or the polymer contained in the implant • EPP patients with significant hepatic involvement. • Personal history of melanoma or dysplastic nevus syndrome. • Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions. • Any other photodermatosis such as PLE, DLE or solar urticaria. • Diagnosed with HIV/AIDS or hepatitis. • Any evidence of clinically significant organ dysfunction or any clinically significant deviation from normal in the clinical or laboratory determinations. • Acute history of drug or alcohol abuse (in the last 12 months). • History of disorders of the gastrointestinal, hepatic, renal, cardiovascular, respiratory, endocrine (including diabetes, Cushing's syndrome, Addison's disease, Peutz-Jeagher syndrome), neurological (including seizures), haematological (especially anaemia of less than 10 g/100 mL) or systemic disease judged to be clinically significant by the Investigator. • Major medical or psychiatric illness • Patient assessed as not suitable for the study in the opinion of the investigator (e.g. noncompliance history allergic to local anaesthetics, faints when given injections or giving blood). • Female who was pregnant (confirmed by positive serum β-HCG pregnancy test prior to baseline) or lactating. • Females of child-bearing potential (pre-menopausal, not surgically sterile) not using adequate contraceptive measures (i.e. oral contraceptives, diaphragm plus spermicide, intrauterine device). • Participation in a clinical trial of an investigational agent within 30 days prior to the screening visit. • Use of regular medications as specified in the protocol (Section 5.4 Prior and Concomitant Therapy). • Any factors that may affect skin reflectance measurements.

Method of randomisation	N/A
Method of blinding	N/A
Intervention(s) (n =) and comparator(s) (n =)	Intervention: afamelanotide (20 mg implant) contained in a poly(D,L-lactide) implant core (n=5) No comparator
Duration of follow-up, lost to follow-up information	N/A
Statistical tests	The primary efficacy endpoint of this study was the time taken for the development of symptoms provoked during phototesting. The primary efficacy analysis compared the "time to appearance of provoked symptoms" before (Day -7) and after afamelanotide treatment (Days 30, 60, 90 and 120) in each patient by Friedman test. H0: there is no difference in "time taken to develop provoked symptoms" before and after treatment.
Primary outcomes (including scoring methods and timings of assessments)	Photoprovocation under standardised laboratory conditions was undertaken before treatment and repeated at days 30, 60, 90 and 120. The mean photoprovocation response time (PRT) increased at day 30 to 347%, day 60 to 595%, day 90 to 663% and day 120 to 1077% of that recorded at baseline. Except for the initially most sensitive individual, all patients reached the maximum PRT of 15 minutes during some point of the study. Changes in PRT over the days of treatment were significant (p = 0.007; Friedman test). The second primary endpoint was not assessed, since no rescue medication was used.
Secondary outcomes (including scoring methods and timings of assessments)	**Melanin Density** Melanin density (MD) which was quantified by spectrophotometry, increased during the first 30 days after administration at all tested sites with one exception in one patient. The change in MD as measured on days 30, 60, 90 and 120 (measured at 6 anatomical sites) was significant different to baseline (p=0.0043). The increase in pigmentation induced darkening of the dermis with a natural appearance. **Quality of Life** Improvement in quality of life was observed at Day 120. These questions referred to reduced pain (mean score: 0.77 to 0.87), reduced nervousness (0.64 to 0.84), lowered abjectness (0.84 to 0.96), decreased downheartedness (0.76 to 1.00) and improved health compared to other people (0.80 to 0.84). **Phototoxic Reactions** The sun exposure times throughout the study were remarkably high in three patients, but low in two patients. The maxima of daily sun exposure were 360, 210, 180, 120, and 30 minutes in the five patients representing 1200%, 350%, 1800%, 2400% and 75% respectively of the maximum each patient tolerated prior to treatment. The three high exposed patients had phototoxic reactions during the first 4 days after first implantation. The intensity grade 1, 2, and 4 on the visual analogue scale (VAS), respectively, multiplied by the number of symptomatic days gave rise to 2, 2 and 8 phototoxicity scores. Thereafter, despite significant sunlight exposure, only 2 low intensity phototoxic reactions were documented. Because patients showed strongly improved tolerance to both artificial and

	natural light the study was terminated preterm at day 120. **Safety** Adverse events were nausea, tiredness, and headache during the first 24 hrs after the first implantation, a further 2 episodes of headache and 2 severe events unrelated to afamelanotide (tibial fracture and lumbar disc herniation). No serious adverse event nor clinically significant aberrations in the safety laboratory tests were observed.

Study name	CUV017 A Phase III, Multicentre, Randomised, Placebo Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable CUV1647 Implants in Patients with Erythropoietic Protoporphyria (EPP). EudraCT: 2007-000636-13
Objectives	The primary efficacy objectives were to determine whether afamelanotide could reduce the number and severity of phototoxic reactions in patients with EPP. To assess pain associated with phototoxicity, patients recorded the pain severity each day on an 11 point Likert scale. This scale used 0 for no pain, scores of 1 to 3 for mild pain, scores of 4 to 6 for moderate pain, scores of 7 to 9 for severe pain and 10 for worst imaginable pain. For the purposes of the tabulations used in analysis, 7 to 10 were used for severe pain.
Location	8 EPP Expert Centres across Australia and Europe
Design	Multicentre, randomised, double-blind, placebo-controlled, two-arm, crossover every 60 days.
Duration of study	12 months
Sample size	Approximately 70 eligible adult EPP patients were planned to be enrolled in total, across all sites. The number of subjects actually enrolled was 100, of whom 93 completed the study, with 60 subjects considered to have challenged themselves sufficiently to sunlight to be included in the primary efficacy analysis. The ITT population included all treated subjects, who provided at least one post-dose efficacy assessment. This was planned to be the main population for all efficacy analyses.
Inclusion criteria	A patient was considered eligible for inclusion in this study only if all the following criteria applied: • Male or female patients with a diagnosis of EPP (confirmed by elevated free protoporphyrin in peripheral erythrocytes) who experience phototoxic reactions of sufficient severity that they have requested treatment to alleviate their symptoms. • Aged 18-70 years. • Written informed consent prior to the performance of any study-specific procedure
Exclusion criteria	Patients with any of the following criteria were not eligible for inclusion in this study: • Any allergy to afamelanotide or the polymer contained in the implant or to lignocaine or other local anaesthetic used during the administration of study medication. • EPP patients with significant hepatic involvement. • Personal history of melanoma or dysplastic nevus syndrome. • Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions.

	• Any other photodermatosis such as PLE, DLE or solar urticaria. • Diagnosed with HIV/AIDS or hepatitis. • Any evidence of clinically significant organ dysfunction or any clinically significant deviation from normal in the clinical or laboratory determinations. • Acute history of drug or alcohol abuse (in the last 12 months). • History of disorders of the gastrointestinal, hepatic, renal, cardiovascular, respiratory, endocrine (including diabetes, Cushing's syndrome, Addison's disease, Peutz-Jeagher syndrome), neurological (including seizures), haematological (especially anaemia of less than 10 g/100 mL) or systemic disease judged to be clinically significant by the Investigator. • Major medical or psychiatric illness • Patient assessed as not suitable for the study in the opinion of the investigator (e.g. noncompliance history allergic to local anaesthetics, faints when given injections or giving blood). • Female who was pregnant (confirmed by positive serum β-HCG pregnancy test prior to baseline) or lactating. • Females of child-bearing potential (pre-menopausal, not surgically sterile) not using adequate contraceptive measures (i.e. oral contraceptives, diaphragm plus spermicide, intrauterine device). • Participation in a clinical trial of an investigational agent within 30 days prior to the screening visit. • Use of regular medications as specified in protocol. • Any factors that may affect skin reflectance measurements.
Method of randomisation	Eligible patients were randomised to a treatment group, and received implants of active treatment (afamelanotide 16mg) or placebo, in alternating crossover fashion according to the following dosing regime: • Group A: active implants on Days 0, 120, 240 and placebo implants on Days 60, 180, 300 • Group B: placebo implants on Days 0, 120, 240 and active implants on Days 60, 180, 300 Each patient was assigned to a treatment arm according to a computer generated randomisation list. For each study site, patients who satisfied the inclusion/exclusion criteria were allocated patient randomisation numbers sequentially and chronologically, based on the timing of their attendance at the clinic for the first study implant.
Method of blinding	This study was a double-blind randomised trial. At the time of implant insertion, neither the subject nor the investigator was aware of the afamelanotide content of the implant. To maintain the study blind at the time of implantation of the study product, the outer packaging and the label on each sealed amber glass vial containing the sterile implant was labelled with both the afamelanotide /placebo batch numbers. All Sponsor, Investigator, site and contract monitor staff involved with the conduct of the study were blinded to the treatment code with the following exceptions: • Unblinded pharmacy monitor • Pharmacy staff preparing treatments • Statistician preparing randomisation

Intervention(s) (n =) and comparator(s) (n =)	Active: afamelanotide (16 mg implant) contained in a poly(D,L-lactide-co-glycolide) implant core Placebo: Poly(D,L-lactide-co-glycolide) implant Cross-over study design, all patients received active and placebo treatments (n=93)
Duration of follow-up, lost to follow-up information	N/A
Statistical tests	Cochran-Mantel-Haenszel test for 2 categorical datasets obtained in a cross-over design.
Primary outcomes (including scoring methods and timings of assessments)	A major observation from the study is that many patients were inclined to avoid light and sun exposure due to their lifelong conditioned behavior and ingrained anxiety for second degree burns. On the majority of study days, most patients did not report any phototoxicity, "pain". Fifty-eight (58) patients reported at least one episode of moderate "pain" and 25 patients reported at least one episode of severe "pain". In analysing phototoxicity by all seasons, a non-parametric test was used to test for association between the 2 treatments. The distribution of frequency of days on which patients experienced pain in the various pain severity categories is consistent with the mean scores and was different between the active and placebo groups (p=0.0042; Cochran-Mantel-Haenszel test). As reported in the EPP literature, the symptoms manifested in this patient population were worse during the spring and summer seasons. Spring-summer was defined according to the following rules: • Germany/Netherlands/Sweden/United Kingdom – 15 March to 1 October • France/Italy/Switzerland – 1 March to 15 October, and • Australia – 1 September to 15 April. There was a significant difference between afamelanotide and placebo recipients, with more moderate and severe "pain" experienced by placebo recipients overall (p=0.0009 Cochran- Mantel-Haenszel test) in spring and summer. The average "pain" severity experienced by patients was also analysed. The assessment of all individual daily "pain" scores was significantly lower following afamelanotide treatment than when patients were receiving placebo [p=0.0017; t-test].
Secondary outcomes (including scoring methods and timings of assessments)	**Sunlight exposure** Patients recorded the quantity of sunlight exposure in daily diaries. These entries were recorded in CRFs at the end of each 60-day treatment interval and verified by the investigators. These exposures were divided into the following categories: none, < 1 hour, 1 to 3 hours, 3 to 6 hours and > 6 hours per day. There was significantly more sun exposure in patients receiving afamelanotide (p = 0.0136; Cochran-Mantel-Haenszel test), suggesting that afamelanotide facilitated outdoor activity. **Quality of life** Baseline SF-36 values were higher than expected, with the mean across all patients of the eight quality of life scales and the physical and mental component scores being above the population average score of 50. This is probably because patients have developed strategies to be able to live with their disease

	and adapt their daily life to the limits of their disease symptoms without compromising their perceived quality of life. It may also reflect the reluctance of some EPP patients to admit that they have a disease which can alter their lifestyle. There were no marked trends over time between the two groups associated with the dose administered per period.

Study name	CUV029. A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP). EudraCT: 2009-011018-51 NCT00979745
Objectives	According to the protocol, the primary objective of this study was to determine whether afamelanotide can reduce the severity of phototoxic reactions in patients with EPP. In preparation of the Statistical Analysis Plan, the primary objective was modified as follows, to determine whether afamelanotide can enable patients to expose themselves to direct sunlight during the most intense periods of sunlight during the day in spring and summer. This modified wording recognises the interdependence of the duration of voluntarily experienced sunlight (between 10:00 and 15:00 hours, and 10:00 and 20:00 hours) and pain or phototoxic reaction in patients with EPP. Without sunlight exposure (UV or visible light) as a causative factor, no pain or phototoxic reaction is possible. Efficacy was assessed by number and severity of phototoxic reactions and duration of light/sunlight exposure, as recorded in a daily patient diary between days 0 and 270. Severity of phototoxicity was recorded on an 11-point Likert scale (0 – no pain, 10 – worst imaginable pain).
Location	8 EPP Expert Centres across Europe
Design	Multicentre, randomised, double-blind, placebo-controlled study conducted in two parallel study arms for a 9-month period (5 doses).
Duration of study	Nine months
Sample size	Seventy-six (76) adult EPP patients were enrolled in the study, of whom 74 received afamelanotide or placebo according to the dosing regimen described in the sections below.
Inclusion criteria	Subjects had to fulfill all the following inclusion criteria to be considered eligible for study participation: • Male or female subjects with a diagnosis of EPP (confirmed by elevated free protoporphyrin in peripheral erythrocytes) of sufficient severity that they had requested treatment to alleviate their symptoms • Aged 18 – 70 years (inclusive) • Written informed consent prior to the performance of any study-specific procedures.
Exclusion criteria	Subjects were not eligible for study participation if they met any of the following exclusion criteria: • Any allergy to afamelanotide or the polymer contained in the implant or to lignocaine or other local anaesthetic to be used during the administration of study medication. • EPP patients with significant hepatic involvement.

	• Personal history of melanoma or dysplastic nevus syndrome. • Current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions. • Any other photodermatosis such as polymorphic light eruption (PLE), discoid lupus erythematosus (DLE) or solar urticaria. • Any evidence of clinically significant organ dysfunction or any clinically significant deviation from normal in the clinical or laboratory determinations. • Acute history of drug or alcohol abuse (in the last 12 months). • Patient assessed as not suitable for the study in the opinion of the Investigator (e.g., noncompliance history, allergic to local anesthetics, faints when given injections or giving blood). • Female who was pregnant (confirmed by positive serum β-human chorionic gonadotropin (β-HCG) pregnancy test prior to baseline) or lactating. • Females of child-bearing potential (pre-menopausal, not surgically sterile) not using adequate contraceptive measures (i.e. oral contraceptives, diaphragm plus spermicide, intrauterine device). • Sexually active men with partners of child bearing potential not using barrier contraception during the trial and for a period of three months thereafter. • Participation in a clinical trial of an investigational agent within 30 days prior to the screening visit. • Prior and concomitant therapy with medications which could have interfered with the objectives of the study, including drugs that cause photosensitivity or skin pigmentation.
Method of randomisation	Afamelanotide (16 mg afamelanotide implants) or placebo implants according to the following dosing regimen: • Group A was administered afamelanotide implants on Days 0, 60, 120, 180 and 240. • Group B was administered placebo implants on Days 0, 60, 120, 180 and 240. A computer generated randomization list for each study site was used to assign each subject to the treatment arm. For each study site, patients who satisfy the inclusion/exclusion criteria will be allocated patient randomization numbers sequentially and chronologically, based on the timing of their attendance at the clinic for the first study implant.
Method of blinding	This was a randomised, double-blind study. Patients who were deemed eligible for study participation were randomised to receive the active treatment or placebo within each study centre. A patient's randomisation number was corresponding to the blinded medication carton which the patient was also be given at study randomisation. The Sponsor, Investigator, patient and study centre personnel were blinded to treatment group assignment. The randomisation code was kept in sealed code break envelopes. The programmers and statisticians assigned to this project had no access to group assignment until after database lock.
Intervention(s) (n =) and comparator(s) (n =)	Active: afamelanotide (16 mg implant) contained in a poly(D,L-lactide-co-glycolide) implant core (n=38) Placebo: Poly(D,L-lactide-co-glycolide) implant (n=36)
Duration of follow-up, lost to follow-up	Of the five subjects who discontinued study medication prematurely, 2 in the afamelanotide group withdrew consent[redacted]), 1 in the afamelanotide group was withdrawn by physician's decision for clinical reasons

<table>
<tr><td>information</td><td>not related to the study [redacted]1 in the afamelanotide group was withdrawn due to a serious violation of the protocol [redacted] and 1 in the placebo group was withdrawn by sponsor decision ([redacted] One further subject in the placebo group received all required study medication but did not complete the final study assessment visit and was lost to follow-up [redacted]</td></tr>
<tr><td>Statistical tests</td><td>The difference between treatment groups in the amount of light/sun exposure (direct sunlight) between 1000 and 1500 hours was compared using a Kruskal-Wallis test for days on which patients experienced no phototoxicity or “pain” (Likert pain score of 0).</td></tr>
<tr><td>Primary outcomes (including scoring methods and timings of assessments)</td><td>Sun exposure (Direct sunlight between 10:00 and 15:00 hours)
The number of hours of direct light/sunlight reported was significantly higher for subjects in the afamelanotide treatment group than the placebo group on days when no phototoxicity or “pain” was reported and also on days when patients experienced no “pain” or mild “pain” (Likert pain scale scores of 0 to 3). Results are outlined below.
<table>
<tr><th></th><th>Afamelanotide Implant (16 mg) (N=38)</th><th>Placebo (N=36)</th><th>p-value[1]</th></tr>
<tr><td>Hours of Direct Sunlight Exposure per Subject on Days with No Pain, 10:00 to 15:00</td><td></td><td></td><td></td></tr>
<tr><td>Median (min, max)</td><td>5.63 (0, 193.8)</td><td>0.75 (0, 35.8)</td><td>0.006</td></tr>
<tr><td>Hours of Direct Sunlight Exposure per Subject on Days with No Pain or Mild Pain, 10:00 to 15:00</td><td></td><td></td><td></td></tr>
<tr><td>Median (min, max)</td><td>[redacted]</td><td>[redacted]</td><td>0.043</td></tr>
</table>
[1] p-value for Kruskal-Wallis test</td></tr>
<tr><td>Secondary outcomes (including scoring methods and timings of assessments)</td><td>Sun exposure (Direct sunlight between 10:00 and 20:00 hours)
The number of hours of direct light/sunlight reported was significantly higher for subjects in the afamelanotide treatment group than the placebo group on days when no phototoxicity or “pain” was reported (Likert pain scale score of 0) or on days when no “pain” or mild “pain” was reported (Likert pain scale scores of 0 to 3). Results are summarised below.
<table>
<tr><th></th><th>Afamelanotide Implant (16 mg) (N=38)</th><th>Placebo (N=36)</th><th>p-value[1]</th></tr>
<tr><td>Hours of Direct Sunlight Exposure per Subject on Days with No Pain, 10:00 to 20:00</td><td></td><td></td><td></td></tr>
<tr><td>Median (min, max)</td><td>[redacted]</td><td>[redacted]</td><td>0.007</td></tr>
<tr><td>Hours of Direct Sunlight Exposure per Subject on Days</td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

with No Pain or Mild Pain, 10:00 to 20:00			
Median (min, max)	[redacted]	[redacted]	0.026

[1] p-value for Kruskal-Wallis test

Combination sun exposure-pain analysis

Placebo recipients tended to experience an increase in phototoxicity and "pain" with less time spent in direct sunlight, shown with a difference between treatment groups for the periods 10:00 to 15:00 (p=0.043) and 10:00 to 20:00 (p=0.026).

Phototoxic reactions

There were significantly fewer phototoxic episodes per subject reported by the afamelanotide group than the placebo group, and also a reduction in the overall sum of severity across all phototoxic episodes and in the overall maximum severity reported for any episode. Results are summarised below.

	Afamelanotide Implant (16 mg) N=38	**Placebo N=36**	**p-value[2]**
Number of phototoxic episodes[1] per subject			
Mean (SD)	2.0 (2.8)	4.1 (5.1)	
Median (min, max)	1.0 (0,11)	2.0 (0,20)	0.038
Overall sum of severity per subject across all phototoxic episodes [1]			
Mean (SD)	[redacted]	[redacted]	
Median (min, max)			0.025
Overall maximum severity per subject across all phototoxic episodes[1]			
Mean (SD)	[redacted]	[redacted]	
Median (min, max)			0.010

[1] a phototoxic "episode" was defined as a set of consecutive days (as reported within a visit) with phototoxic severity Likert scores ≥ 4.

[2] The p-value for the comparison between treatment groups is based on the asymptotic Wilcoxon rank-sum test.

Quality of life

The supplementary EPP-Specific Questionnaire (EPP-QoL) demonstrated improvements in quality of life over time with afamelanotide treatment compared to placebo. At each time point (Days 60, 120, 180, 240 and 270), the mean EPP-QoL score was lower for the afamelanotide group than for the placebo group (p=0.011 at Day 270).

Study name	CUV030 A Phase II, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP) NCT01097044 IND Number: 103,131
Objectives	The primary objective of this study was to determine whether afamelanotide can reduce the severity of phototoxic reactions in patients with EPP. During data

	analysis for CUV017, the first Phase III EPP study (Australia and Europe), it became apparent that EPP patients remain reluctant to change their conditioned behaviour of sun/light avoidance. Given that exposure to the sun or bright light triggers the chemical reactions that cause the incapacitating pain characteristic of EPP, it is not surprising that the lifelong anxiety of experiencing phototoxicity prevents EPP patients from exposing themselves to sunlight. Consequently, there are few reports of phototoxicity-related pain, originally envisaged as the primary endpoint for the CUV030 study. Final data for CUV017 were not available at the time of protocol development for CUV030. During the initial stages of data analysis, and in order to determine the clinically relevant impact of afamelanotide treatment, the sequence of the study objectives was adapted to assess whether the study subjects are able to modify their lifelong conditioned behaviour. This was assessed by evaluating time spent in direct sunlight while remaining pain free or experiencing only mild pain, during spring and summer months. The clinically relevant primary endpoint was the number of hours that patients exposed themselves to direct sunlight between 10:00-15:00 hours and 10:00-20:00 hours, as recorded in a daily patient diary between days 0 and 120.
Location	Six EPP expert centres across the USA
Design	Multi-centre, randomised, double-blind, placebo-controlled study conducted in 2 parallel study arms for a 6-month period (3 doses).
Duration of study	Six months
Sample size	Seventy-seven (77) adult EPP patients were enrolled and received afamelanotide (16 mg afamelanotide implants) or placebo according to the dosing regimen described in the sections below.
Inclusion criteria	As per CUV029 study (see above) with the addition of: • Willing to take precautions to prevent pregnancy until completion of the study (Day 180)
Exclusion criteria	As per CUV029 study (see above) except: • The exclusion criteria “Acute history of drug or alcohol abuse (in the last 12 months)” of the CUV029 study was replaced by “Acute history of drug or alcohol abuse (in the last 6 months)” in the CUV030 study. • The exclusion criteria “Sexually active men with partners of child bearing potential not using barrier contraception during the trial and for a period of three months thereafter” of the CUV029 study was removed from the CUV030 study.
Method of randomisation	Afamelanotide (16 mg afamelanotide implants) or placebo implants according to the following dosing regimen: • Group A was administered afamelanotide implants on Days 0, 60 and 120. • Group B was administered placebo implants on Days 0, 60 and 120. A computer generated randomisation list for each study site was used to assign each subject to a treatment arm. For each study site, subjects who satisfied the inclusion/exclusion criteria were allocated subject randomization numbers sequentially and chronologically, based on the timing of their attendance at the clinic for the first study implant.
Method of blinding	This was a randomised, double-blind study. Patients who were deemed eligible for study participation were randomised to receive the Active treatment or Placebo within each study centre. A patient’s randomisation number was corresponding to the blinded medication carton which the patient was also given at study randomisation. The Sponsor, Investigator, patient, and study centre

	personnel were blinded to treatment group assignment. The randomisation code was kept in sealed code break envelopes. The programmers and statisticians assigned to this project did not have access to group assignment until after database lock. Implants used in the placebo arm were identical in size to those in the active treatment arm but contained only poly (DL-lactide-co-glycolide) polymer.
Intervention(s) (n =) and comparator(s) (n =)	Active: afamelanotide (16 mg implant) contained in a poly(D,L-lactide-co-glycolide) implant core (n=39) Placebo: Poly(D,L-lactide-co-glycolide) implant (n=38)
Duration of follow-up, lost to follow-up information	[redacted]
Statistical tests	The difference between treatment groups in the amount of light/sun exposure (direct sunlight) between 10:00 and 15:00 hours on days when no phototoxicity or "pain" (Likert pain score of 0) was experienced was compared using a Kruskal-Wallis test.
Primary outcomes (including scoring methods and timings of assessments)	The period between 10:00 and 15:00 hours is the period of highest UV and light intensity and is the period of highest risk to patients. The period of evaluation was extended from between 10:00 and 20:00 hours in order to include the timeframe of potential exposure to daylight. Patients who received afamelanotide spent significantly more time in direct sunlight between 10:00 and 15:00 hours (p=0.011) and between 10:00 and 20:00 hours (p=0.006) on "pain"-free days than placebo recipients.
Secondary outcomes (including scoring methods and timings of assessments)	**Combination sun exposure-pain analyses** • Time spent in direct sunlight was also compared between treatment groups on days when no or mild "pain" (Likert pain scores 0 plus scores of 1 to 4) was experienced. Afamelanotide recipients spent significantly more time in direct sunlight between 10:00 to 14:00 hours, 10:00 to 15:00 hours and 10:00 to 20:00 hours than placebo recipients (p=0.031, p=0.029 and p=0.021, respectively) on days with no or mild "pain". • Exposure to sunlight or bright light triggers the chemical reactions in the skin which lead to phototoxicity-related symptoms and pain. In this scenario, the absence of pain in EPP patients is anticipated to encourage more exposure to sunlight or bright light as a patient attempts to normalize their lifestyle. Pain per unit of direct sun exposure between 10:00 to 15:00 hours and 10:00 to 20:00 hours was also assessed. Placebo-recipients experienced significantly more pain relative to time spent in direct sunlight (p=0.026 and p=0.011 respectively). **Quality of Life** The supplementary EPP-Specific Questionnaire demonstrated improvements in QOL with afamelanotide treatment. At each time point (Days 60, 120 and 180), mean change from baseline for the afamelanotide group was approximately twice that of the placebo group (P<0.05). Further summary data are available on request.

Study name	CUV039 A Phase III, Multicentre, Double-Blind, Randomized, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous

	Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP). NCT01605136 IND Number: 103,131
Objectives	To determine whether afamelanotide can enable EPP patients to expose themselves to light/sunlight without incurring phototoxic reactions and "pain". The number and severity of phototoxic reactions, the type and duration of light/sun exposure, treatment-emergent adverse events and the use of concomitant medication were recorded by subjects in daily study diaries between Days 0 and 180. The primary efficacy endpoint was the duration of time (hours) spent in direct light/sunlight between 10:00 and 18:00 hours on days when patients report not experiencing any phototoxic reactions or "pain" (Likert score of 0). The treatment groups were also compared with respect to mean daily "pain-free" direct light/sun exposure (minutes/day). An exploratory analysis was undertaken on the total number of "pain-free" days (per subject) with some direct sunlight exposure.
Location	Seven EPP expert centres across the USA
Design	Multicentre, double-blind, randomised placebo-controlled study conducted in two parallel study groups for a six-month period (three doses).
Duration of study	Six months
Sample size	Ninety-seven (97) adult EPP patients were screened. Ninety-four (94) subjects were randomised to either afamelanotide (n=48) or placebo group (n=46) and ninety-three subjects (93) received at least one dose of study drug.
Inclusion criteria	Subjects had to meet the following inclusion criteria to be considered eligible for study participation: • Male or female subjects with characteristic symptoms of EPP phototoxicity and a biochemically-confirmed diagnosis of EPP. • Aged 18 years old and above (inclusive). • Able to understand and sign the written Informed Consent Form. • Willing to take precautions to prevent pregnancy until completion of the study (Day 180).
Exclusion criteria	As per CUV030 (see above) except: • The exclusion criteria "Any other photodermatosis such as polymorphic light eruption (PLE), discoid lupus erythematosus (DLE) or solar urticaria" of the CUV029 and CUV030 studies was replaced by "Any other photodermatosis such as polymorphic light eruption (PLE), actinic prurigo (AP), discoid lupus erythematosus (DLE), chronic actinic dermatitis (CAD) or solar urticaria (SU)" in the CUV039 study.
Method of randomisation	To account for the differences in climatic conditions between the study sites and the potential impact that this may have had on phototoxicity experienced, a computer generated randomisation list for each study site was used to assign each subject to a treatment group. To ensure that treatment was balanced within study sites, the randomisation method used a small block size (four). Five individually sealed sets of computer-generated randomisation codes (each set containing 48 randomised numbers) were provided to the pharmacy. The study pharmacist chose one of the five sealed envelopes and the selected randomisation list was used to randomise the subjects in this study. For each study site, subjects who satisfied the inclusion/exclusion criteria were allocated subject randomisation numbers sequentially and chronologically,

	based on the timing of their attendance at the clinic for the first study implant administration. Subjects received afamelanotide (16 mg implants) or placebo implants according to the following dosing regimen: - ***Group A*** administered afamelanotide implants on Days 0, 60 and 120, or - ***Group B*** administered placebo implants on Days 0, 60 and 120.
Method of blinding	In this double-blind study, all personnel involved, i.e. physicians, site staff, and participants were to remain blinded at all times, except in an emergency where knowledge of the code break was required to provide appropriate treatment. Implants used in the placebo group were identical in size to those in the active treatment group but contained only poly (DL-lactide-co-glycolide) polymer.
Intervention(s) (n =) and comparator(s) (n =)	Active: afamelanotide (16 mg implant) contained in a poly(D,L-lactide-co-glycolide) implant core (n=48) Placebo: Poly(D,L-lactide-co-glycolide) implant (n=45)
Duration of follow-up, lost to follow-up information	Approximately six months after completion of the study (Day 360), subjects returned to the study site for a safety follow-up visit. Three (3) subjects in each treatment group who received treatment terminated early from the study. Reasons for early termination include: physician decision (clinical reasons not related to IMP) for 2 subjects/ subject decision (withdrawal of subject's consent) for 2 subjects/ Other (Lost to follow-up) for 2 subjects.
Statistical tests	The treatment groups were compared using the non-parametric Kruskal-Wallis test and the treatment difference was estimated using the Hodges-Lehmann estimate together with the corresponding 95% confidence interval. Compliance of diary completion was very high. There were 185 out of 15608 diary days (1.2%) with missing Likert pain scores, and 296 diary days (1.9%) with missing information about time outdoors. Analyses were performed on a best and worst cases imputation, as described in the statistical analysis plan. Last observation carried forward for missing phototoxicity or "pain" scores on days after a "pain" score of greater than 2 was applicable to only 4 subjects, for a total of 6 diary days.
Primary outcomes (including scoring methods and timings of assessments)	There was a statistically significant difference between the treatment groups with respect to total "pain"-free direct light/sun exposure between 10:00 and 18:00 hours over the study period (Kruskal-Wallis test, p=0.044). The difference (Hodges-Lehmann estimate) was 24.0 hours (95% CI: 0.3, 50.3) in favour of afamelanotide across the 6 month study period in the ITT (Diary Data) population. The treatment effect of 24.0 hours was 59% higher than the median recorded in the placebo group of 40.8 hours. A supportive exploratory analysis of the total number of "pain"-free days (per subject) with some direct light/sunlight exposure between the corresponding 10:00 and 18:00 hours period was statistically significant (Kruskal-Wallis test, p=0.005) in favour of afamelanotide. The treatment difference was 29.0 days (95% CI: 9.0, 50.0) over the 6 month study period. The treatment effect of 29 days was 54% higher than the median recorded in the placebo group of 54 days.
Secondary outcomes (including scoring methods and timings of assessments)	**Combined sun exposure and phototoxic pain:** The difference between the treatment groups with respect to total direct light/sunlight sun exposure on days when no phototoxicity or mild "pain" was experienced (Likert pain scores of 0 to 3) between 10:00 and 18:00 approached statistical significance (Kruskal-Wallis test, p=0.053). The difference (Hodges-Lehmann estimate) was 26.8 hours (95% CI: -0.3, 57.5) in favour of afamelanotide across the 6 month study period in the ITT (Diary Card)

	population. The treatment difference was similar in magnitude to the corresponding “pain”-free endpoint although the medians for each treatment were around 10 hours larger with the expanded criterion of Likert pain scores of 0 to 3. **Sun exposure:** A supportive exploratory analysis of the total number of phototoxic-free or “pain”-free or mild “pain” days (Likert pain scores of 0 to 3) per subject with some direct sunlight exposure between the corresponding 10:00 and 18:00 hours period was statistically significant (Kruskal-Wallis test, p=0.004) in favour of afamelanotide. The treatment difference was 32.0 days (95% CI: 9.0, 54.0) over the 6 month study period. **Quality of life:** Assessed by DLQI and EPP-QoL measured at baseline and Study Days 60, 120 and 180. Quality of life (QoL) was assessed using two quality of life assessment tools: the EPP-QoL developed by porphyria expert physicians responsible for the healthcare of EPP patients and the generic DLQI. The EPP-QoL has undergone psychometric validation by Oxford Outcomes (an ICON plc company). Assessment of the results of the EPP-QoL was performed prospectively against the original scoring algorithm (as was done in the CUV029 and CUV030 studies) and a slightly revised scoring algorithm derived during the EPP-QoL validation work. The DLQI which is a generic dermatology quality of life assessment tool was also used but not deemed applicable in EPP in any of the studies, since this questionnaire was not developed to capture the impact of light on skin and its influence on the lives of patients. Treatment–related improvements were demonstrated in quality of life (EPP-QoL) at each time point (Days 60, 120 and 180). The lower the score, the better was the quality of life. The total scores range from -10 (best possible) to 35 (worst imaginable). Median change from baseline for the afamelanotide group was between 1.6 and 1.9 times that of the placebo group using the original scoring algorithm (data can be provided on request). The differences between the treatment groups at Days 60, 120 and 180 were statistically significant in favour of the afamelanotide group.

Table C6 Summary of methodology for observational studies

Study name	Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria
Objective	Determine long-term impact of patient quality of life and patient demand for treatment, monitor safety
Location	EPP expert centres in Switzerland and Italy
Design	Open label observational study
Duration of study	Ongoing
Patient population	Adult EPP patients
Sample size	146 (115 in peer-reviewed paper)
Inclusion criteria	Phototoxicity since childhood and significantly elevated protoporphyrin levels.

Exclusion criteria	"Current contraindications include pregnancy, lactation and age below 18 years, personal history of melanoma or dysplastic naevus syndrome, current Bowen's disease, basal or squamous cell carcinoma, or other malignant or premalignant skin lesion." (Biolcati et al 2015a)
Intervention(s) (n =) and comparator(s) (n =)	Afamelanotide 16mg (n=146) No comparator
How were participants followed-up	Observational follow up of patients from 2006-2014, extended to 2015 in conference presentation (Biolcati et al 2015b).
Statistical tests	"Mean, median, SD and interquartile ranges (IQR) were calculated by Excel 2007. The t-test with unequal variance was applied to data with symmetric distributions but unequal variance. The nonparametric Mann–Whitney and Kruskal–Wallis tests were applied to asymmetric distributed data (http://vassarstats.net). The Mann–Whitney test was used to compare two groups, the Kruskal–Wallis to compare more than two groups and ANCOVA to compare two groups with an additional concomitant variable." (Biolcati et al. 2015a).
Primary outcomes (including scoring methods and timings of assessments)	"(i) The discontinuation rates were low despite the long duration of treatment and the considerable sacrifice of time and costs that had to be carried by the patients. (ii) Only three of the 115 patients indicated that afamelanotide did not improve their condition. Most others who left did so for compelling reasons, such as intended pregnancy or intolerable financial burden. (iii) The QoL scores being only 32% of maximum before initiation of afamelanotide treatment rose strongly after initiation of treatment to 74% and remained stable at this level during the whole 6 years of observation." (Biolcati et al. 2015a)
Secondary outcomes	Safety was reported anecdotally: "Afamelanotide caused only mild adverse effects" (Biolcati et al 2015a) "Spectrum of probably or likely afamelanotide-related adverse effects unchanged, i.e. most frequent is nausea, headache, and pigmentation changes" (Biolcati et al. 2015b)

Study name	A Post-Authorisation Disease Registry Safety Study to Generate Data on the Long-Term Safety and Clinical Effectiveness of SCENESSE® (Afamelanotide 16mg implant) in Patients with Erythropoietic Protoporphyria (EPP) CUV-PASS-001
Objective	To monitor long term safety and effectiveness endpoints
Location	European EPP Expert Centres (data reported only from Erasmus MC, Rotterdam)
Design	Non-interventional PASS
Duration of study	Longitudinal (no completion date) Data reported from 23 June 2016 – 31 May 2017
Patient population	Adult EPP patients
Sample size	104

Inclusion criteria	Per CUV-PASS-001 protocol/ SCENESSE® SmPC
Exclusion criteria	Per CUV-PASS-001 protocol/ SCENESSE® SmPC
Intervention(s) (n =) and comparator(s) (n =)	Afamelanotide 16mg (n=104) No comparator
How were participants followed-up	According to CUV-PASS-001 protocol. One patient discontinued treatment.
Statistical tests	N/A for this set of data reported
Primary outcomes	96 patients experienced adverse events, four serious adverse events (three unrelated to treatment). No unexpected adverse reactions reported. 1 report of lack of effect resulting in discontinuation.
Secondary outcomes	Small decrease in length and severity of phototoxicity reported. Trend towards improved patient Quality of Life using EPP-QoL. Note that more time is required to evaluate effectiveness endpoints for this study.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

The open label study reported above (Biolcati et al. 2015a; 2015b) incorporates data from the CUV010 (Phase II) and CUV017 (Phase III cross-over) studies, as well as ongoing use in compassionate use and expanded access programs.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

Not applicable

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Not applicable

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Not applicable

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Overall patient withdrawal rates were low across the clinical trial program. Across the three late stage studies (CUV029, CUV030 and CUV039), 17 patients did not complete the full protocol, including three who were lost to follow up but received all study medication. Given the low numbers and the reasonably even distribution of withdrawals, these withdrawals were not considered to have had an impact on the outcome of the overall assessment of the study endpoints.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

CUV010 (Harms et al. 2009) and the two observational studies (Biolcati et al 2015a, Langendonk, 2017) listed in Table C6 did not involve randomisation of trial subjects since the data were generated under conditions of use. The cross-over design of CUV017 meant all patients received active and placebo implants during the study on a 1:1 ratio, rather than involving a 'control' group. Studies CUV029 (Langendonk et al. 2015), CUV030 and CUV039 (Langendonk et al. 2015) utilised identical randomisation processes, described in the Table C7.

Table C7 Critical appraisal of randomised control trials

Study name	**CUV029-CUV030-CUV039**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomised 1:1 active: placebo on a site basis to maintain a geographic/climatic balance between treatment arms.
Was the concealment of treatment allocation adequate?	Yes	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Due to the limited potential sample size (i.e. orphan indication), it was not possible to actively control groups at baseline. At no point in the evaluations of these studies (including by EMA) was concern raised on this issue.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of	Yes	

these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Study drop-outs were minimal and generally balanced between active and placebo.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT was used but the principle of last value carried forward was not considered appropriate to the assessment of the chosen endpoints in this indication. Sun exposure and phototoxicity are not endpoints where the last value carried forward would give meaningful results because both are quite variable day to day. As an example, if a patient dropped out because they experienced a severe phototoxic reaction with a pain scale score of 10, then that values would need to be imputed for all future assessment points – this would be nonsensical.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table C8 Critical appraisal of observational studies

Study name Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	N/A	
Was the exposure accurately measured to minimise bias?	N/A	
Was the outcome accurately measured to	N/A	

minimise bias?		
Have the authors identified all important confounding factors?	N/A	
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	
Was the follow-up of patients complete?	No	
How precise (for example, in terms of confidence interval and p values) are the results?		
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

Table C9 Outcomes from published and unpublished studies

Study name		CUV010 A Multicentre, Phase II, Open Label Study to Evaluate the Safety and Efficacy of Subcutaneous Implants of CUV1647 (afamelanotide) in Patients with Erythropoietic Protoporphyria (EPP)
Size of study groups	**Treatment**	n=5
	Control	N/A
Study duration	**Time unit**	4 months
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	Time to appearance of provoked symptoms
	Unit	Photoprovocation response time (PRT), minutes
Effect size	**Value**	The mean PRT increased at day 30 to 347 (±115) %, day 60 to 595 (±431) %, day 90 to 663 (±353) % and day 120 to 1077(±867) % of that recorded at

		baseline.
	95% CI	N/A
Statistical test	**Type**	Friedman-test
	p value	P=0.007
Comments		Trial terminated early due to evidence of efficacy.

Study name		CUV017 A Phase III, Multicentre, Randomised, Placebo Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Bioresorbable CUV1647 Implants in Patients with Erythropoietic Protoporphyria (EPP).
Size of study groups	**Treatment**	n=93 (cross-over design)
	Control	n=93 (cross-over design)
Study duration	**Time unit**	12 months
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	Distribution of frequency of days on which patients experienced pain in the various pain severity categories in spring and summer only
	Unit	Number of Days
Effect size	**Value**	More moderate and severe pain experienced by placebo recipients overall
Statistical test	**Type**	Cochran-Mantel-Haenszel test
	p value	p=0.0009
Other outcome	**Name**	The distribution of frequency of days on which patients experienced pain in the various pain severity categories is consistent with the mean scores and was different between the active and placebo groups
	Unit	Number of Days
Statistical test	**Type**	Cochran-Mantel-Haenszel test
	p value	p=0.0042
Other outcome	**Name**	Sunlight exposure
	Unit	Number of days of exposure, categorised as: none, < 1 hour, 1 to 3 hours, 3 to 6 hours and > 6 hours per day
Statistical test	**Type**	Cochran-Mantel-Haenszel test
	p value	p=0.0136
Comments		Due to the requested format of the data, effect size information (contained in study report tables) cannot be provided. Further relevant information can be provided on request.

Study name		CUV029. A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP).
Size of study groups	**Treatment**	n=38
	Control	n=36
Study duration	**Time unit**	9 months
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	The difference between treatment groups in the amount of light/sun exposure (direct sunlight) between 1000 and 1500 hours was compared for days on which patients experienced no phototoxicity or “pain” (Likert pain score of 0).
	Unit	Hours (H)
Effect size	**Value**	Median: 5.63 H (active) vs 0.75 H (placebo)
	95% CI	Range: 0 – 193.8 H (active) vs 0 – 35.8 H (placebo)
Statistical test	**Type**	Kruskal-Wallis
	p value	p=0.006
Other outcome	**Name**	Hours of Direct Sunlight Exposure per Subject on Days with No Pain or Mild Pain, 10:00 to 15:00
	Unit	Hours (H)
Effect size	**Value**	Median: 7.5 H (active) vs 5.38 H (placebo)
	95% CI	Range: 0 – 200.3 H (active) vs 0 – 46.0 H (placebo)
Statistical test	**Type**	Kruskal-Wallis
	p value	p=0.043
Comments		Further results are provided in tables C5 in section 9.4.1

Study name		CUV030 A Phase II, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP)
Size of study groups	**Treatment**	n=39
	Control	n=38
Study duration	**Time unit**	6 months
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	The difference between treatment groups in the

		amount of light/sun exposure (direct sunlight) between 10:00 and 15:00 hours was compared for days on which patients experienced no phototoxic reaction or “pain” (Likert pain score of 0).
	Unit	Hours (H)
Effect size	**Value**	Median: 8.88 H (active) vs 0.75 H (placebo)
	95% CI	Range: 0 – 48.3 H (active) vs 0 – 70.3 H (placebo)
Statistical test	**Type**	Kruskal-Wallis
	p value	p=0.011
Other outcome	**Name**	The difference between treatment groups in the amount of light/sun exposure (direct sunlight) between 10:00 and 20:00 hours was compared for days on which patients experienced no phototoxic reaction or “pain” (Likert pain score of 0).
	Unit	Hours (H)
Effect size	**Value**	Median: 16.0 (active) vs 1.25 (placebo)
	95% CI	Range: 0 – 126.3 (active) vs 0 – 106.3 (placebo)
Statistical test	**Type**	Kruskal-Wallis
	p value	p=0.006
Comments		Further results are provided in tables C5 in section 9.4.1

Study name		CUV039 A Phase III, Multicentre, Double-Blind, Randomized, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP).
Size of study groups	**Treatment**	n=48
	Control	n=46
Study duration	**Time unit**	6 months
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	Duration of time spent in direct light/sunlight between 10:00 and 18:00 hours on days when patients report not experiencing any phototoxic reactions or “pain” (Likert score of 0).
	Unit	Hours (H)
Effect size	**Value**	Active recipients spent a median of 24 H longer in direct sunlight over the course of the study (Hodges-Lehmann shift, Estimate)
	95% CI	0.3, 50.3
Statistical test	**Type**	Kruskal-Wallis test
	p value	p=0.044
Other	**Name**	Duration of direct sunlight exposure between 10:00

outcome		and 18:00 hours on days when no phototoxicity or no or mild “pain” was experienced (Likert scores of 0 to 3).
	Unit	Hours (H)
Effect size	**Value**	Active recipients spent a median of 26.8 H longer in direct sunlight over the course of the study (Hodges-Lehmann shift, Estimate)
	95% CI	-0.3, 57.5
Statistical test	**Type**	Kruskal-Wallis test
	p value	p=0.053
Comments		Further results are provided in tables C5 in section 9.4.1

Study name		Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria
Size of study groups	**Treatment**	146 (115 in peer-reviewed paper)
	Control	N/A
Study duration	**Time unit**	N/A (ongoing use)
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Outcome	**Name**	Treatment discontinuation
	Unit	N/A
Effect size	**Value**	Only three patients considered afamelanotide did not meet their expectations for symptom improvement; 23% discontinued the treatment for other, mostly “compelling”, reasons such as pregnancy or financial restrictions.
	95% CI	N/A
Statistical test	**Type**	N/A
	p value	N/A
Other outcome	**Name**	Quality of life (QoL) score (in Switzerland)
	Unit	N/A
Effect size	**Value**	Before the first implantation of afamelanotide, the mean QoL score was 32 ± 22% (Oxford Outcome revised questionnaire 31 ± 24%) of maximum. In the first 6 months of treatment with afamelanotide, it rose to 74 ± 17% (74 ± 17%) and remained between 69% and 91% (66% and 84%) of maximum during the whole observation period of 6 years.
	95% CI	N/A
Statistical test	**Type**	N/A
	p value	N/A

Comments	Refer to publication (Biolcati et al. 2015a).

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

Not applicable

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

All studies outlined in section 9 were considered to include data on the adverse event profile of SCENESSE® in EPP. Use of a separate methodology is not required.

9.7.2 Provide details of all important adverse events reported for each study.

As SCENESSE® is EMA-approved for the indication outlined in the scope, the most accurate safety profile of the product is provided in the SmPC, published by the EMA. CLINUVEL provides Periodic Safety Update Reports (PSURs) to the EMA which confirm that the safety profile of the product is unchanged, but continues to be monitored.

The adverse reactions reported during clinical trials conducted with SCENESSE® are listed in the Table C10 by MedDRA system organ class and frequency convention. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table C10 Tabulated list of adverse reactions (per SCENESSE® SmPC)

System organ class	Very common	Common	Uncommon
Infections and infestations		Upper respiratory tract infection	Influenza Gastrointestinal infection Gastroenteritis

System organ class	Very common	Common	Uncommon
			Folliculitis Candidiasis Nasopharyngitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Haemangioma
Blood and lymphatic system disorders			Leukopenia
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia Increased appetite
Psychiatric disorders			Depression Depressed mood Insomnia
Nervous system disorders	Headache	Migraine Dizziness Lethargy Somnolence	Syncope Restless leg syndrome Hyperaesthesia Presyncope Post-traumatic headache Burning sensation Poor quality sleep Dysgeusia
Eye disorders			Eyelid oedema Ocular hyperaemia Dry eye Presbyopia
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Palpitations Tachycardia
Vascular disorders		Flushing Hot flush	Haematoma Diastolic hypertension Hypertension
Respiratory, thoracic and mediastinal disorders			Dysphonia Sinus congestion Rhinitis Nasal congestion
Gastrointestinal disorders	Nausea	Abdominal pain Abdominal pain upper Diarrhoea Vomiting	Lip oedema Lip swelling Gastroesophageal reflux disease Gastritis Dyspepsia Cheilitis Abdominal distension Gingival pain Abdominal discomfort Toothache Abdominal symptom Bowel movement irregularity Flatulence Gingival discolouration Hypoaesthesia oral Lip discolouration Tongue discoloration
Skin and subcutaneous tissue disorders		Erythema Melanocytic naevus Pigmentation disorder Skin discolouration Skin hyperpigmentation Ephelides Pruritus	Lichen planus Rash vesicular Pruritus generalised Rash Rash erythematous Rash papular Rash pruritic Skin irritation Vitiligo Acne

System organ class	Very common	Common	Uncommon
			Eczema Pigmentation lip Post inflammatory pigmentation change Seborrhoea Skin exfoliation Skin hypopigmentation Hair colour changes Hyperhidrosis
Musculoskeletal and connective tissue disorders		Back pain	Arthralgia Myalgia Pain in extremity Muscle spasm Musculoskeletal pain Musculoskeletal stiffness Joint stiffness Groin pain Sensation of heaviness
Renal and urinary disorders			Cystitis
Reproductive system and breast disorders			Menorrhagia Dysmenorrhoea Breast tenderness Menstruation irregular Vaginal discharge Libido decreased
General disorders and administration site conditions		Implant site hypersensitivity Implant site reaction Implant site pain Implant site haematoma Implant site erythema Implant site irritation Asthenia Fatigue Implant site discolouration Feeling hot	Oedema peripheral Oedema mucosal Pain Implant site oedema Pyrexia Chills Injection site haematoma Injection site irritation Implant site hypertrophy Implant site pruritus Device expulsion Application site discolouration Hangover Influenza like illness
Investigations		Blood creatine phosphokinase increased	Alanine aminotransferase increased Aspartate aminotransferase increased Liver function test abnormal Transaminases increased Transferrin saturation decreased Blood cholesterol increased Blood glucose increased Blood iron decreased Blood pressure diastolic increased Blood urine present Biopsy skin
Injury, poisoning and procedural complications			Wound complication Open wound Fall Procedural nausea

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Clinical trials

The safety of SCENESSE® has been evaluated in all clinical trials of the product conducted to date and the product maintains a positive safety profile. Across the four placebo controlled EPP studies described in section 9 (CUV017, CUV029, CUV030 and CUV039), no serious treatment related adverse events were reported. Headache and nausea were the most commonly reported adverse events related to the study drug.

Compassionate use and special access schemes

SCENESSE® has been used in extended compassionate use and special access schemes for the treatment of EPP patients. The two longest treatment programmes, operating at EPP expert centres in Italy and Switzerland, have been subject to ongoing safety reporting. A 2015 publication (Biolcati et al. 2015a) from this programme reported on 115 EPP patients treated for up to eight years with SCENESSE®. This report noted the most frequent adverse events (related and unrelated) were nausea, headache, administration site conditions and fatigue.

Risk management plan (RMP)

A strict RMP has been agreed between the EMA and CLINUVEL, and the Company has a compliant pharmacovigilance system in place (MHRA Inspection January 2017). SCENESSE® is a black triangle product subject to additional reporting/monitoring.

Additional monitoring is required for EPP patients treated with SCENESSE® for whom there are no/limited clinical data (elderly and significant co-morbidities). A summary of safety concerns per the RMP is provided below.

Important identified risks

- Change of pigmentary expressions “lesions”
- Administration site reactions
- Important potential risks
- Allergy and hypersensitivity
- Off-label use in paediatric patients
- Off-label use in adults
- Use in pregnancy and lactation
- Administration error

Missing information

- Use in the elderly (>70 years of age)

- Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment
- Long-term safety data
- Pharmacokinetic data.

Risk minimisation measures have been developed and implemented by CLINUVEL to monitor the ongoing safety of the product according to the RMP. This monitoring is conducted through the PASS protocols and controlled distribution of the product through European EPP Expert Centres.

9.8 Evidence synthesis and meta-analysis

A meta-analysis is not considered appropriate for the appraisal of SCENESSE® due to the lack of scientific tools, alternative therapies and the extensive evaluation of the product in clinical trials compared to placebo (standard of care).

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

From clinical evidence originating from 2005 to 2017, the clinical benefit and effectiveness of SCENESSE® is summarised as follows:

- EPP patients' ability to gradually partake in activities they never had been able to in prior life
- ability to tolerate light sources without experiencing the prodromal symptoms/phase
- ability to expose to light, sun and outdoors without incurring characteristic burns and anaphylactoid reactions.

The difficulty has been for patients to lose their lifelong learned behaviour of isolationism and avoidance while overcoming the ingrained anxiety of burns and sequelae. During the clinical trials the added benefit was modest due to the lack of scientific instruments to measure the impact of disease and therapy on the patients' lives.

The adverse events consist mostly in 12% of the EPP patients out of

1. transient headaches (first 48 hours)
2. nausea
3. gastro-intestinal discomfort (infrequent)

4. transient darkening of the epidermis (expected sequelum of the hormonal therapy).

As per statistical analyses the power of the studies was individually determined for CUV017-CUV029-CUV030 and CUV039.

The NNT and NNH are not applicable.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

SCENESSE® was approved by the European Medicines Agency (EMA) in December 2014 as the first ever treatment for adult EPP patients. The product was approved under exceptional circumstances, with EMA recognising the **lack of available scientific instruments** available to measure the impact of EPP or a treatment, but acknowledging the marked improvement in patient quality of life when receiving SCENESSE®.

Some factors are relevant when reviewing CLINUVEL's clinical trial program:

- EPP expert physicians were never forced to characterise EPP patients, since there had been no clinical therapy. Patients reported once per annum for medical consultation and hepatic check-up without having the hope of receiving effective therapy.
- EPP patients report phototoxicity as the main symptom, consisting of second degree burns, and inexplicable internal "pain" due to endothelial damage (there is no medical nomenclature, hence "pain"; NSAIDs and opioids do not alleviate or treat the internal ordeal).
- Patients have learned to cope with, manage, and accept their disorder since birth and are conditioned to avoid light sources.
- The median delay in diagnosis is 12 years in the UK, but 16 and 18 years respectively in Sweden and Switzerland.
- Patients have learned that there is no treatment and the environment does not recognise the disorder since symptoms are invisible unless a second degree burn occurs.
- Uniquely, EPP patients experience a prodromal phase, signifying that the seconds/minutes of insulting emitted light cause afferent nerve stimulation, which compels patients to withdraw from light sources and avoid further exposure.

Assumptions made during the clinical program (CUV010-CUV017-CUV030-CUV029-CUV039):

- Patients can overcome their lifelong conditioned behaviour and anxiety for light
- Patients are willing to expose themselves to light sources as part of the study
- Patients challenge themselves to light sources beyond the prodromal phase and experience the benefit of the drug

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The scope and trial populations don't deviate. SCENESSE® has been shown in long-term use to have benefits for patients beyond individual health states, such as societal inclusion, opportunities for work and education, and improvement of family life (Biolcati et al. 2015a). For more, see sections 7.2 and 12.3.10 for greater depth on these topics.

Introduction of SCENESSE® in the UK will result in the first ever treatment being available for EPP patients, with the product being used in a multidisciplinary setting in expert centres, and is expected to result in the development of treatment guidelines for patients in years to come. The lack of guidelines stems from the fact that this is the first therapy ever developed for EPP patients.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Not applicable

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

EPP patients show signs of mental distress and anxiety throughout their lives, based on their aversion to light exposure (sunlight, ambient and artificial light sources). Patients are aware that the consequences of light exposure are anaphylactoid reactions and second-degree burns due to the accumulation of protoporphyrin IX in the dermis. Isolation, social withdrawal and depression due to light avoidance are common.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

EPP has a substantive impact on patients' QoL and HRQoL although the impact is impossible to explicitly quantify due to the unique nature and

behaviour of EPP patients. The lack of existence of scientific tools to accurately measure the impact of EPP (and the impact of a treatment) was recognised by the EMA in its evaluation of afamelanotide and subsequent granting of European marketing authorisation under exceptional circumstances.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The afamelanotide development programme has been marked as one being supported by the global scientific experts in porphyria and rare genetic disorders as well as leading global EPP experts (35 known in Europe and the US). Their input led to the creation of a disease specific HRQoL questionnaire: the EPP-QoL questionnaire (subsequently revised as part of the validation process to remove 3 questions). The EPP-QoL includes 12 questions and is scored from –10 to +35, with –10 the worst and +35 the best quality of life. At present there is no mapping algorithm to map EPP-QoL to a utility measure. The value of this questionnaire was its ability to overcome potential limitations of HRQoL data collected using the SF-36 and DLQI instruments in the afamelanotide trial program. In particular, EPP-QoL data was believed to be better at identifying the nuances of the underlying condition and quantifying their impact on HRQoL.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

There is no mapping algorithm to map EPP-QoL to a utility measure.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

Not done.

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

EPP-QoL data collected in the clinical studies described in section 9.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

Not applicable

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

As discussed in sections 6 and 7, EPP has a significant impact on health-related quality of life which is inadequately captured by generic quality of life measures such as the SF-36 or EQ-5D. The EPP-QoL tool was developed to better quantify the quality of life of patients with EPP; there is no mapping algorithm to utilities from this disease specific measure. Further consideration of the inadequacy of the utility measures for EPP has led us to question the appropriateness of generating a cost per QALY analysis in this disease area. The disease is life-long and described as “a persistent, severely painful, socially disabling disease with a marked impact on Quality of Life (QoL)” (Holme et al. 2006). Rather than just affecting quality of life there is a broader ranging impact which better fits the concept of burden of disease. It was therefore considered more appropriate to utilise the global burden of disease and cost per disability adjusted life year (DALY) model. Simply, a DALY can be thought of as 1 lost year of ‘healthy’ life.

The WHO Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) aims to quantify health losses from a wide array of diseases and injuries. Although covering a broad array of conditions the GBD list is finite. Premature mortality and the time spent in these reduced states of health are expressed in units of DALYs. The GBD works to produce disability weightings for a number of different health states, conditions and diseases; in the context of the GBD disability refers to any short- or long-term loss of health. The most recent disability weights were published in 2012 and did not include disability weightings for EPP or what was considered the most applicable proxy, hereditary angioedema (HAE). Our approach to utilising the EPP-QoL data and DALY approach is outlined below.

Proxy disability weights

The GBD has not produced a disability weight for EPP. When considering potential proxies the most appropriate comparable disease was considered to be HAE: the acute or subacute reaction seen in HAE resembles best the anaphylactoid reaction observed in EPP patients at the start of a phototoxic episode, whereby oedema, distress and untreatable ‘pain’ dominate the clinical course. Again, disability weights for HAE have not been produced; therefore alternative proxies were considered:

[redacted]

Although the reasons are different, behaviour adopted by individuals with EPP can be likened to that of individuals who suffer from [redacted] due to a fear of certain environmental factors. [redacted] is clinically considered as a DSM-IV

[redacted]

The GBD categorises [redacted] into three groups; mild, moderate and severe with the respective DALY weights being 0.030, 0.149 and 0.523 respectively (Table D4).

[redacted]

In research conducted by CLINUVEL, people with EPP were likened to people suffering with [redacted] (data on file). A study by Henrard (2014) was recently conducted in Belgium to determine the health and economic burden of disease for [redacted] in the country. The health burden for [redacted] was expressed in DALYs, with disability weights for mild, moderate and severe [redacted] provided. The respective weights in each of these categories are [redacted] (Table D4).

Table C11: Global burden of disease (GBD) disability weightings

Severity	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]

<u>Using the EPP-QoL to estimate DALY weights</u>

The afamelanotide development programme has been marked as one being supported by the global scientific experts in porphyria and rare genetic disorders as well as leading global EPP experts (35 known in Europe and the US). Their input led to the creation of a disease specific HRQoL questionnaire: the EPP-QoL questionnaire (subsequently revised as part of the validation process to remove 3 questions). The EPP-QoL includes 12 questions and is scored from –10 to +35, with –10 the worst and +35 the best quality of life. There is currently no algorithm to map EPP-QoL to a utility measure. The value of this questionnaire was its ability to overcome potential limitations of HRQoL data collected using the SF-36 and DLQI instruments in the afamelanotide trial program. In particular, EPP-QoL data was believed to be better at identifying the nuances of the underlying condition and quantifying their impact on HRQoL.

The EPP-QoL scale is from –10 to +35 which accounts for a continuous 45-point scale which can then be converted to a 0–100 scale to ease interpretation of the results (higher scores indicating improved quality of life). The three proxy disability weights identified above (Table D4) as potentially appropriate, provide three weights for each condition, labelled as mild, moderate, or severe.

To use these proxies we analysed the EPP-QoL data from three afamelanotide clinical trials (CUV029, CUV030, and CUV039; NCT00979745, NCT01097044, and NCT01605136, respectively). The longest follow-up interval available in all trials was 120 days. The individual patient data for EPP-QoL scores was provided and the baseline/ 120-day data were used to stratify the results into three EPP-QOL groups

- 'severe' – 0 to 33.3
- 'moderate' – 33.4 to 66.6
- 'mild' – 66.7 to 100.

A division of three was used in order to utilise the three groups in each of the disability weight proxies identified. The proportion of individuals in each group is provided in Table D5 according to treatment.

Table C12: EPP-QoL: groupings for disability weighting

	Baseline		120 days	
EPP-QoL Score	**Afamelanotide (%)**	**SoC (%)**	**Afamelanotide (%)**	**SoC (%)**
66.7 to 100 [mild]	[redacted]	[redacted]	[redacted]	[redacted]
33.4 to 66.6 [moderate]	[redacted]	[redacted]	[redacted]	[redacted]
0 to 33.3 [severe]	[redacted]	[redacted]	[redacted]	[redacted]

By assigning the proxy weight to the proportion of patients in each group at 120 days, a weighted average could then be calculated to provide a single disability weight for afamelanotide and SoC (i.e. historical SoC). The adjusted disability weight used in the model using each proxy is presented in Table D6.

Table C13: Disability weightings, 120 days, used in model (proxy dependent)

	Disability weight used in the model depending on proxy	
	[redacted]	[redacted]
Afamelanotide	[redacted]	[redacted]
SoC	[redacted]	[redacted]

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Not applicable

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The earliest afamelanotide trial collected SF-36 data, however, as previously discussed, generic quality of life measures do not adequately measure quality of life in an EPP patient. As such, this data was not considered further.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Quality of life is constant over time.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

See details in section 10.1.9.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed?

Treatment continuation is at the discretion of the patient and/or treating physician.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

In 2015, Schuller et al published a systematic review of economic evaluations of ultra-orphan drugs with marketing authorisation in Europe (Schuller et al. 2015). No economic evaluations of EPP were identified in this publication. The search of PubMed described in section 9.1 was conducted to identify relevant clinical studies and economic evaluations. No economic evaluations were identified.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

Table D1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Adult patients with erythropoietic protoporphyria
Interventions	Afamelanotide subcutaneous implant
Outcomes	Any
Study design	All
Language restrictions	English
Search dates	10 June 2017, 15 July 2017

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

No studies were identified.

11.1 Description of identified studies

11.1.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

Not applicable

11.1.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Not applicable

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

Adult patients with erythropoietic protoporphyria (EPP).

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

Not applicable

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

[redacted]

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

Overview

This is an evaluation of the cost-effectiveness of afamelanotide (SCENESSE®) compared to standard of care (SoC; no therapy) in patients with EPP.

A cost-effectiveness analysis (CEA) framework rather than a conventional cost-utility analysis (CUA) was used in which benefits are expressed as Disability Adjusted Life Years (DALYs) averted rather than Quality Adjusted Life Years (QALYs) gained. The rationale for this is the extreme paucity of robust utility data on which to inform a CUA approach and the fact that a cost

per DALY averted framework provides a better fit for the condition and treatment provided (Salomon et al. 2012). In producing the model the World Health Organisation (WHO) definitions and guidelines (WHO, undated) were followed.

EPP is a chronic, long-term disorder with a potential infaust prognosis depending on the development of hepatic disease that could lead to liver failure; hepatic disease affects 10–15% of patients with EPP. [redacted]

[redacted]

[redacted]

[redacted]

Valuation of health states and other benefits

Individuals with EPP are left to modify their natural behaviour by leading an indoors-based life deprived or starved of light sources (Lecha et al. 2009), while seeking ways to manage their anxiety of long-lasting burns. As a result, the ability to lead a 'normal' life in the community is severely impacted. Such impacts include choice of education at an early age, social development and interactions, access to further education and ultimately employment (Holme et al. 2006; Biolcati et al. 2015a). Conceptually, the nature of the afamelanotide therapy results in a prevention or reduction of symptoms, which in turn reduces anxiety and potentially facilitates access to a more acceptable or complete lifestyle. This in turn should lead to an improvement in HRQoL (Biolcati et al. 2015a).

The WHO Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) aims to quantify health losses from a wide range of diseases and injuries. Although covering a broad array of conditions the GBD list is finite. Premature mortality and the time spent in these reduced states of health are expressed in units of DALYs. Simply, a DALY can be thought of as 1 lost year of 'healthy' life. The GBD works to produce disability weightings for a number of different health states, conditions and diseases; in the context of the GBD disability refers to any short- or long-term loss of health. The most recent disability weights were published in 2012 and did not include disability weightings for EPP or what was considered the most applicable proxy, hereditary angioedema (HAE; Salomon et al. 2012).

Model characteristics

[redacted]

[redacted]

[redacted]

Resource use

EPP is a disease that requires lifelong and cyclical management, typically from February to November each year during the period of highest light intensity and highest risk of anaphylactoid burns. It is assumed that whilst successful afamelanotide treatment would reduce or prevent the occurrence of symptoms patients still require regular follow up and per protocol clinical visits. It has therefore been assumed that there is a difference in the number of follow up visits required for people receiving active treatment vs those choosing not to receive treatment. The use of resources is assumed to be different between the treated and untreated patient population (Table D4).

[redacted]

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Lifetime horizon: with the exception of the 2-5% of EPP patients who experience liver failure, EPP has no know impact upon life expectancy. The ICER is independent of time horizon; we do not assume any impact of treatment on overall survival and this means that in every model cycle there are an identical number of patients alive on each treatment arm. Since the cost of treatment, proportion on treatment, and distribution of patients across each of the EPP-QoL categories is fixed over time, it follows that this ratio is also fixed over time as there are no time effects in the model that would allow it to change. Discounting can also be ignored as this is the same in both arms.

Average [redacted] per patient per annum: represents average seen in expanded access and commercial distribution of the drug to date across the expected EPP patient population.

[redacted] **weights are used as a disability weight proxy,** giving a weighted average disability weighting of [redacted] for afamelanotide and [redacted] for SoC.

Exclusion of all societal costs: As outlined in the *Guide to the methods of technology appraisal* (NICE, 2013), societal costs have not been included in the base case of the model. The impact on society is however an important consideration: as a direct result of the condition, patients with EPP modify their behaviour to avoid phototoxic reactions. This will have an effect on their ability to attend school and employment. A sensitivity analysis assessing societal impact has been included in an attempt to quantify this.

The societal costs are indirect and originate from the teenage years of each patient unable to take long term decisions, which affect his/her further employment.

Costs and benefits discounted at 3.5% per annum: As outlined in the *Guide to the methods of technology appraisal* (2013).

Overall budget impact models assume all relevant costs are borne by the NHS for treatment.

12.1.6 Define what the model's health states are intended to capture.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D2.

Table D2 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime	EPP does not affect life expectancy	Biolcati et al. (2015a)
Discount of 3.5% for costs	3.5%	-	NICE (2013)
Perspective (NHS/PSS)	NHS	-	NICE (2013)
Cycle length	1 year	EPP is a seasonally exacerbated, life-long disease. To capture all costs and benefits within the year, a 1 year cycle was selected.	-
NHS, National Health Service; PSS, Personal Social Services			

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

EPP is a poorly characterised rare disease. The accumulation of protoporphyrin when exposed to light causes painful phototoxic reactions debilitating the patient whilst a reaction is occurring and, with the lack of any alternative, causing them to structure a life which prioritises avoidance of light resulting in a significant impact on their quality of life. Clinically, a reduction or prevention in protoporphyrin accumulation is measured by symptom prevention and the impact on a patient's quality of life. The specific EPP-QoL tool – developed in collaboration with global EPP experts – was also used in the clinical trials to measure quality of life and is discussed further below. There is currently no algorithm available to map to a utility score.

As stated earlier, patients with EPP have a dramatically diminished quality of life because of their need to avoid exposure to light (both natural and artificial), and such avoidance becomes learned behaviour and the 'norm'. Even when under treatment patients are resistant to normal levels of exposure to light due to the painful nature of their condition. Thus the nature of EPP symptoms and their impact on patients' quality of life are more suitable to evaluation by the DALY, rather than the QALY.

As stated earlier, patients with EPP have a dramatically diminished quality of life because of their need to avoid exposure to light (both natural and artificial), and such avoidance becomes learned behaviour and the 'norm'.

Thus the nature of EPP symptoms and their impact on patients' quality of life are more suitable to evaluation by the DALY, rather than the QALY.

Whereas the QALY measures burden of disease represented by both the quality and the quantity of life gained by the use of an intervention, the DALY measures avoidance of premature mortality and time spent in a state of reduced health and interventions are evaluated based on the reduction in diminished quality of life lived (years lived with a disability) and avoidance of premature mortality (years of life lost).

Generation of DALY weights from the EPP-QoL have been described in section 10.1.9.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

The ICER is independent of time horizon; we do not assume any impact of treatment on overall survival and this means that in every model cycle there are an identical number of patients alive in each treatment arm. We also have only [redacted] meaning that we can define the number of people alive as N and write down the ICER calculation at each time point as follows:

$$ICER(t) = \frac{(N_t * TotalCosts_{Rx,t}) - (N_t * TotalCosts_{Pbo,t})}{(N_t * TotalBenefits_{Rx,t}) - (N_t * TotalBenefits_{Pbo,t})}$$

Or

$$ICER(t) = \frac{N_t * (TotalCosts_{Rx,t} - TotalCosts_{Pbo,t})}{Nt * (TotalBenefits_{Rx,t} - TotalBenefits_{Pbo,t})}$$

i.e.

$$ICER(t) = \frac{TotalCosts_{Rx,t} - TotalCosts_{Pbo,t}}{TotalBenefits_{Rx,t} - TotalBenefits_{Pbo,t}}$$

Since the cost of treatment, proportion on treatment, and distribution of patients across each of the EPP-QoL categories is fixed over time, it follows that this ratio is also fixed over time as there are no time effects in the model that would allow it to change. Although standard discounting of 3.5% is used for costs and quality of life, in practice this can also be ignored as this is the same in [redacted] arms.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No. Treatment effect was measured using change in EPP-QoL from baseline to day 120 (the longest follow up period in all afamelanotide clinical trials).

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

No. There is no indication from the use of afamelanotide in EPP that the adverse events which have been seen in the use of the product have any impact upon the cost-effectiveness calculation.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Since at the time of the clinical development programme there was no treatment approved for EPP and there were no contemporary clinical studies in this patient population in the published literature, the efficacy endpoints, study design and data analysis had to be developed *de novo* and modified as new scientific knowledge became available from data analysis of completed clinical trials.

The endpoints used in the EPP clinical program were developed in consultation with expert physicians specialising in the treatment of the disease both in Europe and in the United States. Because of the innovative nature of the program, the consultation process continued up to and during data analysis.

[redacted]

[redacted]

[redacted]

Quality of Life

Since publications report a reduced quality of life for EPP patients (Holme et al., 2006), the inclusion of quality of life measurements was considered important to assess the impact of afamelanotide on the lives of these patients. CLINUVEL used three different quality of life assessment tools, SF-36, Dermatology Life Quality Index (DLQI) and a purpose developed EPP-specific quality of life questionnaire (EPP-QoL). Earlier studies (CUV010 and CUV017) used the SF-36 questionnaire. This tool did not prove to be useful for the assessment because most patients reported a very high quality of life from baseline assessments onwards. This finding was contrary to the published literature and demonstrated that a questionnaire more specific to EPP was required. A panel of world experts in porphyria management (drawing from APC and EPNET) prepared a 15-question assessment tool referred to in this application as the EPP-QoL. This questionnaire and the DLQI were used in the CUV029, CUV030 and CUV039 studies

[redacted]

[redacted]

[redacted]

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D3 below.

Table D3 Summary of variables applied in the cost-effectiveness model

Cost		Cost per administration/ visit	Source
Treatment	Afamelanotide implant	£12,020	CLINUVEL
	β-carotene (vitamin A)	£0.05	Over the counter pharmacy
	Vitamin D + Calcium	£0.04	Over the counter pharmacy
Laboratory tests	Erythrocyte total protoporphyrin	£2.00	NHSSRC; Integrated blood services [DAPS03]
	Plasma porphyrin	£2.00	NHSSRC; Integrated blood services [DAPS03]
	Complete blood count	£2.00	NHSSRC; Integrated blood services [DAPS03]
	Ferritin	£2.00	NHSSRC; Integrated blood services [DAPS03]
	Liver functioning	£1.00	NHSSRC; Clinical biochemistry [DAPS04]
Staffing	Principal physician	£135.00	PSSRU 2016; Consultant: medical
	Consultant	£135.00	PSSRU 2016; Consultant: medical
	Nurse	£35.00	PSSRU 2016; Nurse, Band 5

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There is currently no treatment available for EPP.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

EPP is a disease that requires lifelong and cyclical management, typically from February to November each year during the period of highest light

intensity and highest risk of anaphylactoid burns. It is assumed that whilst successful afamelanotide treatment would reduce or prevent the occurrence of symptoms patients still require regular follow up and per protocol clinical visits. It has therefore been assumed that there is a difference in the number of follow up visits required for people receiving active treatment vs those choosing not to receive treatment. The use of resources is assumed to be different between the treated and untreated patient population; these have been determined from the long term observational study reported by Biolcati et al. (2015a) and the specifications determined by the EMA the PASS protocol (see Appendix 5).

Table D4: Additional resource use specific to afamelanotide administration

Resource use component	Afamelanotide	Source
Implant injection visit		
- Principal physician (30 mins)	30 mins	Erasmus Medical Center
- Consultant (30 mins)	30 mins	Erasmus Medical Center
- Consultant (15 mins)	15 mins	Erasmus Medical Center
- Nurse (1 hour)	1 hour	Erasmus Medical Center
Final visit of the year		
- Principal physician (15 mins)	15 mins	Erasmus Medical Center
- Consultant (15 mins)	15 mins	Erasmus Medical Center
- Consultant (15 mins)	15 mins	Erasmus Medical Center
- Nurse (1 hour)	1 hour	Erasmus Medical Center
Total number of follow up hours required	4 hours	

[redacted]Vitamin D + calcium is given to patients every day throughout the year.

Table D5: Estimation of the average number of annual doses of afamelanotide

Injections per annum per patient	Proportion of patients	Source
[redacted]	[redacted]	CLINUVEL data on file
[redacted]	[redacted]	CLINUVEL data on file
[redacted]	[redacted]	CLINUVEL data on file
[redacted]	[redacted]	CLINUVEL data on file
[redacted]	[redacted]	CLINUVEL data on file
[redacted]	[redacted]	

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

Not applicable

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

£12,020 net per injectable implant

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

Not applicable

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Table D6 Annual costs associated with treatment

Items	Value	Source
Price of the technology per treatment/patient	[redacted]	CLINUVEL ([redacted] implants per year)
Administration cost (inc. monitoring and tests)	£328.61	Biolcati 2015a; EMA (PASS protocol); NHS reference costs
Total cost per treatment/patient	[redacted]	

*assuming and based on the average use of [redacted] per patient

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

[redacted]

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

There is no indication from the use of afamelanotide in EPP that the adverse events which have been seen in the use of the product have any impact upon the cost-effectiveness calculation.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

None.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

EPP is recognised as having a significant impact upon patient quality of life, with conditioned behaviour restricting patients' ability to function, as well as their options and choices with regards schooling and careers. The financial impacts of these factors have not been possible to account for in the model.

EPP patients show signs of mental distress and anxiety throughout their lives, based on their aversion to light exposure (sunlight, ambient and artificial light sources). Patients are aware that the consequences of light exposure are incur anaphylactoid reactions and second-degree burns due to the accumulation of protoporphyrin IX in the dermis. Isolation, social withdrawal and depression due to light avoidance are common (Rufener, 1987).

Holme et al. (2006) emphasised the impact of EPP on choice of profession, while Stafford et al. (2010) showed that patients with photodermatoses (including EPP) experienced significantly higher rates of unemployment compared to the healthy population.

Unique to EPP – and not seen in any other light induced disease – are the phenomena of prodromes and priming. During first exposure to light sources, patients uniquely experience a warning symptom (prodrome) of the skin manifested as discomfort and burning sensation, and early oedema as part of first anaphylactoid reactions. These prodromes reinforce learned behaviour to avoid further light exposure. Further, patients experience a 'priming', meaning that exposure and symptoms are cumulative over several days or weeks, enabling a personal variance to the disorder not seen in other disorders (including photodermatoses). These two phenomena, combined with the necessity of light avoidance, have a significant impact on a patient's ability to participate in normal activities, such as schooling or work. EPP patients are

handicapped for life, while their environment does not understand the extent of their plight (Holme et al. 2006; Rufener, 1987).

From a health intervention perspective, most patients suffer from low vitamin D levels due to their inability to expose to light and sun (Holme et al. 2008; Wahlin et al. 2011). The long-term impacts of vitamin D deficiency are still not well understood (Holme et al. 2008), and it is not yet possible to determine whether treatment with SCENESSE® may have a positive effect upon patients' vitamin D levels, however the ability of EPP patients to expose their skin to light may have a positive impact for patients.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Owing to the rarity of the untreated disease and relatively limited data available for EPP patients, the base case results include a number of assumptions. Therefore, a number of sensitivity analyses have been conducted in which each aspect of the model is changed individually to evaluate the impact of each assumption on model results.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

All sensitivity analyses were one-way scenario based deterministic sensitivity analyses.

DALY proxy

In the base case, [redacted] were used as the proxy for disability weighting in the DALY calculation. To explore different scenarios, we calculated two multiplying factors for moderate and severe weights from the disability weights of [redacted]. These were then applied to new values for mild disease in order to obtain new disability weights that could reflect the increase in severity reported for [redacted] in the GBD. In a further scenario we used the disability weights reported for [redacted], which has also been identified as a potential viable proxy for EPP.

Table D7: DALY proxy weights – sensitivity analysis

	Mild	Moderate	Severe	Afamelanotide	SoC
Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Age of the cohort

In the base case we assumed that the cohort was aged 38 years at the time of entering the model and time horizon was set at 35 years. A new scenario was explored, with the cohort at 18 years of age on entry, and a time horizon of 60 years.

Number of afamelanotide implants per year

The base case is calculated according to the predicted number of afamelanotide implants received per year ([redacted]) according to CLINUVEL data obtained from conditions of use. New scenario analyses were conducted altering the number of implants to 0, 1, 3, or 4 per year.

Inclusion of societal costs

As the societal impact is based on loss of earnings or restricted potential for earnings for a patient, there is no change in the incremental DALY. The analyses show how the magnitude of difference between groups influences the model results. The bigger the difference between the groups the more favourable the ICER becomes.

It should be emphasised that the 50% employment capacity is an average, while the distribution of the restricted capacity to work during the daytime is perhaps not evenly distributed over the EPP patient population: a proportion of EPP patients is known to be unemployed, others are limited in their productivity, some have full employment, and others have taken up nocturnal employment.

Table D8: Inclusion of societal costs – sensitivity analysis

Proportion of the average weekly wage earned	
Afamelanotide	**SoC**
Core assumptions (see text)	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

As described in section 12.4.2 above.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Cost and resources remained constant.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with

baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

The following key assumptions were made in the base case model:

a lifetime time horizon

- [redacted]cost of afamelanotide at £12,020 per implant [redacted]
- exclusion of all societal costs
- all costs and benefits are discounted at 3.5% per annum.

Base case results are provided in Table D9.

The incremental cost of approximately [redacted] is largely driven by the additional cost incurred by the afamelanotide implant as additional treatment; visit costs for treated patients have a small impact on total costs.

The incremental benefit observed in patients with afamelanotide compared to those who are untreated is close to [redacted], demonstrating that there is a benefit to the patients of receiving treatment.

The base case incremental cost effectiveness ratio (ICER) is £278,471 per DALY averted. This is calculated as the ratio between the incremental costs and the incremental DALYs averted (or QALYs gained).

Table D9: Base case results (benefits expressed as DALYs averted)

Intervention	Discounted costs	Discounted DALYs
Afamelanotide	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Difference (Δ)	[redacted]	[redacted]
ICER		£278,471 per DALY averted

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences

between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The accumulation of protoporphyrin when exposed to light causes painful phototoxic reactions debilitating the patient whilst a reaction is occurring and, with the lack of any alternative, causing them to structure a life which prioritises avoidance of light resulting in a significant impact on their quality of life. Clinically, a reduction or prevention in protoporphyrin accumulation is measured by symptom prevention and the impact on a patient's quality of life; therefore health-related quality of life was the only outcome included in the model. As previously described, DALY proxies were used with the EPP-QoL score to generate the quality of life measures in the model and therefore cannot be matched to the clinical trial results.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

[redacted]

Table D10: Proportion of patients in each state

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table D11: DALY accumulation over time

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table D12: Model outputs by clinical outcomes

Outcome	Cost (£)	DALY
Afamelanotide		
BSC		

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table D13: Summary of DALY averted (discounted)

Intervention	Discounted costs	Discounted DALYs
Afamelanotide		
Placebo		
Difference (Δ)		
ICER		£278,471 per DALY averted

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table D14: Summary of DALY averted (undiscounted)

Intervention	undiscounted costs	undiscounted DALYs
Afamelanotide	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Difference (Δ)	[redacted]	[redacted]
ICER		£278,500 per DALY averted

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

The comparator in the model is best supportive care which includes monitoring visits and the cost of supplements (detailed in resource use section; total cost £328.61); all costs which are also applied to the treatment arm of the model. Therefore the only cost difference in the model is the cost of the afamelanotide implant (£12,020 per implant).

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Not applicable

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not applicable

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Table D15: Sensitivity analysis results

Scenario	Analysis	Incremental costs	Incremental DALYs	ICER
	Base case	[redacted]	[redacted]	**£278,471**
DALY proxy change	Scenario 1	[redacted]	[redacted]	£208,854
	Scenario 2	[redacted]	[redacted]	£417,707
	[redacted]	[redacted]	[redacted]	£727,143
Age of cohort	18	[redacted]	[redacted]	£278,471
Number of implants per year	N=3	[redacted]	[redacted]	£378,561
	N=4	[redacted]	[redacted]	£503,672
Inclusion of societal impact	See text for core assumptions	[redacted]	[redacted]	£172,302
	Afa: 50%, SoC: 0%	[redacted]	[redacted]	£165,442
	Afa: 50%, SoC: 20%	[redacted]	[redacted]	£210,654
	Afa: 50%, SoC: 10%	[redacted]	[redacted]	£188,048
	Afa: 90%, SoC: 10%	[redacted]	[redacted]	£97,624

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Not applicable

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Not applicable

12.5.14 What were the main findings of each of the sensitivity analyses?

DALY proxy

Because of the reduced difference in averted DALYs using the disability weights for [redacted] this scenario produces the highest ICER. The most cost-effective scenario is when the multiplying factors are applied to the disability weight of 0.40 for the mild disease, generating an ICER of £208,854 per DALY averted.

[redacted]

[redacted]

12.5.15 What are the key drivers of the cost results?

Key cost drivers are the choice of DALY proxy, the number of implants a patient receives annually and the potential societal impact. For more information on societal impact see section 12.3.10.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

Not applicable

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

No subgroup analysis was undertaken.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

To our knowledge, this is the first economic evaluation of EPP attempted, therefore it was not possible to validate to external evidence sources. Internal validation of the model was conducted by a senior health economist not involved in the initial model build.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

To our knowledge, this is the first economic evaluation of EPP attempted.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

When considering an appropriate framework to assess the cost-effectiveness associated with Afamelanotide compared to SoC for treatment of EPP, specific consideration was given to the disease and its impact on patients. As discussed above, burden of disease associated with EPP lends itself to be more closely associated with a DALY based approach. A DALY focuses more on disease and disability rather than the broader health and well-being. We believe this is a key strength of the model and should be considered when interpreting its results; EPP is a debilitating disease that has a significant effect on patients.

The most appropriate measure of quality of life in an EPP patient, the EPP-QoL measure, cannot be mapped to a utility score. In addition, the Global Burden of Disease does not provide disability weights for EPP. Therefore, in order to incorporate the EPP-QoL into the model, proxy disability weightings were generated (section 10.1.9). Though it is informed by data collected from the clinical trial programme, a weakness of the model is this reliance on proxy data. In the absence of alternative options this was deemed to be the most appropriate solution.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

There is a lack of data available for EPP since there are no scientific instruments to measure disease impact or therapy (as confirmed by EMA in 2014). The analysis would be improved by the availability of disease specific disability weightings in the Global Burden of Disease list.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that there are currently 513 EPP patients eligible for treatment in England.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

[redacted]

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Additional visits required as part of the PASS study has been outlined previously (Table D4) and are included in the budget impact estimation.

13.4 Describe any estimates of resource savings associated with the use of the technology.

None

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The likely societal impact of the introduction of afamelanotide has previously been discussed.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Not applicable

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Year 1*	Year 2*	Year 3*	Year 4*	Year 5*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The budget impact model is generated from the cost effectiveness model; therefore all inputs match those previously described.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

Due to the lack of available EPP data it is not possible to provide accurate data on the costs/savings outside of the NHS. It must then be assumed that the majority of costs, and any savings, will be incurred within the NHS.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Not applicable

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Not applicable

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

The majority of family care occurs during childhood, when families embark on a diagnostic odyssey and seek to adapt the family's environment (home, school, vehicles etc) to better seek assistance in finding a diagnosis and therapy for their children. This burden and time spent falls outside the scope of NHS. It is well recognised among the clinical and academic community recognised that EPP places a burden on families.

A long-term study into the use of afamelanotide in EPP (Biolcati et al. 2015a) reported an ability of patients to re-engage with society, including participating in normal family life (such as caring for children or participating in outdoor activities at home/work).

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

The expert centres administering SCENESSE® will be encouraged to provide treatment only under the approved EMA's Post Authorisation Safety Study (PASS) protocol. This non-interventional study may include the entry and upload of pseudonymised patient data into the European EPP Disease Registry (EEDR) as well as intensive patient monitoring for defined subpopulations (i.e. patients over 70 years of age). The PASS enrolled its first patient in June 2016 [redacted]

The study (protocol appended) collects safety and effectiveness endpoints from the ongoing use of SCENESSE® in adult EPP patients and integrates with CLINUVEL's global pharmacovigilance system to monitor the ongoing safety of the product.

It is expected that the PASS protocol will add to the understanding of the product's long-term safety profile, as well as facilitating significantly greater research into EPP through the first ever international EPP registry (EEDR).

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Two UK sites were involved in the clinical development programme for SCENESSE® (Salford Royal Trust in Manchester and University Hospital of Wales in Cardiff), with up to eight expert centres across the UK expected to facilitate EPP patient treatment if given access to SCENESSE®. Access to SCENESSE® will enable these centres to continue to lead research and treatment for EPP patients in Europe, as well as opening opportunities for research into further disorders with the product.

CLINUVEL has already been approached by one university centre in the UK with a request to access the product. Having access to the product in adult EPP patients will undoubtedly product greater benefit to future research.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

CLINUVEL has established the European EPP Disease Registry (EEDR), hosted by the Erasmus Medical Center (Rotterdam, Netherlands). The EEDR captures safety and effectiveness data from European EPP Expert Centres involved in the PASS study. The first safety data from the EEDR have been reported to the EMA, with subsequent annual reports to be submitted in December each year. Should SCENESSE® be made available in the UK, all UK EPP Expert Centres would be encouraged to enrol patients in the PASS protocol and incorporate their data in the EEDR.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

The effectiveness endpoints of the PASS study utilise the EPP-QoL and daily activity inventory questionnaires, along with patient statements and patient diaries.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

SCENESSE® is only administered by healthcare professionals trained and accredited by CLINUVEL. Only centres with existing, recognised expertise in EPP are considered for training and accreditation, generally as members of the European Porphyria Network (EPNET) and/or the British and Irish Porphyria Network (BIPNET).

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Not beyond the training and accreditation of centres and establishment of the PASS protocol at Expert Centres.

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

Not applicable

15.2 Describe the specifics of the MAA proposal, including:

- *The duration of the arrangement, with a rationale*
- *What evidence will be collected to reduce uncertainty*
- *How this evidence will be collected and analysed*
- *The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA*
- *Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)*
- *Funding arrangement, including any commercial proposals or financial risk management plans*
- *The roles and responsibilities of clinical and patient groups during the MAA*
- *What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed*

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

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16.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

16.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Due to the orphan nature of EPP and CLINUVEL being the only supplier of SCENESSE® (the only afamelanotide formulation licensed for use in human clinical trials to date), a review of both external and internal Company databases was considered appropriate. A structured search was conducted on the US National Library of Medicines PubMed.gov (National Institutes of Health).

16.1.2 The date on which the search was conducted.

10 June 2017, replicated on 15 July 2017.

16.1.3 The date span of the search.

No limitation.

16.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Open search: *“afamelanotide” OR “cuv1647” OR “NDP-MSH” AND erythropoietic protoporphyria*

This search was intended to identify any publications involving the indication in the scope and the product. The three bracketed terms all refer to the generic product now known as afamelanotide.

16.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Results from the PubMed search were manually compared to CLINUVEL's internal reference library, and no additional original research publications were identified. Lead clinical staff involved in the afamelanotide development programme were also consulted to ensure any publications of data were not excluded.

A search of the two leading international clinical trial databases was also conducted – NIH ClinicalTrials.gov and Eudract – to identify any additional (published or unpublished) studies. An identical search string to the NIH PubMed search was used and identified no further clinical or observational trials of afamelanotide in EPP patients.

16.1.6 The inclusion and exclusion criteria.

Inclusion: all publications on original research from clinical and/or observational studies.

Exclusion: review articles with no new clinical data.

16.1.7 The data abstraction strategy.

Due to the volume of articles identified this process was not required.

16.2 Appendix 2: Search strategy for adverse events

The following information should be provided.

16.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable.

16.2.2 The date on which the search was conducted.

Not applicable.

16.2.3 The date span of the search.

Not applicable.

16.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable.

16.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

CLINUVEL maintains an in-house pharmacovigilance database and, as an approved product, SCENESSE® has an approved Summary of Product Characteristics from which the adverse event profile of the product has been provided.

16.2.6 The inclusion and exclusion criteria.

Not applicable.

16.2.7 The data abstraction strategy.

Not applicable.

16.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

16.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Per Appendix 1.

16.3.2 The date on which the search was conducted.

Per Appendix 1.

16.3.3 The date span of the search.

Per Appendix 1.

16.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Per Appendix 1.

16.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Per appendix 1.

16.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

16.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Due to the limited nature of studies with afamelanotide (CLINUVEL is the only company to have conducted research into the product in EPP patients), an extensive literature search was not deemed appropriate for this purpose. A review of the Company's own database and the NIH's National Library of Medicine (PubMed) was conducted, alongside a search of ClinicalTrials.gov and the EU Clinical Trials register.

16.4.2 The date on which the search was conducted.

10 June 2017, replicated on 15 July 2017

16.4.3 The date span of the search.

No limitations

16.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Open search: *"afamelanotide" OR "CUV1647" OR "NDP-MSH" AND erythropoietic protoporphyria*

NB: CUV1647 and NDP-MSH are earlier names used for the product now known as ‘afamelanotide’.

16.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

CLINUVEL maintains an in-house database on the commercially available software Reference Manager (v 10). The Company performs weekly literature searches for relevant topics beyond the scope of the above search to capture literature. No articles which weren’t identified in the PubMed search were identified in the in-house database search.

16.4.6 The inclusion and exclusion criteria.

All articles which clearly reported on the use of afamelanotide in EPP were included

16.4.7 The data abstraction strategy.

Due to the volume of articles identified this process was not required.

16.5 Appendixes 5-7

The following documents have been provided as separate appendices in PDF format:

Appendix 5: [redacted]

Appendix 6: SCENESSE® Summary of Product Characteristics (English)

Appendix 7: [redacted]

17 Related procedures for evidence submission

17.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

17.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

17.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria ID927

Dear Lachlan,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 21st August by Clinuvel. The ERG and the NICE technical team would like further clarification relating to some of the data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the 'essential' questions outlined in this letter by **5pm** on **8th September 2017**. We have made these questions available ahead of the timelines provided in the invitation to participate because the ERG is unable to undertake its critique and analysis without this information. Responses to the remaining questions may be provided in line with the clarification timelines previously provided, that is, by 25th September 2017. An additional set of clarification questions will be sent through on 8th September. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Mary Hughes, Technical Lead (mary.hughes@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

A1. **Essential Question:** For each of the studies CUV017, CUV029, CUV030 and CUV039, please provide the following EPP-QOL results by study group for each measurement timepoint (0 days, 60 days, 120 days etc. up to final assessment):

- Absolute EPP-QOL scores (n, mean and standard deviation)
- Change in EPP-QOL scores from baseline (n, mean and standard deviation)
- Number (and %) of patients with 'mild' (0-33.3), 'moderate' (33.4 to 66.6) and 'severe' (66.7 to 100) levels of disease

  Please use the 0-100 scale for EPP-QOL, based on the 12-item Oxford Outcomes revised version. Present data in tables in the format used in Table 4 in Langendonk et al (NEJM 2015): using separate tables for each study and for the absolute, change from baseline, and severity frequency statistics.

A2. **Essential Question:** For study CUV039, please present summary statistics for the DLQI by study group and for each time point (day 0, 60, 120, 180 and 360)

- Absolute DLQI scores (n, mean and standard deviation)
- Change in DLQI scores from baseline (n, mean and standard deviation)
- Number (and %) of patients grouped by levels of severity, as specified by the Cardiff University Department of Dermatology (0-1, 2-5, 6-10, 11-20 and 21-30)
- Absolute DLQI scores (n, mean and sd) by EPP-QOL levels of severity (0-33.3, 33.4-66.6%, 66.7 to 100).

A3. **Priority Question:** Please provide clinical study reports containing full detailed methods and results for the CUV017, CUV029, CUV030 and CUV039 studies. Please can you also supply the protocols (including statistical analysis plans) for these studies.

A4. **Priority Question:** For study CUV017, please present summary statistics for the SF-36 by study group and for each time point (day 0, 60, 120, 180, 300 and 360)

- Absolute SF-36 scores for 8 domains, and PCS and MCS (if available) (n, mean and standard deviation)

A5. **Priority Question:** For CS table C12, please provide the patient numbers (numerator and denominator), and confidence intervals around the percentage values. Please also describe the method used to pool the three trials CUV029, CUV030 and CUV039, for example, whether an adjusted comparison or unadjusted (naïve) comparison of study groups was done across the trials.

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A6. The trials and CS provide a range of descriptions of light exposure, including (among others) “direct sunlight exposure” (e.g. CS Page 32), “direct light/sunlight exposure” (e.g. CS page 32), “light/sun exposure” (e.g. CS page 36) “some direct light/sunlight exposure” (e.g. CS page 36), and “total direct light/sunlight sun exposure” (e.g. CS page 37). For all included trials please provide definitions of the light exposure outcomes as precisely as possible, to clarify whether exposure occurred under blue sky, cloudy or other outdoor shade conditions, and/or combinations of outdoor/indoor light conditions.

A7. For the trial CUV030 please explain the meaning of “per unit of direct sun exposure” (CS page 35)

A8. In the journal publication of the CUV029 and the CUV039 trials (Langendonk et al, NEJM 2015) it is stated that “the increased skin pigmentation in participants who received afamelanotide partially unblinded the trial” (page 53). Please can you provide more information on this statement including which of the two trials this occurred in, how many patients it refers to, at what point in time unblinding occurred, and what impact this is considered to have on the study outcomes?

A9. How many UK patients were enrolled in the clinical trials? Studies CUV017, CUV029 are reported to have included European centres, and we note from the journal publication of CUV029 that some UK centres were involved (Newport, Manchester, Oxford).

A10. Please provide a reference for, and a description of, the 11-point Likert scale that was used to score pain. What was the justification for a score threshold of 4 or higher for a phototoxic reaction (reported in CS page 33)?

A11. Please provide a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) style flowchart reporting the number of published and unpublished studies included and excluded at each stage of the review, as per section 9.2.2 and 9.2.4 of the submission template.

A12. On page 23 of the submission under section 9.3.1 it is stated that 18 peer reviewed journal articles were identified. However, citations to articles in the subsequent paragraphs do not sum to 18. Please provide a full reference list for these 18 articles, stating the reasons for excluding any of the articles from the submission.

A13. What would be the likely significance of the difference in the percentage of patients in the European Union trial (CUV029) with skin type 1 (Langendock et al 2015). Would the higher percentage of patients (33% with skin type 1 in the placebo group vs 16% in the afamelanotide group) bias sun exposure times and other outcomes measured?

A14. Please can you clarify whether there are any data available on the impact on the quality of life of carers and family members.

Section B: Clarification on cost model and value for money

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B1. **Essential Question**: The consultancy retained by Clinuvel, ICON, produced an analysis using mapped SF-36 utility scores to perform a cost-utility analysis with QALYs as the measure of benefit (Thompson et al. 2016 Value in Health 19 (2016) A249). Please provide an executable model and a full description of the methods and detailed results of this analysis, including:

- which clinical trial(s) provided the quality of life data for this analysis
- the mapping equation used (with reference) for this analysis
- the SF-36 scores (n, mean and standard deviation by SF-36 dimensions) used
- the estimated utility values (n, mean and standard deviation) for patients with mild, moderate and severe EPP
- the resulting estimates of QALYs, costs and incremental cost per QALY and
- a discussion of the limitations of this analysis.

B2. **Essential Question**: Please justify your division of the EPP QoL scale into three equal segments to define 'mild', 'moderate' and 'severe' EPP health states. In particular, please provide evidence that this division reflects clinically meaningful differences in symptom burden for patients. Alternatively, please provide EPP-QOL cutpoints that do define clinically meaningful definitions of mild, moderate and severe EPP.

We note that lay descriptions of the WHO disability states for mild/moderate/severe anxiety that you use in your DALY model are given in the supplementary appendix to Salomon et al 2012. The states defined for EPP in your DALY model should be analogous in severity to those defined by Salomon et al 2012 for anxiety disorders.

B3. **Essential Question**: Please use DLQI data to map to EQ-5D utility values for patients with mild, moderate and severe levels of disease. Data on EPP-QOL and DLQI is available from study CUV039, and DLQI to EQ-5D mapping algorithms are available in the literature (database of mapping studies, Ali 2017). Please justify your choice of mapping algorithm, and provide the means, standard deviations, and numbers of observations for each mapped utility score. Please conduct a cost-utility analysis substituting these utility weights for the DALY weights used in your economic model. If this is not provided the committee will only be able to take into account the ERG's cost-utility analysis in its decision making. If you intend to address this question, but need additional time to do so, please state your intention in your response to this letter (NICE would accept these analyses by 25th September 2017).

B4. **Priority Question**: Please provide sample sizes and state the source of data for the average number of implants per year in Table D5 (CS page 76). The table merely states the source as 'CLINUVEL data on file', and the model specifies 'EMA'. Which studies did these data come from?

B5. **Priority Question**: Please provide information on the number of implants used in the UK centres in study CUV029: number and % of participants using 0, 1, 2, 3, 4 & 5 implants.

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B6. Please state how the estimated prevalence of 513 EPP patients in England was calculated (as reported on CS page 16 and page 91).

B7. Please provide detail on the training that is required for UK expert centres prior to the use of the product (CS page 20, section 8.8), in terms of duration and frequency of training last; who were the training recipients; and estimated costs of training.

Section C: Textual clarifications and additional points

C1. Please provide the full text of the following references cited in the submission (but not supplied with the submission)

Balwani M. A Phase II, multicentre, double-blind, randomised, placebo-controlled study to confirm the safety and efficacy of afamelanotide implants in patients with erythropoietic protoporphyria (EPP). International Congress of Porphyrins and Porphyrias, EPP Satellite Symposium. Luzern, Switzerland. 2013.

Minder EI, Biolcati G, Deybach JC et al. Afamelanotide in Erythropoietic Protoporphyria (EPP): a randomised, placebo controlled multicenter phase III trial. 19th European Association of Dermatology and Venereology Congress, Gothenburg, Sweden. 2010.

Minder EI. Exploiting the photoprotective potential of afamelanotide – Erythropoietic Protoporphyria. 20th European Association of Dermatology and Venereology Congress, Lisbon, Portugal. 2011.

C2. Please supply the reference for the following citation in the CS (page 58) “A study by Henrard (2014) was recently conducted in Belgium to determine the health and economic burden of disease for haemophilia in the country” (The reference does not appear in the reference list).

C3. In the checklist of confidential information in relation to Appendix 5 (page 104 of the CS) it is stated that “The PASS protocol is commercially sensitive. Its inclusion in the dossier is not”. Please can you clarify whether this appendix is or is not commercial in confidence for this appraisal.

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Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Dear Lachlan,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 21st August by Clinuvel and the ERG and the NICE technical team requested early clarification relating to some of the data on the 1st September 2017.

NICE is keen to ensure that HST committee has the ability to review all the available evidence and information fully. This will enable them to undertake the evaluation fairly, transparently and with all relevant and important data. In order to do this the ERG and the NICE technical team have additional clarification questions (see questions at the end of the letter) over and above the previous questions posed and request Clinuvel review these questions and provide a response).

We recognise there may be some limitations to what the company can share with NICE but would request that all questions are considered carefully and all confidential information is kept to a bare minimum. Please also share any relevant rationale as to why data cannot be shared.

The ERG and the technical team at NICE will be addressing the issues highlighted in this letter to produce their reports for consideration.

Please provide a written response to these additional clarification questions by **5pm** on **25th September 2017**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow. As described before please aim to keep this to a minimum so we can undertake the evaluation as transparently as possible.
If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Mary Hughes, Technical Lead (mary.hughes@nice.org.uk). Any procedural

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questions should be addressed to Joanne Ekeledo, Project Manager (joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority Question:** Please provide critical appraisal for trials CUV017 and CUV010 (CS Table C7). Please provide full critical appraisal of the observational study reported by Bialcati et al (2015a, 2015b) (CS Table C8 contains almost no information).

A2. *Further to question A9 in the early clarification questions sent by NICE on 1st September 2017*, did increased skin pigmentation also lead to unblinding in CUV030?

A3. *Further to question A11 in the early clarification questions sent by NICE on 1st September 2017*, please provide a reference for, and a description of, the 11-point Likert scale that was used to score pain. Trials CUV029 and CUV039 defined mild pain as a Likert score of 1-3 but trial CUV030 defined mild pain as a Likert score of 1-4 (CS Table C5). What was the justification for a score threshold of 4 (or 5) or higher for a phototoxic reaction and why did the threshold differ between the trials?

A4. Please clarify the scoring system for the EPP-QoI instrument. On CS page 38 it is stated "The total scores range from -10 (best possible) to 35 (worst imaginable)" In contrast, on CS page 55 and 58 it is stated that "The EPP-QoL includes 12 questions and is scored from –10 to +35, with –10 the worst and +35 the best quality of life". Please can you clarify this discrepancy in the direction of scoring of worst-best and confirm which is correct. Please can you also clarify which version of the EPP-QoI it refers to. We are aware of three different versions:

1. 18 item version as reported by Biolcati et al 2015. Scored from 0 to 54, lower scores signify worse quality of life. No minus scores possible. (Biolcati G, Marchesini E, Sorge F, et al. Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol 2015a;172(6):1601-12).

2. 15 item version included in the protocol for study CUV039. Scored from -10 to + 35. Lower scores signify better quality of life. (Protocol for: Langendonk JG, Balwani M, Anderson KE, et al. Afamelanotide for erythropoietic protoporphyria. N Engl J Med 2015;373:48-59. DOI: 10.1056/NEJMoa1411481).

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3. 12 item version presented in Table S1 in the supplemental appendix to Langendonk (2015). Scored between 0 and 36, with lower scores signifying worse quality of life. (Langendonk JG, Balwani M, Anderson KE, et al. Afamelanotide for erythropoietic protoporphyria. N Engl J Med 2015;373:48-59. DOI: 10.1056/NEJMoa1411481.

The only version where minus scoring appears to be included is the 15 item version. The 12 item version appears to be the revised version following validation by Oxford Outcomes – please can you confirm this is correct. Please provide a copy of this if it is any different from the version in (3) above. If a report of this validation is available please could you provide it. Please also confirm which version of EPP-QoI was used in studies CUV029, CUV030 and CUV039.

A5. Please can you provide full baseline data for all patients in the RCTs if not provided the clinical study reports, including % skin type, age, race in the study.

A6. If not already included in the clinical study reports please provide CONSORT flowcharts for all included RCTs, showing the numbers of patients involved at all stages of the study, including withdrawals and reasons for withdrawal (as required in section 9.4.5 of the HST company submission template).

A7. It is stated that sunlight exposure recorded in patient diaries in trial CUV017 was "verified by the investigators" (CS page 29). Please explain what this means.

A8. Please report whether the selection criteria for clinical evidence were applied to the results of the literature search from all sources (i.e. titles and abstracts, and full texts) by a single reviewer, or whether it was done independently by two reviewers. Likewise, please confirm if data extraction from clinical evidence study reports and critical appraisal of study methodology was done by a single reviewer, or by more than one reviewer?

Section B: Clarification on cost model and value for money

No further questions

Section C: Textual clarifications and additional points

No further questions

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation
The National Institute for Health and Care Excellence
10 Spring Gardens
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SW1A 2BU
Submitted via NICE docs

CC: Marie Manley [redacted] Bristows LLP

12 September 2017

Re: Afamelanotide for treating erythropoietic protoporphyria ID927

Dear Ms Upadhyaya,

Responses to the further questions from the ERG

As discussed by phone on 07 and 08 September it appears from the questions posed by NICE on 01 September, that the ERG has failed to understand the Company's position with regards economic modelling and erythropoietic protoporphyria (EPP).

As you will be aware, SCENESSE® (afamelanotide 16mg) was granted a marketing authorisation ("MA") under "exceptional circumstances"[1] by the European Commission on the basis of the positive opinion of the European Medicines Agency (EMA). The EMA scientific committee understood and took into consideration the specific characteristics of EPP and the innovative treatment proposed. It is CLINUVEL's view that those specificities are also relevant to NICE's assessment, as they render it impossible for CLINUVEL to comply with the reviewed standards set out by NICE in the HST procedure to demonstrate the efficacy of SCENESSE® for EPP patients. In addition, NICE had changed its standards while it had erroneously rejected SCENESSE® for HST assessment at the expense of 16 months delay for all patients involved.

As you are aware, EPP is a complex and extremely unusual medical condition, which renders the conduct of traditional clinical trials impossible. Indeed, CLINUVEL found that EPP patients were unable to overcome their lifelong conditioned behaviour and risk aversion to light sources in a clinical trial setting due to their ingrained anxiety. This is due to various factors such as disease-specific prodromes, which forewarn patients of classical EPP symptoms, coupled with anxiety associated with the potential risk of dermal burns and anaphylactoid reactions (phototoxic burns). Furthermore, there are currently no appropriate scientific instruments or tools developed to capture relevant data on the disease, its impact or the impact of an interventional treatment (i.e. to measure graduation of tissue destruction in EPP, the occurrence of prodromes nor measure patient exposure to the visible light spectrum). Therefore, it was impossible to find EPP patients willing to submit themselves to such a trial and it would have been unethical to even contemplate the collection of such data by asking them to risk incurring phototoxicity and burns. Existing HR QoL questionnaires (DLQI and SF-36) are not suitable to measure the effects of a condition which has such profound effects on the patient as EPP. An EPP-specific tool

[1] Article 22 Directive 2001/83/EC and Article 14(8) Regulation 726/2004, both as amended.

has been proposed, [redacted]. Put another way, attempts to quantify the quality of life impact in EPP are totally impaired by the limits of current scientific understanding of EPP, a limitation which has been well recognised by European regulatory authorities.

In the eight years prior to obtaining the MA, CLINUVEL and the global experts in porphyria exhausted all possibilities of developing a study design which could unequivocally demonstrate the efficacy of SCENESSE® in treating EPP patients. In section 2.5.3 of the European Public Assessment Report dated 23 October 2014 as adopted by the CHMP (the "**EPAR**") the EMA's Committee for Medicinal Products for Human Use (CHMP) agreed that "*Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease and 'visible light' to exposed skin*". Section 2.5.3 went on to conclude that the EMA was "*of the view that comprehensive data on the efficacy and safety under normal conditions of use could not be generated*".

The CHMP of the EMA accepted that there were no assessment tools available to capture meaningful and comprehensive efficacy data and "*patients are so rarely identified that conduct of a controlled clinical trial would be unachievable*" (section 2.5.3 of the EPAR). The EMA (then endorsed by the European Commission) accepted that results of five clinical trials had trends in favour of SCENESSE® in comparison to a placebo[2] (section 2.5.4 of the EPAR) together with the testimony of expert physicians and patients on the efficacy of SCENESSE®[3] in their decision to recommend its approval. It was on this basis that SCENESSE® was approved by the EMA under exceptional circumstances.

Certain of the questions asked by NICE indicate that NICE is proposing to use a QALY based assessment of the SCENESSE® data. However, as previously corresponded, the DALY model is the best model to approximate the lifelong handicap posed by the disease and was provided to NICE as an indication. QALYs and a cost-utility analysis (CUA) are an inappropriate measure as they rely heavily on the capture of comparable quality of life data from clinical trials in order to determine overall impact. Therefore, as explained above, the difficulties of capturing robust evidence from clinical trials meant making the like-for-like comparisons necessary in a QALY model was impossible to arrive at. Furthermore, QALYs are considered a poor model for comparing new interventional therapies against "Standard of Care" where no previous therapy existed, as the ICER will consistently struggle to compete economically with "no care" as a comparator.

Instead CLINUVEL worked with a number of health economists to arrive at a cost-effectiveness analysis (CEA) framework rather than the CUA, which would reflect the value of SCENESSE® in EPP. The approximated benefits of SCENESSE® are expressed in DALYs rather than QALYs due to the extreme paucity of robust utility data on which the CUA is based and the fact that a DALY CEA framework is a better fit for the condition and treatment provided. The DALY calculation was based on a universal set of standard weights (from the WHO GBD) rather than data from clinical trials. By using the DALY, the model approximates the impact of EPP against similar disorders [redacted] Furthermore, in producing the model WHO definitions and guidelines were followed.

Given the above the Company has sought to provide answers to those questions from ERG which are appropriate to the review of SCENESSE® using a DALYs rather than QALYs (see Appendix).

The information requested by NICE is disproportionate to any other European pricing procedure the Company has participated in to date, and has placed a significant resource burden on CLINUVEL as a SME, [redacted]. Other eminent authorities have recognised the benefit afforded by SCENESSE® to EPP patient and recommended it be adopted

[2] Five "main" studies were submitted. While it was noted, due to the reasons set out above, there were issues with the robustness and good clinical practice regarding these trials, it was concluded that study CUV039 showed a benefit effect and all five clinical trials had trends in favour of afamelanotide.

[3] During the marketing authorisation appraisal an Ad Hoc Expert Group was convened at the EMA (the "**Group**"), which consisted of patients, their representatives and expert physicians. The position of the Group was set out in section 2.5.3 of the AR and they considered that "evidence through individual case description has its value and should be taken into account in particular for this condition".

as a standard of care. Of particular note, during the review in Germany the Federal Joint Committee agreed that there was a non-quantifiable benefit to the drug in EPP, which was in line with the EMA's 2014 assessment that no scientific instruments exist to measure EPP or a therapy [redacted] Also during a review [redacted] it was accepted that there was an unquantifiable benefit of the drug based on patient and physician testimonies and, while unfamiliar with the DALY model, [redacted] would be willing to accept it for an ultra-orphan indication. Therefore, based on the above explanation CLINUVEL trust that NICE will now appreciate it would be irrational, unfair and inappropriate to insist on the use of an economic model based on a QALY measurement in order to appraise SCENESSE®.

NICE's duty to assess new medicine and use of discretion

As you will be aware, under section 233 of the Health and Social Care Act 2012, *"In exercising its functions NICE must have regard to— (a) the broad balance between the benefits and costs of the provision of health services or of social care in England, (b) the degree of need of persons for health services or social care in England, and (c) the desirability of promoting innovation in the provision of health services or of social care in England."* Therefore, NICE has a duty to assess new medicines taking into consideration the specificities of the medical condition (i.e. EPP). Therefore, regarding SCENESSE®, NICE's requests for information must be tailored and adequate to enable a fair assessment of the medicine which is essential to patients suffering from EPP. Requesting information that is impossible to deliver due to the specificities of the medical conditions goes against the task that NICE has been entrusted with (i.e. assessing new technologies in order to determine their cost-effectiveness).

Furthermore, following NICE guidance on HST evaluations and under the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulation 2013 (**"SI 2013/259"**), once the Department of Health refers HST evaluation topics NICE should appraise these referred products and on this basis decide whether the make recommendations. Therefore, now that the Department of Health has referred SCENESSE® - after admission of its previous error with the consequence of patients incurring another 16 months delay - to the HST process, NICE is required to assess it.

By rejecting the only evidence that CLINUVEL is able to provide in order for NICE to carry out its assessment, which was accepted by the EMA and other regulatory bodies similar to NICE, NICE would be acting irrationally.

Finally, CLINUVEL respectfully requests that NICE uses it discretionary powers to accept the DALY model rather than insisting on the QALY model. This is supported by section 8(8) of SI 2013/259 and at paragraph 36 of Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes, which states that "*the Evaluation Committee has discretion to consider those factors it believes are most appropriate to each evaluation*", as well as at paragraph 41 which states "*[t]he Evaluation Committee has the discretion to take account of the full range of clinical studies*" which can include "*qualitative evidence related to the experiences of patients, carers and clinical experts who have used the technology*" and that "*[i]n evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions.*" Furthermore, at paragraph 44, the Evaluation Committee have discretion to determine which factors they will take into account in the assessment of clinical effectiveness.

Therefore, it is clear that NICE has significant discretion in determining the procedure and the criteria for assessing medicinal products under the HSTs appraisal process. As such, CLINUVEL respectfully requests that, as other Agencies have done previously and for all the reasons explained above, NICE accepts to assess SCENESSE® based on a DALY economic model rather than unreasonably further insisting on a QALY model.

Furthermore, the Company intends to provide a response to the Commercial In Confidence request from Ms Ekeledo by 9am on Monday 18 September. Responses to the ERG's non-essential questions will be provided by the deadline of 25 September, however, the principles explained in this letter will also apply to those responses.

Of course we will be happy to make ourselves available to discuss the above further. Considering that this matter has been going on since 2012 through no fault of CLINUVEL, we would greatly appreciate if the assessment of SCENESSE® could be prioritised and moved forward as a matter of urgency for the benefit of EPP patients who are suffering for those unnecessary delays.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

Appendix

[redacted]

Section A (Clarification on effectiveness data): Essential Questions

Question A1

[redacted]

Question A2

[redacted]

Section B (Clarification on cost model and value for money): Essential Questions

Question B1

[redacted]

[redacted]

[redacted]

Question B2

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Question B3

[redacted]

[redacted]

Section C Textual clarifications and additional points

Question C1
Please provide the full text of the following references cited in the submission (but not supplied with the submission) [omitted for brevity]

Abstracts from all three studies were provided. Further permissions from academics are being sought to provide these data.

Question C2
Please supply the reference for the following citation in the CS (page 58) "A study by Henrard (2014) was recently conducted in Belgium to determine the health and economic burden of disease for haemophilia in the country" (The reference does not appear in the reference list).

The requested document is provided via NICE docs.

Question C3
In the checklist of confidential information in relation to Appendix 5 (page 104 of the CS) it is stated that "The PASS protocol is commercially sensitive. Its inclusion in the dossier is not". Please can you clarify whether this appendix is or is not commercial in confidence for this appraisal.

This appendix is commercial in confidence.

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation
The National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
Submitted via NICE docs

CC: Marie Manley, Bristows LLP via email

26 September 2017

Re: Afamelanotide for treating erythropoietic protoporphyria ID927

Dear Ms Upadhyaya,

Responses to the further questions from the ERG

Per my correspondence of 12 September it appears from the questions posed by NICE on 01 September, that the ERG has failed to understand the Company's position with regards economic modelling and erythropoietic protoporphyria (EPP).

The Company's detailed concerns in this regard have been set out in our letter of 12 September, and the issues raised therein are equally applicable to the questions addressed in this letter. CLINUVEL has additional concerns regarding the current questions and the evaluation of SCENESSE® (afamelanotide 16mg) by NICE.

Much of the data requested is not considered to bring any value to the ERG's assessment, over and above the data already provided, in the context of the deliberations.

The European Medicines Agency's (EMA's) Committee on Medicinal Products for Human Use (CHMP) has deliberated during 2.5 years the complexity of the innovative treatment of a poorly characterised disorder, EPP. It arrived at a positive benefit-risk assessment on the basis of diligence involving all stakeholders. Questions relating to endpoints and effectiveness have been answered from 2012-2014. CLINUVEL has addressed the questions where possible on the basis of the current status of the known science.

Furthermore, in order for a fair, rational, and procedurally correct assessment of SCENESSE® to be made by NICE, it is essential that NICE ensures the following:

- It does not attempt to re-open the conclusions of the CHMP and the Commission regarding the efficacy of SCENESSE® nor insist on a demonstration of efficacy which goes beyond that required by the CHMP;
- It takes into account the evidence and consensus of the clinical experts (including the CHMP) that have been involved in the development and approval of SCENESSE® including in relation to:
    - the inability of EPP patients to expose themselves to "light" (and light sources) during the clinical programme;
    - the lack scientific tools and instruments available to quantify EPP or the impact of therapy (as concluded by the CHMP); and

    - the fact that neither the DLQI nor the SF-36 QoL questionnaire is appropriate for assessing the quality of life of EPP patients due to the very unique and serious nature of the condition.
- It has read (in full) and understood all the data that has been provided to it by the Company, so that it includes all relevant data in its assessment, does not give weight to irrelevant data and does not suffer under errors of fact.

As you are aware, through no fault of CLINUVEL the NICE appraisal started in 2012, while the marketing authorisation for SCENESSE® was granted in 2014. Due to an error by NICE, and its unwillingness to verify the prevalence data CLINUVEL had already submitted, 16 months of review time were lost. This has resulted in a further delay of 16 months withholding EPP patients of a treatment which had never existed. Unfortunately, NICE has not publicly apologised to patients or the company for its error. NICE should not further delay review of SCENESSE® for EPP.

Commercial in confidence information
The Company's responses to the CIC request are detailed in Appendix 2. NICE must recognise, given CLINUVEL's position as a small, publicly-listed firm with a single approved drug, that the nature of confidential information is significantly different to other firms with which NICE is used to interacting. As a result, the Company insists that large portions of its submission remain confidential, including its economic modelling. This request has been accepted by all of NICE's peers to date. Per our submission on 22 August, the Company would welcome a discussion with NICE as to the most appropriate way to handle CIC to enable the evaluation of SCENESSE®. A revised version of the Appendix D, reflecting changes in CIC highlighting, has been attached.

We look forward to hearing from you.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

Appendix 1 – ERG questions

[redacted]

A3. Priority Question

Please provide clinical study reports containing full detailed methods and results for the CUV017, CUV029, CUV030 and CUV039 studies. Please can you also supply the protocols (including statistical analysis plans) for these studies.

The Company has submitted all data from these studies, as well as protocols and analysis plans, to CHMP for scientific review. These data are identical to those submitted to NICE. The CHMP recognised that the design of clinical trials for the evaluation of a treatment in EPP was most challenging. It was also acknowledged that the evaluation of a therapy which abrogates the effects of light along the visible spectrum was complex due to the innovative scientific approach. The CHMP chose to evaluate pivotal study CUV039, as can be found in the EPAR.

A4. Priority Question

For study CUV017, please present summary statistics for the SF-36 by study group and for each time point (day 0, 60, 120, 180, 300 and 360)

Per previous submissions to NICE, expert EPP physicians determined during the course of the clinical development programme of SCENESSE® that the SF-36 was not a suitable tool for the evaluation of the quality of life impact of EPP. This finding is consistent with the medical literature (see, for example, Rufener 1987) and the determination of CHMP that there are no scientific tools or instruments available to quantify the impact of EPP.

A5. Priority Question

For CS table C12, please provide the patient numbers (numerator and denominator), and confidence intervals around the percentage values. Please also describe the method used to pool the three trials CUV029, CUV030 and CUV039, for example, whether an adjusted comparison or unadjusted (naïve) comparison of study groups was done across the trials.

Since there are no scientific tools or instruments to quantify the treatment effect of SCENESSE®, [redacted]

A6.

The trials and CS provide a range of descriptions of light exposure, including (among others) "direct sunlight exposure" (e.g. CS Page 32), "direct light/sunlight exposure" (e.g. CS page 32), "light/sun exposure" (e.g. CS page 36) "some direct light/sunlight exposure" (e.g. CS page 36), and "total direct light/sunlight sun exposure" (e.g. CS page 37). For all included trials please provide definitions of the light exposure outcomes as precisely as possible, to clarify whether exposure occurred under blue sky, cloudy or other outdoor shade conditions, and/or combinations of outdoor/indoor light conditions.

CLINUVEL has been the only company/research group to evaluate the excitation of protoporphyrin IX by "visible light" (>408nm). [redacted]

A7.

For the trial CUV030 please explain the meaning of "per unit of direct sun exposure" (CS page 35)

We kindly refer you to the European Public Assessment Report.

A8.

In the journal publication of the CUV029 and the CUV039 trials (Langendonk et al, NEJM 2015) it is stated that "the increased skin pigmentation in participants who received afamelanotide partially unblinded the trial"

(page 53). Please can you provide more information on this statement including which of the two trials this occurred in, how many patients it refers to, at what point in time unblinding occurred, and what impact this is considered to have on the study outcomes?

This issue was addressed by CHMP in the EPAR:

> The tanning effect of afamelanotide probably led to in factual unblinding in many patients (although no practical way of blinding has yet been described). The expert panel, and particularly the patients, acknowledged that study subjects will likely have had the knowledge of the treatment assignment due to the tanning effect of afamelanotide on their skin but did not consider it measurable on the perceived effect. This is because beta carotene that was evaluated in EPP patients and causes tanning has no treatment effect and therefore do not translate in a change in the EPP patient's behaviour.

Since CLINUVEL has never assisted or ghost written a scientific publication, we often are the recipient of the information. [redacted]

A9.

How many UK patients were enrolled in the clinical trials? Studies CUV017, CUV029 are reported to have included European centres, and we note from the journal publication of CUV029 that some UK centres were involved (Newport, Manchester, Oxford).

	CUV017	*CUV029*
Newport [redacted]	*N/A*	*12*
Manchester [redacted]	*3*	*4*

[redacted]

A10.

Please provide a reference for, and a description of, the 11-point Likert scale that was used to score pain. What was the justification for a score threshold of 4 or higher for a phototoxic reaction (reported in CS page 33)?

[redacted]

A11.

Please provide a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) style flowchart reporting the number of published and unpublished studies included and excluded at each stage of the review, as per section 9.2.2 and 9.2.4 of the submission template.

Per the original submission, CLINUVEL is the only company to have conducted clinical trials of afamelanotide in EPP, and is aware of all published and unpublished studies. The burden of this administrative request is disproportionate to any potential benefit which may be derived from them; the company's methodology was very clear in the submission.

A12.

On page 23 of the submission under section 9.3.1 it is stated that 18 peer reviewed journal articles were identified. However, citations to articles in the subsequent paragraphs do not sum to 18. Please provide a full reference list for these 18 articles, stating the reasons for excluding any of the articles from the submission.

Eighteen articles were identified in the literature search:

1. Balwani M, Bloomer J, Desnick R; Porphyrias Consortium of the NIH-Sponsored Rare Diseases Clinical Research Network. Erythropoietic Protoporphyria, Autosomal Recessive. 2012 Sep 27 [updated 2017 Sep 7]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N,

Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from http://www.ncbi.nlm.nih.gov/books/NBK100826/ PubMed PMID: 23016163.
2. Biolcati G, Marchesini E, Sorge F, Barbieri L, Schneider-Yin X, Minder EI. Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol. 2015 Jun;172(6):1601-12. doi: 10.1111/bjd.13598. Epub 2015 Apr 30. PubMed PMID: 25494545.
3. Böhm M, Luger TA. [Alpha-melanocyte-stimulating hormone. From bench to bedside]. Hautarzt. 2010 Jun;61(6):497-504. doi: 10.1007/s00105-009-1891-1. Review. German. PubMed PMID: 20512306.
4. Fabrikant J, Touloei K, Brown SM. A review and update on melanocyte stimulating hormone therapy: afamelanotide. J Drugs Dermatol. 2013 Jul 1;12(7):775-9. Review. PubMed PMID: 23884489.
5. Harms J, Lautenschlager S, Minder CE, Minder EI. An alpha-melanocyte-stimulating hormone analogue in erythropoietic protoporphyria. N Engl J Med. 2009 Jan 15;360(3):306-7. doi: 10.1056/NEJMc0805682. PubMed PMID: 19144952.
6. Harms JH, Lautenschlager S, Minder CE, Minder EI. Mitigating photosensitivity of erythropoietic protoporphyria patients by an agonistic analog of alpha-melanocyte stimulating hormone. Photochem Photobiol. 2009 Nov-Dec;85(6):1434-9. doi: 10.1111/j.1751-1097.2009.00595.x. PubMed PMID: 19656325.
7. Kim ES, Garnock-Jones KP. Afamelanotide: A Review in Erythropoietic Protoporphyria. Am J Clin Dermatol. 2016 Apr;17(2):179-85. doi: 10.1007/s40257-016-0184-6. Review. PubMed PMID: 26979527.
8. Lane AM, McKay JT, Bonkovsky HL. Advances in the management of erythropoietic protoporphyria - role of afamelanotide. Appl Clin Genet. 2016 Dec 12;9:179-189. doi: 10.2147/TACG.S122030. eCollection 2016. Review. PubMed PMID: 28003770; PubMed Central PMCID: PMC5161401.
9. Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell DM, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips JD, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ. Afamelanotide for Erythropoietic Protoporphyria. N Engl J Med. 2015 Jul 2;373(1):48-59. doi: 10.1056/NEJMoa1411481. PubMed PMID: 26132941; PubMed Central PMCID: PMC4780255.
10. Lengweiler S, Kreim S, Barman-Aksözen J, Maurer M, Minder EI. Evaluation of the immunogenicity of the synthetic α-melanocyte-stimulating hormone (α-MSH) analogue afamelanotide ([Nle4-D-Phe7]-α-MSH, Scenesse®) in erythropoietic protoporphyria patients by ELISA detecting both anti-afamelanotide and anti-α-MSH antibodies. Skin Pharmacol Physiol. 2015;28(2):103-13. doi: 10.1159/000362174. Epub 2014 Nov 13. PubMed PMID: 25402764.
11. Luger TA, Böhm M. An α-MSH analog in erythropoietic protoporphyria. J Invest Dermatol. 2015 Apr;135(4):929-931. doi: 10.1038/jid.2015.16. PubMed PMID: 25785940.
12. Mazza JM, Zippin JH. Alpha-melanocyte stimulating hormone analogues: the perils and the promise. J Drugs Dermatol. 2009 Aug;8(8):772-6. Review. PubMed PMID: 19663117.
13. Minder EI, Barman-Aksoezen J, Schneider-Yin X. Pharmacokinetics and Pharmacodynamics of Afamelanotide and its Clinical Use in Treating Dermatologic Disorders. Clin Pharmacokinet. 2017 Aug;56(8):815-823. doi: 10.1007/s40262-016-0501-5. Review. PubMed PMID: 28063031.
14. Minder EI, Schneider-Yin X. Afamelanotide (CUV1647) in dermal phototoxicity of erythropoietic protoporphyria. Expert Rev Clin Pharmacol. 2015 Jan;8(1):43-53. doi: 10.1586/17512433.2014.956089. Epub 2014 Dec 3. Review. PubMed PMID: 25470471.
15. Minder EI, Schneider-Yin X, Minder CE. Patient-recorded outcome to assess therapeutic efficacy in protoporphyria-induced dermal phototoxicity: a proposal. Health Qual Life Outcomes. 2010 Jun 21;8:60. doi: 10.1186/1477-7525-8-60. PubMed PMID: 20565969; PubMed Central PMCID: PMC2905349.
16. Minder EI. Afamelanotide, an agonistic analog of α-melanocyte-stimulating hormone, in dermal phototoxicity of erythropoietic protoporphyria. Expert Opin Investig Drugs. 2010 Dec;19(12):1591-602. doi: 10.1517/13543784.2010.535515. Epub 2010 Nov 13. Review. PubMed PMID: 21073357.
17. Spichty R, Balimann M, Barman J, Minder EI. A bioassay for the detection of neutralizing antibodies against the α-melanocyte stimulating hormone analog afamelanotide in patients with erythropoietic protoporphyria. J Pharm Biomed Anal. 2013 Mar 5;75:192-8. doi: 10.1016/j.jpba.2012.11.040. Epub 2012 Dec 5.PubMed PMID: 23277150.

18. Urbanski U, Frank J, Neumann NJ. [Erythropoietic protoporphyria : Clinical manifestations, diagnosis and new therapeutic possibilities]. Hautarzt. 2016 Mar;67(3):211-5. doi: 10.1007/s00105-015-3733-7. Review. German. PubMed PMID:26669872.

A13.

[redacted]

A14.

Please can you clarify whether there are any data available on the impact on the quality of life of carers and family members.

The company is not aware of any published data on the impact of EPP on the quality of life of carers or family members. Significant anecdotal evidence exists from the patient population as to the impact of EPP upon patients' families. The ERG is encouraged to review the transcripts of the FDA's Scientific Workshop, available online (https://www.fda.gov/downloads/Drugs/NewsEvents/UCM530480.pdf) and appended to this submission.

B5. Priority Question

Please provide information on the number of implants used in the UK centres in study CUV029: number and % of participants using 0, 1, 2, 3, 4 & 5 implants.

[redacted]

B6.

Please state how the estimated prevalence of 513 EPP patients in England was calculated (as reported on CS page 16 and page 91).

[redacted]

NICE is encouraged to review correspondence from CLINUVEL to NICE on 23 December 2016 outlining the methodology used.

B7.

Please provide detail on the training that is required for UK expert centres prior to the use of the product (CS page 20, section 8.8), in terms of duration and frequency of training last; who were the training recipients; and estimated costs of training.

Appendix 2 – CIC review

The confidentiality checklist states that there is confidential information on pages 57 and 58, but there are no data highlighted in the submission on these pages. Please update the checklist.

[redacted]

1) Page 31 + 32. The number of people who withdrew consent in CUV029 and discontinued early has been reported in Langendonk 2015 [redacted]
2) Page 32. The hours of direct sunlight exposure per subject on days with no pain 10:00 to 15:00 has been published (table 2 Langendonk 2015)
3) Page 33. The number of phototoxic episodes per subject has been published (table 2 Langendonk 2015)
4) Page 37. Discontinuation and reasons for discontinuation in CUV 039 have been published in the EMA Assessment Report and Langendonk 2015)
5) Pages 65 and 85. The average age of the people in CUV029 and CUV039 has been published in Langendonk 2015

The above points are accepted and CIC highlighting has been removed.

6) Page 71. Please remove the confidentiality marking from the section entitled 'Quality of Life'. Holme et al is a published study and its conclusions are not confidential. The use of SF-36, DLQ1 and EPP-QoL in the afamelanotide clinical trial programme is in the public domain and the EPP-QoL questionnaire is described in the supplementary appendix to Langendonk 2015

The Company agrees that elements of this section are not CIC, [redacted]

Please consider the confidentiality marking of the description of the model on pages 64, 65, 66, 67, 77, 83 and 87; including:

[redacted]

It is unclear why these data are commercially sensitive and the restriction would make it impossible to transparently demonstrate that NICE methodology has been followed, which would mean recommendations could not be issued.

[redacted]

[redacted]

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation
The National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
Submitted via NICE docs

CC: Marie Manley, Bristows LLP

02 October 2017

Re: Afamelanotide for treating erythropoietic protoporphyria ID927

Dear Ms Upadhyaya,

Highly Specialised Technology evaluation of afamelanotide for treating erythropoietic protoporphyria (EPP) [ID927] – Outstanding clarification and confidentiality marking

Thank you for your correspondence of 27 September requesting responses to what you refer to as "the outstanding clarifications and confidentiality markings". We refer to our correspondence of 26 September and 12 September which explains very clearly the reasons behind the data that we have submitted to date.

CLINUVEL correspondence and the information supplied to NICE to date has consistently explained the lack of scientific tools and instruments available to quantify the impact of EPP on patients as well as the benefits of SCENESSE® for EPP patients. This is in line with the Committee for Medical Products for Human Use (CHMP) Opinion and the decision of the European Commission which granted marketing authorisation for SCENESSE® under 'exceptional circumstances'. This was on the basis of not just the clinical data submitted, but also the expert evidence and certain 'real world' data. This means that the clinical data in the European Public Assessment Report (EPAR) for SCENESSE® is, by its nature, limited. Clinical data for orphan and ultra-orphan products is usually limited due to the small population size. In the case of SCENESSE® not only is the population size small, but the data are further limited by this lack of scientific tools available to assess EPP and the benefits of SCENESSE®. The limitations to the data due to the population size and the lack of tools/instruments to quantify the impact of SCENESSE® **extend to the inability to arrive at a comparable pharmacoeconomic evaluation as sought by the ERG**.

Furthermore, we considered that the requests from ERG show that NICE is working beyond its mandate (acting in an *ultra vires* capacity) by refusing to accept the assessment of the CHMP and by imposing what appears to be a second scientific review of SCENESSE®. Whilst NICE's remit is to review the cost effectiveness of products, it is not mandated to re-open an efficacy assessment conducted by the CHMP.

Rather than engaging with the DALY model provided by CLINUVEL, ERG has previously stated its desire to build its own QALY model despite no existing validated tool for capturing, for instance, QoL in EPP, and despite the feedback from clinical and academic porphyria experts that the impact of the treatment with SCENESSE® upon patient QoL is significantly greater than that seen in the clinical trials. Attempting to conduct a QALY based analysis is not consistent with the opinion of clinical and academic porphyria experts and the

determination of the CHMP (following a two-and-a-half-year scientific review process) without justification and it results therefore in an irrational approach.

A number of the outstanding questions posed on 26 September have already been addressed by CLINUVEL in the responses to previous questions from ERG. However, for the sake of completeness we have re-stated these explanations in relation to the questions in Appendix 1.

We will again be raising the above concerns with senior members of NICE since they relate to policy issues which extend beyond the ERG.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

Appendix 1

1. **Early clarification letter sent from NICE 1st September 2017**

Priority Question: Please provide sample sizes and state the source of data for the average number of implants per year in Table D5 (CS page 76). The table merely states the source as 'CLINUVEL data on file', and the model specifies 'EMA'. Which studies did these data come from?

[redacted]

2. **Clarification letter with additional questions to early clarification sent on 11th September 2017**

A1. **Priority Question:** Please provide critical appraisal for trials CUV017 and CUV010 (CS Table C7). Please provide full critical appraisal of the observational study reported by Bialcati et al (2015a, 2015b) (CS Table C8 contains almost no information).

Per section 9.5.1 of the CS:

> CUV010 (Harms et al. 2009) and the two observational studies (Biolcati et al 2015a, Langendonk, 2017) listed in Table C6 did not involve randomisation of trial subjects since the data were generated under conditions of use. The cross-over design of CUV017 meant all patients received active and placebo implants during the study on a 1:1 ratio, rather than involving a 'control' group.

Trial CUV010 was an open label study. Trial CUV017 was not a traditional RCT but involved a cross over design where subjects took both active and placebo treatments during the study. Hence it is <u>not</u> appropriate to conduct a critical appraisal of either of these studies within this section of the CS.

Regarding Biolcati et al (2015), [redacted] *Biolcati et al (2015) reports clinical experience in special access schemes in an ultra-orphan indication and did not follow RCT standards applicable to the needs of table C8 hence a critical appraisal of this data is not considered appropriate.*

A2. *Further to question A9 in the early clarification questions sent by NICE on 1st September 2017*, did increased skin pigmentation also lead to unblinding in CUV030?

The response provided to question A9 from 1 September 2017 is applicable to the entire clinical trial programme. This issue was addressed by CHMP in the EPAR:

> The tanning [melanogenic skin darkening] effect of afamelanotide probably led to in factual unblinding in many patients (although no practical way of blinding has yet been described). The expert panel, and particularly the patients, acknowledged that study subjects will likely have had the knowledge of the treatment assignment due to the tanning effect of afamelanotide on their skin but did not consider it measurable on the perceived effect. This is because beta carotene that was evaluated in EPP patients and causes tanning has no treatment effect and therefore do not translate in a change in the EPP patient's behaviour.

A3. *Further to question A11 in the early clarification questions sent by NICE on 1st September 2017*, please provide a reference for, and a description of, the 11-point Likert scale that was used to score pain. Trials CUV029 and CUV039 defined mild pain as a Likert score of 1-3 but trial CUV030 defined mild pain as a Likert score of 1-4 (CS Table C5). What was the justification for a score threshold of 4 (or 5) or higher for a phototoxic reaction and why did the threshold differ between the trials?

[redacted]

A4. Please clarify the scoring system for the EPP-Qol instrument. [redacted] Please can you clarify this discrepancy in the direction of scoring of worst-best and confirm which is correct. Please can you also clarify which version of the EPP-Qol it refers to. We are aware of three different versions:

1. 18 item version as reported by Biolcati et al 2015. Scored from 0 to 54, lower scores signify worse quality of life. No minus scores possible. (Biolcati G, Marchesini E, Sorge F, et al. Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol 2015a;172(6):1601-12).
2. 15 item version included in the protocol for study CUV039. Scored from -10 to + 35. Lower scores signify better quality of life. (Protocol for: Langendonk JG, Balwani M, Anderson KE, et al. Afamelanotide for erythropoietic protoporphyria. N Engl J Med 2015;373:48-59. DOI: 10.1056/NEJMoa1411481).
3. 12 item version presented in Table S1 in the supplemental appendix to Langendonk (2015). Scored between 0 and 36, with lower scores signifying worse quality of life. (Langendonk JG, Balwani M, Anderson KE, et al. Afamelanotide for erythropoietic protoporphyria. N Engl J Med 2015;373:48-59. DOI: 10.1056/NEJMoa1411481.

[redacted]

Per section 12.2.5 of the CS:

> Quality of Life
> Since publications report a reduced quality of life for EPP patients (Holme et al., 2006), the inclusion of quality of life measurements was considered important to assess the impact of afamelanotide on the lives of these patients. CLINUVEL used three different quality of life assessment tools, SF-36, Dermatology Life Quality Index (DLQI) and a purpose developed EPP-specific quality of life questionnaire (EPP-QoL). Earlier studies (CUV010 and CUV017) used the SF-36 questionnaire. This tool did not prove to be useful for the assessment because most patients reported a very high quality of life from baseline assessments onwards. This finding was contrary to the published literature and demonstrated that a questionnaire more specific to EPP was required. [redacted] 15-question assessment tool referred to in this application as the EPP-QoL. This questionnaire and the DLQI were used in the CUV029, CUV030 and CUV039 studies. Following the CUV029 and CUV030 studies, the EPP-QoL underwent validation work. [redacted]

A5. Please can you provide full baseline data for all patients in the RCTs if not provided the clinical study reports, including % skin type, age, race in the study.

Baseline demographics for CUV029 and CUV039 are provided in Langendonk et al (2015) However, there is no evidence that gender, age, skin type or the concept of race have any impact upon the safety or efficacy of SCENESSE®.

A6. If not already included in the clinical study reports please provide CONSORT flowcharts for all included RCTs, showing the numbers of patients involved at all stages of the study, including withdrawals and reasons for withdrawal (as required in section 9.4.5 of the HST company submission template).

Enrolment and withdrawal data for all trials are provided in Table C5, but to produce the flowcharts requested will involve a significant burden and will not add any value to the data that has already been provided given that the study population is so small and the numbers of withdrawals and reasons for withdrawal have already been provided. (We would note that CONSORT flowcharts are primarily for use in larger trials where understanding a pattern of withdrawals may be complex.)

A7. It is stated that sunlight exposure recorded in patient diaries in trial CUV017 was "verified by the investigators" (CS page 29). Please explain what this means.

[redacted]

A8. Please report whether the selection criteria for clinical evidence were applied to the results of the literature search from all sources (i.e. titles and abstracts, and full texts) by a single reviewer, or whether it was done independently by two reviewers. Likewise, please confirm if data extraction from clinical evidence study reports and critical appraisal of study methodology was done by a single reviewer, or by more than one reviewer?

[redacted]*Due to the limited number of clinical trials conducted in EPP, all of which were sponsored by CLINUVEL, and the controlled distribution of the product, the Company is aware of all published clinical work to date.*
The clinical sections of the CS were written by a single author and reviewed by two others.

3. **Confidentiality marking**

Clinical and quality of life data marked as confidential is anticipated to prevent the transparency of evidential base for the recommendations
Please reconsider the confidentiality marking of clinical and quality of life data marked as confidential in your submission. It is unclear why these data are commercially sensitive and NICE are concerned that the restriction would make it impossible to show the evidential base for the benefits of afamelanotide in our guidance.

The results of the cost effectiveness modelling are marked as confidential and will not allow transparency of the committee's consideration of cost effectiveness of afamelanotide.

Data that are likely to be fundamental to the Evaluation Committee's decision making cannot be marked as confidential (see Guide to the processes of Technology Appraisal section 3.1.24). This includes the list price of afamelanotide and the incremental cost effectiveness ratio.

1. We note that the list price of afamelanotide has been marked confidential in the company submission. With the exception of the draft scope, NICE will not make public, or circulate among consultees and commentators any documents for consultation or guidance on a technology until UK regulatory approval has been granted and the technology's price is publicly available. Please remove the confidentiality marking on the list price.
2. Please remove the confidentiality marking of all ICERs presented in the submission (including cost per DALY avoided).
3. Please remove the confidentiality marking of the incremental costs and incremental DALYs in your submission. NICE do not consider that releasing these data will allow a back calculation of commercially sensitive data. If you consider a back calculation is possible please show the steps by which this could be done.

The Company accepts NICE's comments on confidentiality. A revised version of the Appendix D and Appendix E documents will be provided by close of business on 06 October 2017.

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Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name:
[redacted]

Name of your organisation:
The British Porphyria Association (BPA)

Brief de*scrip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

The BPA is a national charity that supports people with all types of porphyria. BPA funds derive predominantly from membership subscriptions, donations and fundraising efforts. The BPA currently has 495 UK members. Just over 100 of those members have EPP – 90 of these live in England. It is believed that we have around 25% of UK EPP patients on our database.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- √ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc). Vice chairman and helpline administrator (part time employed 26hrs per month)
- other? (please specify)

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

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How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Years of Suffering before Diagnosis

The median diagnosis age has been reported to be 22 years, although for most the conditions exists from birth or soon after. EPP diagnosis is often delayed due to the complicated nature of the condition. The main challenge in diagnosing EPP is that for some people skin symptoms are not visible, despite severe and unrelenting pain following exposure to visible light. Public awareness of the condition is extremely low - approaching zero apart from people who are extremely close to those who have actually achieved a successful diagnosis. Detailed awareness and understanding of EPP in general medical practice is also low. Patients are therefore highly reliant on successful referral to one of a few specialist centres in the UK. It is therefore not surprising that many patients live through many years of suffering, isolation and severe pain before they are diagnosed.

Whilst there are a number of symptoms that present to varying degrees, the main threads amongst all EPP patients are:

- **Severe pain on exposure to light.**
- **Extreme tiredness as a result of the EPP reaction.**

Pain…Real Pain

The onset of this pain is often rapid, even exponential. On a scale of 1-10 some patients report the time taken for pain to develop, from 1-2 right up to unbearable 8-9 even 10, as less than 5 minutes in the light. Even on total retreat from light into a darkened room, it can take days, in some cases weeks for body and skin to return to the point where light can once again be tolerated.

The intense burning may be accompanied by a swelling to areas of skin that have been exposed to light and an 'itching' sensation. Wheals, redness and oedema may appear. When exposed to sunlight for a prolonged time, second-degree burns may occur in the vessels causing blood to leak into the skin. EPP reactions make normal activity completely unmanageable. Moreover, once a reaction has been suffered, painkillers – even in industrial doses – are not effective against the severe, specific and unrelenting pain caused by the nerve and tissue damage from exposure.

"*The skin which has been affected during an attack cannot be touched by even a sheet, as that feels like a knife on your body – even opiates are ineffective for the pain."*

The pain is accurately described by American Savannah Folkerson as like *"lava being poured [over skin]… burning from the inside out…"*.

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We do not have any video footage of patients during times they are suffering, such as the extreme pain in the distressing footage in the ABC newsreel portraying Savannah's story. However, the hardest stories we have heard are the stories of parents or spouses sitting outside a bedroom unable to provide comfort or consolation for a loved one in pain for days on end. **Once an EPP episode starts, there is nothing anybody can do to ease the pain even amongst adult sufferers**. Even the heat of another person's body is too painful to endure any physical contact. The whole family senses the pain.

All Encompassing Tiredness

Another key factor that is common to all EPP sufferers is the all encompassing extreme tiredness that comes with having a body (more specifically a blood supply) that is constantly trying to heal from the damage the EPP reaction causes in the haem formation process.

"I just can't carry on sometimes, I ache, my head hurts, my stomach is upset ... all a side effect of a reaction!"

"*EPP reactions just lay me flat. When I'm not suffering an EPP reaction I'm a very energetic person. But when the EPP hits I'm absolutely useless to myself, my employers and everyone around me. All I can do is retreat to bed and wait for my body to repair itself. This can take days. Until then every little thing is a huge effort. The frustration with not being able to function is intense. I become grumpy, unsociable and hit out at even the simplest request. Were my family not so understanding I'd be living a very lonely life by now!"*

In addition to the severe pain, it is this extreme tiredness that is a key factor in disrupting patients' lives. It inhibits or impinges on work, causes friction in the home, prevents even simple household tasks from being carried out without great difficulty, and combined with the pain, makes social activity impossible for periods of many days at a time. Career options become limited, capacity to share household chores is severely diminished; the capacity to engage for self or home improvement disappears until the EPP reaction has fully disappeared.

The frustration and inability to carry out even simple tasks, participate in normal activity and meet commitments associated with work is that EPP reactions in turn induce significant stress-related complications. We fear that these are not well documented, but as a national patient body we are very aware that our EPP patients suffer them.

Diagnosis…but no Cure

For many conditions diagnosis can open the door to a cure. This is not the case for EPP. Worse still, in the UK, t**here are no specific pharmacological treatments for EPP**, **and our members have reported little success with any of the current regimes for attempting to improve quality of life.** Accessing the therapies presently used on EPP patients generally involves referral to one of the UK's few specialist centres. Even when home location and work/education makes access possible, the therapies on offer have not been specifically tested for their efficacy against EPP. None of the current therapies cure or even prevent EPP reactions.

This sparsity of specialist care, extremely low incidence of the condition and low level of awareness and understanding frequently results in individuals disengaging from clinical support after attempts at treatment using present regimes have delivered little benefit, and in many cases before diagnosis. Formal links between clinical teams and those offering psychological support are only now in their infancy and often rely on being in the right place at the right time, or in the worst cases years of personal struggle before support can be accessed. **Patients suffer in silence, the true impact of EPP on their life and quality of life remaining hidden.**

Delayed diagnosis can mean that patients are incorrectly assumed to have allergies, or are simply thought to be overly dramatic. Patients are often left alone with their burning and painful skin and suffer isolation and incomprehension from those in their immediate surroundings, e.g. family, work, or when seeking help from medical professionals.

A Life In The Shadows - Impact on Patients

EPP severely affects quality of life for patients and often compromises quality of life for families and carers too. Patients have no control over prevailing outside light conditions on any given day. The impact of a phototoxic reaction is severe and takes days, even weeks to recover from.

A patient's daily life is primarily driven by the need to remain safe and secure from the light that triggers the phototoxic reactions. This is true for all degrees of severity. Although the physical effects of the condition are well documented, the study and treatment of its psychological effects remains in its infancy. **Even patients amongst the least severely affected have reported suicidal feelings during the periods they are suffering a reaction.**

The impact of these physical effects and the life limiting nature of EPP starts in the pram and builds from there. Children are not able to attend school or play normally resulting in bullying, social isolation and life impairing psychological damage and interpersonal difficulties. These problems continue into adulthood, limiting career choices, impairing and preventing relationships and much more.

"I would hide my pain from friends or even family which adds another layer of suffering. I have been in severe situations as a child where I have had such an extreme burning sensation on the backs of my hands that the only option to give even a slight instant relief is to lick the backs of my hands."

"I am forced to isolate myself from friendships groups and lack the shared experiences and bonding with them. I often feel down, low and frustrated due to the limitations of my condition."

Study opportunities, job security and career development are negatively affected by days lost to EPP symptoms, which has a subsequent effect on career progression, earnings potential and lifetime earnings.

Compensating for the effects of and preventing phototoxic reactions adds significantly to the costs of carrying out normal daily life. Restricted options and preventative measures required to take part in other normal activities often adds

hundreds, if not thousands of pounds sterling to the cost of living for both patients and their families. Lifetime costs can easily extend into hundreds of thousands of pounds.

Avoiding Phototoxic Reactions - A Family Life Compromised

With regard to family, there is a time and earnings burden that arises through caring for people with EPP. In some cases, a parent suffering from EPP places the burden of responsibility on their children. This can have an impact on the social, educational and career potential for children and other family members.

EPP has also been known to be the cause of relationship breakdowns. Even where partners stay together, family tensions often run high as a result of the direct and indirect impact of phototoxic reactions with detrimental effects on family life.

Children of EPP parents are often unable to take part in events due to being unable to have parental supervision – even when simply playing outside. This can impact on their physical well-being. Furthermore, family members can also experience psychological isolation due to being unable to take part in events, even though they don't have the condition.

Family experiences are limited or undertaken without the EPP patient. When important life experiences are not shared, subtle disconnects emerge. Life paths diverge. Families become separated where children choose to live in locations that preclude travel or light conditions would inevitably cause a phototoxic reaction.

The Importance of an Effective Treatment

The current lack of a viable treatment and cure means EPP patients frequently suffer in silence. These people physically live in the shadows and move around by stepping between shadows. This situation cannot and should not be allowed to continue.

None of the aspects of living with this condition are met with any success by the treatment options currently available – this has a significant and sustained impact on patients, their families and their carers. There is currently no immediate or joined up service to deal with this impact.

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

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EPP affects patients both physically, economically, mentally and socially – with profound effects on quality of life. As a result of the debilitating pain and tiredness, work, travel or schooling can become almost impossible. It also impacts on social and family life, where establishing and maintaining relationships can be extremely difficult, leading to isolation and depression. **EPP's capacity to isolate patients from normal family life also means that patients miss out on even the simplest of pleasures in life.** The simple joy of living in the moment with one's children, family and friends whilst sitting in the garden, playing in the park and paddling in the sea without a painful and exhausting reaction, or at least the fear of one, is unknown to most EPP sufferers. F**ear of failure is a common thread that inhibits many of our EPP members in their approach to life.** As an engrained behaviour this in turn affects education and employment prospects.

Patients suffer stress and anxiety associated with the expectation of pain from EPP symptoms. They become frustrated due to being unable to participate in 'normal' day-to-day life. Day-to-day tasks that most would take for granted, e.g. doing the school run, shopping, carrying out household chores, such as hanging out the washing or emptying bins, gardening, house maintenance, attending school/extra-curricular events, or caring for and spending time with children or family members are not possible without constantly battling the risks of a phototoxic reaction. This can lead to a fragile psychological state and poor emotional well-being due to the isolation and restrictions that their condition forces upon them.

One EPP patient reported, *"I have no freedom, I am ruled by the light! I cannot plan ahead, I cannot just go for a walk or mow my lawn. I cannot pop to the shop, or take my kids to the park! I have to assess how I feel on that day, can I cope with the light? Is it going to get sunnier? What is the UV rating? So .. life becomes a muddled ball of anxiousness!"*

Physical and mental health can be affected due to the lack of opportunity to participate in sport and exercise.

For those so severely affected that even office lights are problematic, it is sometimes impossible to succeed in any kind of meaningful employment. Travel to a place of work or study can be unmanageable. These patients tend to face economic dependence on the welfare state, along with the psychological burden that state dependence brings.

Adapting to a life of Compromise

As stated above (1i) a core focus of life with EPP is the acute sense of prevailing light conditions that people who have EPP develop. It is often described as a sixth sense. The reason for the development of this 6th sense should not be underestimated. From discussions with our EPP members and EPP patients from other countries, a core theme has emerged - the need to stay safe from phototoxic reaction.

Every aspect of day-to-day life, no matter where a patient sits on the spectrum of sensitivity, is driven by an innate need to avoid pain that results from reactions. Adaptations reported by our members include:

- Limiting education and career choices so as to avoid time outdoors or even travel to a place of education/work.
- Being forced to enlist help for school runs, shopping and normal everyday activities that 'just need doing'.
- Only daring to venture out of doors after dusk.
- Only engaging in employment that is totally indoors, even just night work so that travel to work is not during daylight hours.
- Limiting employment and/or home address choice to minimise the chance of reactions during commutes.
  "I have some pretty extreme coping behaviours: When I need to drive to a meeting, I will plan the journey days ahead. If I can't drive during the evening and stay overnight, I sit down with my maps and work out what angles the sun will hit the driving position in the car during what hour, by planning each stretch of road, relative to the sun direction. I wear leather gloves and a lightproof buff covering the bottom of my face as well. My worst fear is that the car will break down, the air-con cut out - or both. On one occasion, it did and I was trapped in the car in the sun, it was all I could do to stay in the car and not run across the motorway to where I could see there was shade. I worry that my behaviour becomes really quite extreme once the pain starts."
- Adapting housing and vehicles with filters over glass. Or even living behind closed curtains.
- Limiting exercise due to being unable to find a safe exercise to take part in: *"Lights in a gym* [cause a reaction] *and running is not safe in the dark ….A swimming pool normally has bright lights that are then reflected from the water! Or they tend to put in huge windows! Also, from March to October, that low level pain that is constantly there prevents you from having the energy and it can hurt as you try and dry yourself with a towel or touch a machine button in the gym.*
- Limiting what clothing they own. "*I cannot wear what I want to! This leads to issues with not feeling at your best! It is tough to wear layers in the heat when you are burning already!"*
- Not attending social events such as indoor rock concerts where stage lights may induce phototoxic reactions. Summer festivals which are a source of freedom, release and inspiration for many are pretty much a no-go zone for EPP patients.
- Being unable to hug a child or hold their hand when sore from a reaction. *"That is hard for a child who just needs comforting, they do not always understand, this make it hard for us as sufferers too!"*

In a survey carried out by an EPP patient organisation in the Netherlands:

- 91% percent of patients changed careers because of EPP
- 40% percent of patients reported losing a job because of EPP
- 46% percent of patients took several [multiple consecutive] sick-days after an EPP-attack in the last 5 years
- 35% percent of patients can only work with adjustments

Although we are not aware of a similar study in the UK, engagement with our members suggests these figures are likely indicative for the UK too.

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What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Afamelanotide is a ground-breaking treatment that presently has no major negative side effects.

Fewer, less intense reactions...

This new medicine is, at the moment, the **only** effective treatment available to extend the time skin can be exposed to light before a reaction is experienced and to reduce the severity of the reaction. In addition, patients report that if pain develops, it subsides more rapidly – instead of several days in pain, the symptoms are resolved the next day. Patients under treatment change their behaviour towards a more normal lifestyle and over the time lose their deep-rooted fear of light learned in early childhood.

The treatment significantly prolongs the time patients can spend participating in activities most people take for granted, including work, travel, school and events, or simply playing outside with their children. In an eight-year long-term follow up study including 115 patients, far-reaching and significant impacts on overall quality of life for patients were shown.[1] The same effect can be expected for families and their carers, with family, work, social, emotional and physical impacts.

When pain and exhaustion are so intense, all gains are significant

Even a relatively small increase in the time that light exposure can be tolerated makes a significant difference to those presently most compromised. For those at the less sensitive end of the spectrum reports from Italy, Switzerland and the Netherlands show Afamelanotide to be a complete life changer, effectively eliminating the impact of light exposure on working day life and opening up all but the most exposed of activities to EPP patients.

EPP patients live a life of fear stemming from the intense and uncontrollable pain associated with EPP reactions. Any treatment that extends the length of time a patient can be exposed to light not only reduces, but can eliminate, these regular periods of intense pain. It will also reduce the fear and anxiety in which EPP sufferers live their entire lives.

In the UK, we have only limited evidence of the advantages of the proposed treatment. One of the reasons we feel UK data in this area is possibly significantly understated is the sub-optimal timing of the UK trials and the relatively small number of patients engaged. Despite this, stories from our members who were involved in the trials suggest that the reduction in severity of attacks and reduction in recovery times

[1] Biolcati, G., Marchesini, S. Sorge, F., Barbieri, L., Schneider-Yin, X., and Minder, EI., Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria, *Photobiology*. (30 April 2015).

will greatly reduce and even eliminate some of the factors that presently impinge on quality of life.

We are able to draw on the experiences of EPP patients in other European countries where Scenesse has been used, who report:

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

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

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

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

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

"Both my sister and I were in the Phase III trial for this drug and my sister received the 'real thing' and it positively changed her life during those six months…she was finally able to participate"

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

Afamelanotide is the only clinically tested treatment showing efficacy in increasing tolerance to light and even preventing acutely painful reactions of EPP. In doing so, the debilitating and all-encompassing tiredness are greatly reduced too. **By improving the state of the two most debilitating effects of EPP within only a very short time after administration it has the capacity to reduce the profound**

impacts on quality of life outlined in section 1 above. The information presently available to us indicates that patients who benefit in the short-term sustain those improvements into the long term.

Normal may become possible

Studies, and informal reports from patients with experience of the treatment, report a greatly increased tolerance to light (*please see the patient case studies at the end of the document*), giving them the ability to participate in activities which have, until now, been unavailable to them. Some will retain a conditioned aversion to bright sunlight, but this should decrease over time. Afamelanotide prolongs the time patients can spend participating in activities most people take for granted; they are able to experience social activity outdoors, revise their career expectations and, most importantly, join in a normal family life.

Comments from leading medical specialists in EPP at the recent International Conference on Porphyrins and Porphyrias (ICPP2017) in Bordeaux (not Clinuvel employees) indicate that the magnitude of the measurable improvements may increase in the long-term.

With reduced or even eliminated EPP reactions, the extreme tiredness associated with phototoxic episodes can be relieved. The subsequent beneficial effects on mood, relationships and ability to function day to day cannot be underestimated.

Amongst the most profound effects are lifting of some of the limitations that EPP places on career choice, progression and earnings potential. This economic impact will result from greater freedom to participate in everyday life and reductions of psychological impact and social stigmatisation.

Becoming a more functioning part of the family

A consistent and emotive story has been built up over the years of families who have sacrificed normal lives to cope with one of their number being unable to tolerate normal daylight.

With the new treatment, children of EPP parents may be able to take part in normal childhood activities, as they could be supervised in the light. Or families that have been effectively feeling like one-parent families due to the inability of an EPP parent to fulfil normal parenting responsibilities, may be able to re-balance the roles. This new medicine would allow them, perhaps, to plan holidays away from home and together as a family.

"My daughter has not become light sensitive but my son, now 15, became light sensitive at the age of 8 … A family of three with two light sensitive members means that my daughter has had limitations imposed on her, with her taking on a 'carers' role for both of us. We have had to rely on friends to help her have some form of normality. She has not had a holiday with her brother for five years."

"Luckily after 40 years I found a highly tolerant and understanding partner … When she and my children head off for beach days out and holidays abroad I stay at home, missing out on some of the most enjoyable times associated with family life and my

children growing up. Scenesse's capacity to reduce EPP reactions should change all this. I'll be able to enjoy so many more of those special moments."

They are able to accept invitations to join friends for social events. For the first time, EPP patients will be able to support their children or siblings at school or sports events - or even join in with them.

A lifting of what are presently huge barriers in life

With some of the life and career limiting effects of EPP lifted, we anticipate there to be a significant benefit to family earnings. Further socio-economic benefit will arise from the reduced stress and time that family members input when caring for those who suffer from EPP.

- For those so severely affected that even office lights are problematic, this may be their only option to be able to find any kind of meaningful employment. For some who are particularly badly affected, travel to a place of work or study could become possible for the first time. The new treatment could enable these people to become economically independent and removed from dependence on the welfare state - along with removing the psychological burden that state dependence brings.
- Study opportunities, job security and career development would be positively affected simply by reducing days lost to EPP symptoms. It could significantly improve career progression and earnings potential.
- This treatment could lead to an improved psychological state and emotional well-being due to the ability to be involved with others and less isolated and lonely.
- The treatment could reduce stress and anxiety associated with the expectation of pain from EPP symptoms and frustration of not being able to participate in 'normal' day-to-day life, opening up opportunities such as school run, shopping or household chores, such as hanging out the washing or emptying bins, and attending school/extra-curricular events, caring for and spending time with children or family members without constantly battling the risks of a phototoxic reaction.
- Physical and mental health would be improved from increased opportunities to participate in sport and exercise.
- Significantly lower cost of living, where compensating for the effects of and preventing phototoxic reactions adds significantly to the costs of carrying out normal daily life.
- Patients with EPP are usually deficient in vitamin D due to lack of sunlight exposure. Increasing the time they can spend outdoors may have significant additional health benefits relating to vitamin D levels.
- The time and earnings burden of caring for people with EPP will be reduced, and shared roles at home could increase
- In some cases a parent suffering from EPP places a burden of responsibility on their children. Removal of this burden not only opens up opportunities for the patient, but social, educational and career potential for the child.
- Parents who live their lives without EPP, but carry the gene can be relieved of the guilt burden.
- EPP has been known to be the cause of relationship breakdowns. Even where partners stay together, family tensions often run high as a result of the direct and indirect impact of phototoxic reactions with a detrimental effects on family life. An

effective treatment has the potential to keep families together but also enhance the benefits of togetherness.

In short, any reduction in the extreme pain and tiredness experienced by EPP patients would have a huge impact on the emotional well-being of the entire family. We simply don't yet have a true baseline from which to measure the extent of these improvements in quality of life amongst EPP patients, where they have experienced and learned to accept these problems all their life.

3. Disadvantages
Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

We cannot envisage any real disadvantages of Afamelanotide. Presently, it does not appear to have any major negative side effects or safety concerns and the method and frequency of administration means that it would have a low impact on work and family life.

The implant is very small, likened to the size of a grain of rice and administration has been described by a patient as '*painless'.*

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

Whilst experiences for all patients are different and the level of benefit may be more accelerated for some people compared to others, we have not come across any patient who has taken Afamelanotide who did not report significant benefit.

Patients on the trials reported the treatment to be '*completely life-changing'*, noting that for the first time ever they were able to '*step out of the shadows'*. On cessation of trials, it was reported that *"off treatment I am socially isolated again*", while one person stated, "*I almost wish I had not seen what life was like with SCENESSE as now I feel like my life has been taken away from me again*".

Indeed, in European countries where the treatment is readily available to patients, it is notable that patients continue to receive Afamelanotide; this is in stark contrast to some other regimes aimed to improve quality of life – such as beta-carotene and phototherapy, where many patients stop after a short period of time due to the ineffectiveness.

In fact, some patients travel thousands of miles and pay privately to obtain Afamelanotide, so that they can enjoy a little of 'normal' life. Unfortunately, costs of

accessing private treatment are beyond the reach of most patients, especially when the costs of regular travel and accommodation outside the UK are considered.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Due to the nature of the condition, it can be unpredictable how little exposure will cause pain on a particular day. Those affected by EPP often learn to fear any light exposure at all. The people that may benefit most from the treatment are those that are able to gradually recondition themselves to exposure to light. This view is formed from gathering opinion from within our patient members and correlates with consensus themes that emerged from presentations and discussions at the recent (June 2017) medical conference International Conference on Porphyrins and Porphyrias (ICPP2017) - Bordeaux.

6. Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

There are no specific pharmacological treatments available in the UK for EPP, and our members have reported little, if any, measurable improvement in quality of life from any of the current regimes for attempting to improve quality of life, as noted in 1(i).

A summary of the practices presently available in the UK is outlined below, however, please note:

- **None of the following have been tested under strict clinical trials with EPP patients and any claim of efficacy is anecdotal.**
- **None have been proven to have significant or long-term quality of life benefits**, indeed patient testimonies confirm that they only serve to raise false hopes, leading to a significant negative psychological impact when they fail to deliver**.**
- **Afamelanotide is the only treatment which has shown clinical benefit under strictly regulated testing conditions.**

In the absence of any treatment that has been developed for EPP and proven to have clinical benefits our UK members have been offered a range of therapies. None of these therapies were developed and approved specifically for the treatment of EPP. It would appear that their application is simply to offer the chance of some benefit in a world formerly devoid of a treatment designed and tested specifically for EPP.

High doses of oral beta-carotene**:** a meta-study by E Minder (2009) demonstrated beta-carotene to have ***no benefit to EPP patients***. Most patients who trial this

treatment, stop taking it after a short period of time, endorsing the lack of benefit. Furthermore, high-dose beta-carotene comes with considerable safety concerns - a key ingredient of the pharmaceutical grade beta-carotene (standard over-the-counter products are not effective or safe), contains an ingredient which can cause a deposition of crystals in the retina, making long-term use inadvisable. In addition, recent studies of beta-carotene use in large cohorts of smokers showed an increased risk of lung cancer, at much lower doses than prescribed for EPP.

***UV phototherapy*:** has been used on some patients in an attempt to induce pigmentation and thicken the skin. It relies on the availability of specialist equipment and expert centres, to provide exposure to UV light for incrementally greater periods, three times a week for twenty sessions. However, no controlled trials exist, presumably because most patients are unable to tolerate UV light tubes used for other conditions as they also give wavelengths causing painful EPP skin reactions. Furthermore, long-term use of light therapy increases the risk of skin cancer. Even patients who use UV treatment complain that maintaining the schedule of appointments can place stress on work, and sustained treatment is often not practical due to the impact on earnings, career progression opportunities and family/carer commitments.

***Creams*:** EPP reactions result from light in the visible spectrum, meaning that conventional sunscreens are of no practical use. Indeed many commercial and prescription creams can actually exacerbate the problems of EPP - their effect being to weaken the skins natural defences to light, or to actually multiply the intensity of light. More than one of our patients has reported increased reaction when using a cream even when made available through a specialist centre. Needless to say they immediately discontinued its use.

'Dundee cream' - with a high Titanium Dioxide constituent - is moderately effective in some cases, but gives the user a very conspicuous and undesirable appearance when in use. Dundee cream can be ruinous to clothing and does not withstand physical exertion well. As with all topical creams it relies on correct application each time it is applied. Combined, these factors are even considered by many of our EPP patients to lower rather than improve quality of life.

"...when you already have to dress and act differently, putting on a thick, skin colour altering cream that doesn't fully prevent EPP reactions is the last thing you want. It ruins my clothes. Wear it to a job interview? Forget it. Wear it when out socially – especially as a 20 something already finding it difficult to fit in (because of EPP) and attract the opposite sex; you've got to be joking!"

There being no effective treatment, the options for managing the condition are effectively limited to light avoidance strategies, for example avoiding sunlight exposure by staying indoors (impractical on an everyday basis), seeking shade during sunny periods (which is usually insufficiently protective), or using sunlight blocking clothing including umbrellas, gloves and facemasks. However, such protective measures are hot, uncomfortable, awkward to maintain and outside of Western norms, where society often reacts with deprecating comments, leading patients into psychological distress and social isolation. In addition, artificial light

sources can cause harm as well, such measures are not feasible indoors. Again does this approach really improve overall quality of life?

Also important to note, none of the above regimes act to relieve the severe pain associated with phototoxic reactions or act to reduce the extreme tiredness that is experienced as a result of the phototoxic reactions.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Patient testimonies from those on the continent and elsewhere, who have been able to access Afamelanotide, portray life-transforming improvements in their ability to live with the condition, access employment and partake in 'normal' family life.

In addition to dramatically increasing the ability to tolerate light, those who have used the treatment see it as a platform via which they can access the outdoors. **The treatment's capacity to increase light tolerance amongst all levels of sensitivity is a hugely significant factor.** By increasing tolerance to light, EPP reactions are reduced both in number and severity. This in turn means EPP patients suffer much less pain. With fewer and less intense reactions comes less exhaustion meaning EPP patients can function more normally in the workplace and at home.

Administration via subcutaneous injection eliminates the need for patients to remember to take the treatment and offers high levels of control over dosage. Once administered there is no reliance on the patient to take the treatment until the next administration is due. Patients gain the benefit of a treatment, but without any disruption to daily life apart from on treatment administration days. This has the secondary benefit of potentially making studies that evaluate the most effective dosage more robust.

A low frequency of appointments for treatment administration/monitoring of Afamelanotide would have a low impact on family and work life.

Despite the EMA stipulation that the treatment is administered by specialist centres, the low frequency of administration would make travel for accessing the treatment practical for the vast majority of patients.

Although subcutaneous, the method of application is an uncomplicated outpatient procedure that we believe is accessible to all patients falling into the groups approved for the treatment by EMA.

We are not aware of any major side effects that have been attributed to Afamelanotide.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We are not aware of any significant side effects that have been attributed to Afamelanotide.

We are not aware of any instances where administering Afamelanotide has reduced the capacity to withstand exposure to light, or where quality of life has been worsened. **Critically, we are not aware of any instances where levels of pain from EPP have been increased as a result of the treatment.**

Whilst a subcutaneous implant is more invasive than taking tablets our members, and patients in other countries **have not** reported this to be a disadvantage of the treatment.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

Following presentations at the recent International Conference on Porphyrins and Porphyrias, we believe that the true quality of life impact of EPP and other porphyrias has yet to be fully established. Patients suffer EPP from very young and don't have a true concept of normal against which to assess its impact on their life. They have merely learned to adapt their lives and operate as best they can.

Afamelanotide makes increased exposure to light safer for EPP patients, and its full benefits are not revealed without some exposure. Even when treated with Afamelanotide, these life engrained behaviours take time to unlearn. Patients need time to gain confidence in exposing their skin to light. Like many porphyria clinicians, the BPA believe the complexity of the disease, the lack of instruments to quantify efficacy and lack of effective treatments to compare this new treatment with led to an understatement of quality of life benefits that patients derive from the treatment. There was insufficient opportunity for patients to overcome their anxiety relating to

phototoxic reactions. Therefore, the true and full impact of the drug will only be observed as life engrained behaviours are gradually changed.

Furthermore, the increased amount of time that patients treated with Afamelanotide were able to spend in sunlight in clinical studies may equate to an even larger amount of time spent outdoors in the shade which also has a significant benefit to patients with EPP.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

We are not aware of any additional adverse effects that are attributable to the treatment.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Less pain, less exhaustion... the intense need to stay safe diminishes... life opens up

One of the key differences we anticipate is that the treatment would open up freedoms never before experienced by sufferers of EPP. Principally **a relaxation of the need to remain safe from light exposure** that triggers painful phototoxic reactions and induces long spells of extreme tiredness that cause great difficulties in the workplace and home life.

Already outlined above, the impact of this one core difference would include, but not be limited to:

- Improved study opportunities, employment opportunities, job security, economic independence and career development, thus significantly improving career progression and earnings potential.
- Reduced stress and anxiety and improved emotional well-being.
- Ability to participate in ‘normal family life’ without constantly battling the risks of a phototoxic reaction.
- Improved physical and mental health from increased opportunities to participate in sport and exercise.
- Significantly lower cost of living.
- Additional health benefits relating to vitamin D levels.
- Reduced burden of responsibility and guilt on children and family members, alongside increased potential to keep families together.

Further differences would include:

- Being included in family leisure activities (such as cycling, bat and ball sports, music festivals) without incredibly high risk of phototoxic reactions
- Greater access to areas of outstanding natural beauty, in the daylight!
- Being able to drive/travel greater distances without the fear of an EPP reaction.
- Whilst it may not permit sunbathing around a pool on holiday, we anticipate Afamelanotide would make sitting out under the shade of parasol accessible without the intense fear of triggering a reaction.
- Patients are looking to the technology for much more basic improvements to the quality of life such as the benefits of being able to go on the same holidays as non-EPP family members.

In short these latter differences portray a relaxation of the stress that fear of phototoxic reactions induce in everyday life. This in turn would improve the psychology of patients such that they would suffer less from a life full of compromises, frustration and missed opportunities. In business, a life less impinged by fear would potentially reduce risk averse behaviour, opening up new challenges and associated reward.

A more relaxed EPP sufferer, less fearful of reactions would be a brighter presence at home resulting in reduced tensions and in some cases disturbing outbursts.

The EPP sufferer is expected to become less of a spectator in life and more a participant.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

Whilst other research into treatments for EPP is underway, it is still at a very early stage of development and it will be many years, if not decades, before studies even get to clinical trials in EPP patients.

Afamelanotide is the first and only game changing treatment demonstrated to make a significant difference to lives. It is the only real hope that has come along to offer serious potential for not remaining in the shadows, confined by the need to remain safe and secure from the light that triggers phototoxic reactions.

The condition affects all aspects of a patient's life from work or education, to family and social life and ultimately emotional and psychological well-being. The need for an effective treatment is therefore of the utmost importance.

If this treatment is not made available, these patients will continue to physically live in the shadows and move around by stepping between shadows. This situation cannot and should not be allowed to continue.

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Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria [ID927]

(iii) Are there groups of patients that have difficulties using the technology?

We do not anticipate any patients within the groups approved under EMA conditions having any difficulty in accessing the treatment.

In time, and following/subject to further evaluation/approval by EMA and other bodies, we see the method of application also being highly accessible to patients under the age of 18.

(iv) Are there any situations where patients may choose not to use this technology?

Some patients may not be confident trying a new technology where the long-term effects are as yet unknown.

Some patients may fear failure of the drug, which emphasises the importance of clinical and psychological support.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

The BPA estimates there to be a total of around 400-500 EPP patients in the UK, with around 400 of those being in England. This number is based on estimates extrapolated from the total UK population. Of these approximately 20-25% (estimated) would be ineligible for the treatment under EMA conditions due to being under 18.

It is worth noting that the advent of Afamelanotide has seen our membership number increase. Interest in the treatment is high, especially as our members are struggling to gain any benefit from other therapies. Despite this only around 25% of predicted EPP patients in the UK are accessible via our member database.

With regard to the number who would be expected to receive the treatment, we do not yet feel in position to provide an accurate number. With limited resources to conduct a formal consultation we are reluctant to reach out to our members until the outcome of this consultation and associated conditions are known. The last thing we want to do is raise false hope and expectation amongst a group who are already facing challenges every day of their life.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which afamelanotide is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Patient case studies below are divided into three sections:

(1) EPP patients who have never had Afamelanotide
(2) EPP patients who have had Afamelanotide
(3) Family and carer perspectives

Section 1 (EPP patients who have never had Afamelanotide)

I am 52 and became light sensitive (with EPP) at the age of one. I was officially diagnosed at the age of 22, after self-diagnosis from extensive personal research. I am severely sensitive to visible, natural light. EPP has dictated the choices I have made in both my personal and professional life and has imposed very many limitations. Due to prolonged unmanageable pain I even researched amputation to gain relief. Using the then limited information available I chose to have children. Unfortunately both inherited the EPP gene. My daughter has not become light sensitive but my son, now 15, became light sensitive at the age of 8. He is severely sensitive to visible light, both natural and a wide range of artificial forms too. He feels he has no hope and no future. His symptoms have escalated causing me to give up work to become his full-time carer.

EPP Patient and Parent of EPP Child

****

I have had symptoms of EPP since I was an infant. I was diagnosed in the 1980s, but this wasn't memorable as there was no support or treatment offered. As a child, I spent hours underneath my parents' bed where I stood a chance of getting out of the light. Desperate for relief from insufferable pain, I would run my hands, burning from the inside out, along the cold iron frame, steeling myself for the different sort of pain the change in temperature would bring. This would be after hours struggling in sunny classrooms, playgrounds etc., where there was no escape. Everyday living was really

difficult, with heavily blistered skin on face and hands, scabs that wept and then blistered once again by further, inevitable exposure to light. Car journeys were an especial nightmare although all outings were deeply challenging, even waking to a sunlit room.

It did not occur to anyone to make special arrangements and I learned to hide my distress, feeling it as an incurable inadequacy which should be secret. The toxic nature of the chemical reaction to light within my system was never discussed, nor were its psychological effects. I have been fortunate that I have not let EPP's pain define my life, though it has taken a huge toll. My brother, also a sufferer, has been seriously blighted. He does not have children and mine are adopted, a life choice made in part to avoid passing on this scourge.

I live in fear of being caught by strong light. I stick to the shadows, scurrying through sunlit areas and dressing in protective clothing. Despite all this, the light still gets to me, and pain is almost always present, building to unbearable levels in sustained good weather. I try to avoid exposure to the level that causes the swelling that splits my skin, but, even after all my years of EPP experience, I can still be caught out. EPP's isolating effects have made me reticent about engaging doctors as, historically, disappointment has always followed, but I am fighting that now. I am more able to recognise the insidious effects of the conditioning of body, mind and spirit which comes with a deep fear of strong light. I am sad for the child I was. I am sad that my honeymoon, all those years ago, was blighted by the effects of unexpected April sunshine. I am sadder still for the days in the sun and summer's carefree happiness which we have been denied as a family. I would so very much love to come out from the shadows to enjoy rather than endure light filled days.

Adult EPP Patient

****

Scenesse would literally transform my life for the better. I suffered with an unknown incurable condition from the age of 2 and until I self-diagnosed in 2014 at the age of 24. This condition as you know is EPP. To my friends and family, I have an extremely high pain threshold. I put this largely down to the fact that I have had to cope with the pain of EPP symptoms during every exposure to sunlight I have endured. Until the age of 24 I didn't tell a single friend that I suffered with EPP due to the psychological issues surrounding this condition. The issues are largely due to the fact that I felt isolated without visibility to and awareness of the condition and also largely due to the fact that I didn't feel 'normal'. When describing the symptoms I have to extended family members, I called them allergies only to undermine the intense pain and severe limitations of my condition. Those who suffer with EPP are extremely resilient because it takes a strong person to go back outside into direct sunlight knowing that an exposure could bring on pain.

The pain I experience starts off as a tingling on my face hands and feet. I would describe the pain as all consuming, burning and unbearable. It starts gradually and is a warning to remove yourself from direct sunlight. Sometimes there is no option to remove yourself from sunlight, which means as an EPP sufferer you are literally fighting against every natural safety instinct in your body. Once the pain begins, I

have minutes to remove myself from sunlight or the pain increases to a severe burning that lies beneath the skin. Medication does not aid or ebb the pain in any way as the damage is already done. Because of the psychological issues surrounding EPP, it meant that I would hide my pain from friends or even family which adds another layer of suffering. I have been in severe situations as a child where I have had such an extreme burning sensation on the backs of my hands that the only option to give even a slight instant relief is to lick the backs of my hands. Another wave of symptoms starts after the exposure in the form of itching on the affected areas. Itching only provides a split second relief followed by a more painful burning sensation which can only be described as agony. After an exposure from the day I am unable to sleep due to the intense burning when staying still. I put cold flannels on my hands and feet but this does not aid the pain. The next few days after exposure results in having sick days because of the next wave of symptoms. I cannot leave the house because even spending 5 minutes in sunlight brings on further pain. I am exhausted, I usually have a headache or migraine due to the stress of the previous day, I lose my appetite and most importantly, I experience an intense painful tingling like shards of glass under my skin if the affected areas come into contact with outside wind or air. Only recently have I trialled the phototherapy treatment. This is not even remotely close to a valuable treatment as the closest hospital is too far away not to disrupt my day-to-day life. It meant that my work time was impaired causing more worry. The treatment itself is not handled with compassion. The nurses are often not aware of my condition therefore do not understand that standing in an enclosed space with UV lights on my skin is fear inducing. It was not a pleasant experience and more importantly, has not relieved my symptoms. If anything, it has encouraged me to avoid sunlight further. As it currently stands for me, there is no cure which gives even slight relief from the physical pain I experience during each exposure, and the emotional impact of this condition.

The impact on the quality of my life has been severe. As a child I called in sick to sports days, my family suffered alongside this avoiding holidays abroad in the 24 years sticking to local UK based holiday areas. I became very skilled in predicting or pre-empting the weather during the summer months at school. I also became very skilled in quickly assessing where shade would be during every exposure. I faced anxiety and worry as a child whenever spending time outdoors was mentioned amongst others. Now as an adult, I still have an entrenched sense of alarm and anxiety to stay safe and keep out of the sunlight whenever the summer months come around. I still avoid holidays with friends which means that I am forced to isolate myself from friendships groups and lack the shared experiences and bonding with them. I often feel down, low and frustrated due to the limitations of my condition. Only on reflection do I realise the sacrifices that I have made living with EPP. I have never been able to travel, I cannot choose the career path I want to, I am unable to share certain experiences with friends and family. Feeling isolated, alone and frustrated because I am often unable to convey to others the type of pain I am experiencing (as the damage to my skin isn't visible). Living with this condition over time you feel isolated, low and completely restricted and your quality of life is impaired. Constantly compromising, not wanting to 'put others out' when you are spending time outdoors means you learn to 'cope' with the pain and suffering.

When I heard about Scenesse, this was the first and only option that has been presented to me that would give me the potential chance at living a healthy happy life

without the limitations that I have been forced to 'cope' with since an early age. Simply put, having EPP is a life with limitations. Scenesse provides the only option that is even remotely close to a cure or treatment. Scenesse gives me a chance at a life without limitations.
Adult EPP Patient

Section 2 (EPP patients who have had Afamelanotide)

"I had my first Afamelanotide implant at the end of April, and I can tell you it makes SUCH a difference!

Until now, I was never even aware how much FEAR I was dealing with during everyday life. The strict limitation of light exposure is something every EPP patient learns from a very young age, and the reason is quite simple: light means pain. Relentless, disabling pain, that leaves you helpless, that cannot be controlled if it hits you. So we try to limit our light exposure, try to save the possible time "outside / in the sun" for those moments when it cannot be avoided, or to take part in an activity that matters dearly to you. So you choose. In the summer between being without pain and being with your friends and loved ones. Always with the thought "Is that already too much? Will I pay for it?" in the back of your head.

Two weeks after the first implant a colleague of mine asked whether we wanted to sit outside the restaurant and take a coffee after lunch. I was going to automatically say "I'm sorry, but that is not possible", when I caught myself and instead said "Ok, let's try." So we took a coffee to the outside, it was 25°C and sunny, not a cloud in the sky. We sat down, and the next 10 minutes became the hardest time in my life - NOT giving in to the screams inside my head asking me what the heck I was doing there, telling me to get out of the sun RIGHT NOW, or at least lower my head and take my hands below the table top... I used all my willpower to just sit there, in the sun, drinking my coffee and shedding the fear that had taken hold of me for so long. I cannot say I completely did it, (not even now, after ~3 months of treatment), but I stayed. Right there. Afterwards: nothing. No pain, no burning skin, just the feeling of warmth. An amazing feeling. I could have cried.

A person that does not have EPP would probably not understand what we want - just a normal life...

I am still careful, slowly learning to not worry too much, but I am confident that I will make the journey from the shadows into the light!"

Adult EPP Patient

****

For four years, I received afamelanotide. During this time, I finished my doctoral thesis, obtained a very good position in my profession and noticed that I had more of something generally called "a normal life": I met with friends for barbeque at afternoon, went for walks during daytime, I chose the shortest way to work – not the one best protected from sunlight. My life completely changed for the better! However, the real effect of the treatment I only noticed, when due to funding decisions of my health insurance company I did not have access to afamelanotide for one year: Only

then I was able to realize how much my life had changed during the time of treatment, because now I had to again learn to pay attention to the side of the bus the sun shines in and avoid this side, or I had to remind myself that I cannot visit project partners in May at noon. It was under those conditions, that I realized for the first time the full magnitude of the restrictions I already suffered my entire life.

Make a person in a wheelchair first walk again, and then withhold the treatment from him or her – suddenly every stair will not only feel like an environmental hurdle, but like a mean assault on the person's freedom and dignity. For the pain EPP patients suffer from, no adequate description exists. Not being able to be in the light and feel the warmth of the sun, for which everybody – even me – is longing for makes me feel sad and lonely and depressed. Withholding the only treatment which alleviates this pain and enables me to live a normal and full live makes me feel worthless and isolated. For the last four months, I again have had access to the treatment, however, now I have to actively learn to master the reawakened anxiety and regain trust in society.

Adult EPP Patient

****

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

****

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

****

What can I say about EPP. Imagine burning yourself on the iron or pouring boiling water on your skin, now imagine that level of pain on every part of your body that is exposed to the sun. A damaging, debilitating condition, damaging both physically and psychologically. Imagine being terrified to leave the house when the sun shines, imagine being unable to play in the garden with your children or take them to the park, imagine having to wear hat, coat and gloves on the hottest day of the year and being subjected to stares, to snide remarks and to bullying because of this. Imagine not being able to switch on the TV or look at your phone because every time you do you feel like you are on fire. Imagine not being able to do your job because the office lights cause you pain. That is my day, every day, not just in the summer, but even in winter.

Now imagine someone tells you that you can have a new drug which will take away much of this pain and suffering. That's what happened to me. I took part in a clinical trial for afamelanotide. My life changed. I went out of the house in shorts and t-shirt, I

sat in the sun, I had the best year of my life. I went from suffering to enjoyment in a couple of weeks! I could spend hours out in the sun without pain for the first time in my life.

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

This treatment is life changing.

Adult EPP Patient

****

"I'm currently in Paris with my family. With such sunny weather I'd typically be back at the hotel within 30 minutes, but now I've been outside for more than 2 hours, without any problems!"

Adult EPP Patient

****

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

Adult EPP Patient

****

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

Adult EPP Patient

****

"Both my sister and I were in the Phase III trial for this drug and my sister received the 'real thing' and it positively changed her life during those six months…she was finally able to participate"

Adult EPP Patient

Section 3 (family and carer perspectives)

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

When we are in the garden on a warm, sunny day, dad sometimes feels pain on parts of his body that are exposed to the sun. Then he can't really play with me on the trampoline, in the paddling pool or just in the sun on the grass with a ball. He regularly gets frustrated and takes out his anger on me and mummy but he doesn't mean to. On holiday, when we go somewhere like Greece daddy has to stay at home so he can't come into the pool to play with me or on the beach and in the sea. He loves to go cycling, but has to go early in the morning and ends up in pain so he cant play with me. But it is hard for him in the strong sun and he can swell very easily

which leads to me feeling quite lonely on the beach as my mum normally only sun bathes. Then he feels angry with himself and that makes me feel guilty and that it's my fault he has the condition. If he was my only parent, I wouldn't be able to cope very well as I love water and the sun and heat. When I was smaller I didn't understand why daddy couldn't come and play with me and I felt sad when he would not come.

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

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

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

Daughter (aged 10) of EPP Patient

****

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

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

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

Advantages of receiving treatment

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Physical health: treatment will allow my husband to vastly improve his ability to participate in outdoors sporting activities that will help getting and keeping him fit, simply having the opportunity to get out for a run or on a bike or even walking the dog. He has never been able to take part in team sports due to the unreliability of him being able to venture outdoors. This, I believe has a very negative psychological effect on him especially as our children are involved in team sports. He regularly cannot support his children at their sports matches and competitions if he is required to be outdoors; for our family these are cricket, rugby, tennis and lacrosse.
When our garden needs attention, an outdoor physical activity, my husband would be able to do the simple chores such as mowing the lawn and trimming the shrubs at any chosen time of day rather than in the dusk in the late evening. We often have to hire a gardener to complete these jobs.

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

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

For years we have been forced to take separate holidays, my husband takes his holiday away from his family in the winter season whilst the children and I love to visit sunny Mediterranean climates or go camping on the coast around Britain. Imagine not having those holiday memories to share together, this is a cause of sadness and anxiety for all of the family. Given the chance to have this treatment would be life-changing for my husband; giving us as a family simple day to day choices that are currently non-existent with his EPP. He may have missed out on much of his children's early years but with the treatment would be able to make a massive difference to their futures.

Spouse of EPP Patient

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

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

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

Please do not exceed 12 pages.

About you

Your name: [redacted], British Association of Dermatologists' Therapy & Guidelines sub-committee, and co-opted [redacted] and [redacted]

Name of your organisation: British Association of Dermatologists

Are you (tick all that apply):

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

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

Nil to declare.

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What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

EPP is a very rare disorder and everything that experts in this area have witnessed concerning patient numbers with EPP in England is consistent with the number identified by Holme et al. 2006 (1), i.e. that there are approximately 389 living patients, including children under 18 years. The Holme et al. 2006 study was an exacting study, where very thorough methods were used to trace EPP patients, including involvement of all specialist centres in the UK providing the initial diagnosis and further care of these patients. It is the sole available cross-sectional study, and moreover, included patients throughout the UK, not only England.

At the [redacted] both ([redacted]) and [redacted] ([redacted]) have between them only 30 EPP patients, despite the supra-regional nature of their services, and a number of patients travelling long distances to see them. Moreover, these patients are likely to have been counted twice or more at different centres as they travel further afield in their quest for an effective treatment. They see 3 or fewer genuine new cases per year.

In a short-term, incidence-based study (a design open to several assumptions) by Elder et al. 2013 (2), the pan-European incidence rate would suggest no more than 600 patients with EPP in the UK. Therefore, the number for England would be similar to the number identified by the Holme study, and in line with our co-opted experts' experience at their specialist centres.

References:
(1) Holme SA, Anstey AV, Finlay AY, Elder GH, Badminton MN. (2006). Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. Br J Dermatol. 155(3):574-81.

(2) Elder G, Harper P, Badminton M, Sandberg S, Deybach J-C. (2013). The incidence of inherited porphyrias in Europe. J Inherit Metab Dis. 36(5):849-57.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

A specialised service is provided for EPP at nationally identified porphyria centres. EPP patients may also be treated outside of specialist centres, once the diagnosis has been made at a specialist centre.

There is currently no effective treatment available on the NHS that can prevent the debilitating pain caused by light exposure in EPP. Topical sunscreens have low

benefit. Beta-carotene administered orally has historically been used but it produces slight if any effect in practice leaving most patients to discontinue this. Ultraviolet B treatment can sometimes be but it is not often suitable. No painkillers (analgesics) are beneficial.

Afamelanotide (Scenesse) has a considerable advantage in that it is the first effective treatment for EPP. It is a super-potent tanning agent which induces an appreciable tanning response in the skin which is effective even in light-skinned people with normally no or minimal tanning ability. It does not require exposure to light in order to be effective, and therefore avoids the hazard of light exposure.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

No, the long-term prognosis is uniform, although severity of condition can vary from patient to patient.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

Specialist nursing input would be required for administration of the implant and treatment monitoring.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

It is not available in the NHS.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Not applicable.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

In the experience of out co-opted photodermatology experts treating these patients, afamelanotide is the first effective treatment for the condition EPP, thus contrasting with any other measures that could be attempted. Thus, there is no effective

comparison with which to compare this ground-breaking technology. It involves a standard sub-cutaneous implant that is an easy-to-use technology. It may require monitoring, as the EU licence was gained under special measures, as frequently happens when a medical condition is very rare, and in order to provide further data. [redacted] believes that patients will be very content to undergo additional monitoring and blood tests as required for this treatment. The patients that she has treated with afamelanotide in clinical trials have been very happy to travel long distances (100 miles or more) to receive treatment and undergo required tests.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Not applicable.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Combined EU-USA, multi-centre randomised trials have provided the highest quality data resulting in publication by Langendonk et al. 2015 (3) in the world's top medical journal, the New England Journal of Medicine (NEJM), emphasising the ground-breaking nature and efficacy of this treatment. A significant reduction of number of phototoxic episodes was seen, accompanied by a significantly increased amount of time spent outdoors without suffering pain and with significantly improved quality of life. In practice, the patients Patients treated within the afamelanotide trials appeared to have substantially greater benefit than seen in the trials, which may reflect that trials did not fully capture patient benefit. A measure taking into account both time exposed and pain would help, as one negatively influences the other, and thus reduces the benefit captured in trials. Moreover, the data analysis within the NEJM study included days when the patient did not go outside. Thus, while the NEJM paper findings were highly significant, the magnitude of the changes would be higher if a more specific analysis was performed.

The circumstances in which the trials were conducted did reflect current UK practice, indeed, UK centres in Manchester and Cardiff participated in the major EU-USA multi-centre trials as well as previous phase II and III afamelanotide trials in EPP.

Long-term observation study of patients in Europe by Biolcati et al. 2015 (4) have shown that improved quality of life is maintained over at least 8 years, and there was a very high adherence rate of 74% of patients who continue with afamelanotide, even where their patients have to travel very long distances for treatment (the majority of those that discontinued, i.e. 23%, did so for reasons such as finance and pregnancy).

References:
(3) Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell M, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips J, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ (2015). Afamelanotide for erythropoietic protoporphyria. N Eng J Med. 373(1):48-59.
(4) Biolcati G, Marchesini E, Sorge F, Barbieri L, Schneider-Yin X, Minder EI. (2015). Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol 172: 1601–1612

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Earlier formulations of afamelanotide involving sub-cutaneous injections showed a high prevalence of minor side effects including headache, nausea and tiredness due to the serum peak occurring with the injectable form. However, these minor effects have greatly reduced with the slow-release, sub-cutaneous implant formulation, where the dose has also been reduced to 16 mg per implant (3). Patients have found these minor side effects highly acceptable and in several trials [redacted] has performed [redacted] is unaware of any patient discontinuing due to side effects related to the treatment. The tanning (pigmentation) of the skin seen with afamelanotide is accompanied by increased pigmentation of patients' moles and freckles; this is expected and is managed by monitoring the patients' moles.

Reference:
(3) Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell M, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips J, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ (2015). Afamelanotide for erythropoietic protoporphyria. N Eng J Med. 373(1):48-59.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

We are unaware of further information sources.

Implementation issues

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Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra facilities or equipment would be required.

Implant insertion is a simple procedure and skin monitoring is already performed in dermatology departments – basic, in-house training may be required.

Specialist nursing input would be required for administration of the implant and treatment monitoring.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which afamelanotide is /will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

We are unaware of any such impacts.

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

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

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

Please do not exceed 12 pages.

About you

Your name: [redacted]

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

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

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

NO

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What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

The number of patients in England can only be estimated from published data. The two most robust studies available that have attempted to estimate these numbers have used different methodology.

Holme A et al Br J Dermatol 2006 155(3):574-81
This study identified 389 EPP cases from UK clinical databases, estimating a UK prevalence of 1:143,000.

Elder et al J Inherit Metab Dis. 2013 Sep;36(5):849-57.
This prospective epidemiological study estimated an overall prevalence in Europe of 9.2/million but a higher prevalence in the UK of 25.4 per million. This latter figure would give approximately 1524 patients with EPP in the UK. The paper acknowledges that this may be an over-estimate.

Our laboratory provides a diagnostic service for Greater Manchester and many other North West hospitals. We make a small number of new biochemical diagnoses of EPP per year (3-6) but a number of these are adults who may have previously been diagnosed elsewhere. Approximately 30 EPP patients currently attend the Salford Porphyria clinic and we are aware of only small additional numbers seeing local dermatologists in other parts of the North West.

The actual number of patients is likely to lie between the two published estimates and only some (i.ei adults) would be eligible for treatment.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The condition is normally diagnosed clinically by dermatologists and can only be confirmed by specialised laboratory testing. There are specialised Porphyria clinics and Porphyrin laboratory services in England in Salford Royal (Salford), St James' University Hospital (Leeds), Kings' College Hospital (London). Others services in the UK are University Hospital of Wales Cardiff and the Photobiology Unit, Dundee. Patients in these localities are likely to be treated in the specialist clinics but those who cannot easily travel to a specialist porphyria clinic are generally managed in secondary care by local dermatologists. Anecdotally, (via the patients' support group, the British Porphyria Association) we are aware that some EPP patients are not receiving any regular follow up.

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Based on discussions with colleagues in the British and Irish Porphyria Network, we do not believe there is major variation in management practice. Current treatment options are very limited, the mainstay is effective sun protection and correction of Vitamin D deficiency (which is almost universal due to the stringent sun avoidance necessary to avoid provoking painful acute phototoxic reactions).
Other options are oral beta-carotene (typically taken from April to October) and/or a course of narrow band UV-B phototherapy (delivered in advance of summer months). The response to these treatments is very variable and both are of limited efficacy at best. They can be offered each year to those who gain at least a degree of improved sunlight tolerance. It is not uncommon for patients to try these treatments once then decline further courses because of no benefit, inconvenience or unwanted effects.

Beta-carotene is typically given in doses ranging from 50-100mg daily (for children) and 150-300mg daily for adults. The disadvantages are:
Beta-carotene causes an orange tinge to the skin which some patients find unacceptable.
The doses available are 15mg or 25mg capsules which mean taking large numbers of capsules per day for six months per year.
Meta-analyses of risk of long term usage of beta-carotene supplementation in other contexts have not addressed the safety of these high doses. There are no such studies available for EPP.

Narrow band UV-B therapy (also known as TLO-1) requires specialised equipment and patients need to be assessed for their suitability by a qualified medical Photodermatologist. Courses of treatment may require around 12 visits in quick succession (2-3 times per week), which may be inconvenient. To gain maximum benefit over a season, patients then need to "top up" their UV exposure by going out in sunlight. This cannot always be achieved. Total dose exposure must be accurately recorded for long term monitoring. Patients may experience some redness and soreness after individual treatments.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Approximately 15-20% of EPP patients develop gallstones and the most serious complication is liver failure. Published estimates of the incidence of liver failure vary from 1-5% of EPP patients. There are no genetic or biochemical predictors of sub-groups likely to develop these complications. Other genetic variants continue to be described (e.g. X-linked EPP) but as yet there is no clear evidence of genotype-phenotype relationships in respect of long term prognosis.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or

professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

The European Medicines Agency currently stipulates that Afamelanotide implants require a specialised Porphyria service to support the safe delivery and monitoring of the treatment. There would be a requirement for specialist photodermatologist assessment of the eligibility of patients for Afamelanotide treatment, medical /nursing health professionals trained to administer the implants (typically 3-4 implants required per year), medical staff time for increased follow up appointments, laboratory support for additional monitoring investigations and clinical time to collate and submit safety monitoring data in line with a strict Post Authorisation Safety Study (PASS) protocol and regulatory requirements (see below).

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

This technology is not currently available in the NHS. The European Medicines Agency has approved the drug for marketing authorisation under exceptional circumstances for adult patients with EPP. This requires the establishment of the above conditions, including registering all treated patients in a centralised safety monitoring database.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no national or international guidelines for the management of EPP. Consensus opinion among members of the British and Irish Porphyria Network (BIPNET) is broadly that supportive care should include strict photoprotection and use of reflectant sunscreens (such as Dundee suncream). Oral beta-carotene can be offered for approximately six months (April to October) and /or courses of narrow band UV-B treatment are usually offered in spring. Patients need regular monitoring (including full blood count, iron stores, liver function, vitamin D and red cell protoporphyrin).

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Afamelanotide offers significant advantages to adult patients with EPP as the only requirement is to attend for administration of the implant itself (3-4 times per year) and undergo required safety monitoring. The effect of each implant lasts about 60days, hence the estimate of 3-4 implants per patient per year in our UK climate.
This is likely to be more acceptable to patients than taking large numbers of beta-carotene capsules daily for six months of the year or attending for approximately 12 narrow band UV-B treatment in quick succession every spring (this can be problematic for patients who are working or live a long distance from a treatment centre).

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The monitoring requirements impose more frequent out-patient attendances but are unlikely to be regarded as especially inconvenient or onerous.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

To my knowledge, the key trial data is reported in:
Langendonk JG, Balwani M, Anderson KE et al. Afamelanotide for Erythropoietic Protoporphyria
https://www.ncbi.nlm.nih.gov/pubmed/26132941#

The key outcome measures were appropriate (safety, duration of direct sunlight exposure without pain, EPP Quality of life score).

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The published studies indicate a good safety profile though the longest published follow up is 8 years (Biolcati et al, 2015) and EPP is a lifelong condition. I am not aware of any serious concerns about safety that have come to light in participants after clinical trials ended. No additional UK experience is available since the treatment is not currently being used in the NHS.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Clinical experience of use of Afamelanotide since June 2016 in the Netherlands was reported in a plenary session at the 2017 International Congress on Porphyrins and Porphyria, June 25th-28th
Abstract available at:

https://icpp2017.org/wp-content/uploads/2017/06/PLs.pdf

Other treatment programmes are underway in Italy, Switzerland and Germany. Designated treatment centres are required to submit annual reports to EMA.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The expertise and facilities would be available in Salford Royal Academic Photobiology Unit and Porphyria Service. There would be additional costs associated with the provision of the implant service under the EMA conditions required, principally staff time.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which afamelanotide is /will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

The treatment is only authorised for adult patients so children are excluded. EPP is a lifelong condition and symptoms are present from birth.

It is arguable that the negative impact of EPP on a patient's ability to undertake normal daily activities is "substantial".

NICE National Institute for Health and Care Excellence

Clinical expert statement

Afamelanotide for treating erythropoietic protoporphyria [ID927]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Professor Lesley Elizabeth Rhodes
2. Name of organisation	The University of Manchester and Salford Royal NHS Foundation Trust

3. Job title or position	Professor of Experimental Dermatology, Honorary Consultant Dermatologist and Director of the Photobiology Unit
4. Are you (please tick all that apply):	✓ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ a specialist in the treatment of people with this condition? ✓ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to prevent or reduce the disability caused by the skin pain experienced by EPP patients upon their exposure to small amounts of sunlight. Not being exposed to sunlight is incompatible with everyday life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	• Increase in time spent in sunlight without experiencing pain • Reduction in number of phototoxic (painful) episodes • Reduction in severity of pain experienced Good improvement in the above measures within a short term trial is a clinically significant treatment response. Measurement and evaluation of these endpoints is complex, as time spent outdoors influences risk of pain. Moreover, patients are psychologically affected by their previous experience of severe pain, resulting in severe restriction of their behaviour from an early age, and take time to alter their behaviour on effective treatment. These factors tend to lead to the measured benefit seen in clinical trials under-estimating actual real world benefit.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a very significant unmet need for patients, and for health care professionals, in EPP. There is no effective alternative treatment. These patients have a rare metabolic disorder that causes severe and prolonged, debilitating skin pain on exposure to sunlight, necessitating avoidance of sunlight.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	There is currently no effective treatment available in the NHS that can prevent the debilitating pain caused by light exposure in EPP. Topical sunscreens have low benefit as they are geared to protect against ultraviolet radiation and provide very little protection from the visible radiation (peak 405nm; violet light) that triggers EPP. Beta carotene orally has historically been used but it produces slight if any effect leaving most patients to discontinue this. Ultraviolet B treatment can sometimes be used but it is not often suitable. No pain killers (analgesics) are beneficial.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Not applicable
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	A specialised service is provided for EPP patients at nationally identified porphyria centres. Tertiary care specialists are involved in their care at these centres, particularly clinical pathologists with interest in cutaneous porphyria and photodermatologists i.e. dermatologists specialising in photosensitivity disorders. EPP patients may also be treated outside of specialist centres, once the diagnosis has been made at a specialist centre, in secondary care dermatology centres. My experience relates to the national service.
• What impact would the technology have on the current pathway of care?	There could be a tendency for more patients to obtain care from specialist centres rather than outside specialist centres.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Afamelanotide (Scenesse) differs from current care in that it is a step-change, as the first effective treatment for EPP. It is an alpha-melanocyte stimulating hormone (a-MSH) analogue, with super potent tanning properties that induce an appreciable tanning response in the skin; remarkably, it is effective even in light skin (Fitzpatrick skin type I/II) people who normally have no or minimal tanning ability. It does not require exposure to light in order to be effective, and therefore avoids the hazard of sunlight exposure until patients are protected.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, particularly in but not limited to specialist photosensitivity/porphyria clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific facilities or equipment are required. Subcutaneous insertion of an implant is a simple procedure that can be performed after short training. Specialist nursing input is required for administration of the implant and treatment monitoring, which involves straightforward measures.
12. Do you expect the technology to provide clinically	Yes. Highly significant benefits have been seen and experienced by patients in clinical trials, and this has not been observed with current care.

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	I would not expect length of life to change.
• Do you expect the technology to increase health-related quality of life more than current care?	I expect disease-specific quality of life to improve more than with current care. This orphan disorder has unique effect to capture, involving avoidance of severe pain caused upon sunlight exposure and associated disability, and instruments to fully measure EPP are not available.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment is effective for patients with the rare metabolic photosensitivity disorder EPP, and is not appropriate for the general population. Patients with very mild forms of EPP may not require treatment.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	The technology involves a standard sub-cutaneous implant that is an easy to use technology. It may require monitoring, as the EU licence was gained under special measures, as frequently happens when a medical condition is very rare, in order to collect further data.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Specialist nursing input is appropriate for administration of the implant and treatment monitoring, involving the routine measures of blood tests and skin monitoring. I believe patients will be very content to undergo additional monitoring and blood tests as required for this treatment. The patients whom I have treated with Afamelanotide in clinical trials have often travelled long distances from other regions to receive treatment and undergo any required tests. They find the procedures and assessments easy. They report their lives are transformed by the technology. Long-term observation study of patients in Europe by Biolcati et al 2015 over 8 years, showed a very high adherence rate of 74% of patients who continued with afamelanotide, even when they had to travel long distances for treatment (the majority of those that discontinued, i.e. 23%, did so for reasons such as finance and pregnancy). Biolcati G, Marchesini E, Sorge F, Barbieri L, Schneider-Yin X, Minder EI. (2015). Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol 172: 1601–1612
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is anticipated that many patients would require implants only during the spring and summer months.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Yes. This orphan metabolic disorder has unusual features that are not adequately captured by simple QALY assessment. More meaningful multidimensional considerations are required. In this condition the patients have a life-long disability. Uniquely, severe and prolonged skin pain on sunlight exposure occurs, resulting in extreme behavioural and avoidance measures. With these challenges, the good benefit and significant improvement seen within published trials is therefore highly notable. Combined EU-USA multi-centre randomised trials have provided data published

quality-adjusted life year (QALY) calculation?	by Langendonk et al 2015 in the world top medical journal, New England Journal of Medicine (NEJM), emphasising the ground-breaking nature and efficacy of this treatment. A significant reduction of number of phototoxic episodes was seen, accompanied by a significantly increased amount of time spent outdoors without suffering pain and with significantly improved disease-specific quality of life. In practice, patients I treated within the Afamelanotide trials appeared to have greater benefit than measured in the trials which may reflect that trials did not fully capture patient benefit. A measure taking into account both time exposed and pain could help, as one negatively influences the other, and thus reduces the benefit captured in trials. Of significance, the data analysis within the NEJM study included days when the patients did not go outside. Thus while the NEJM paper findings were highly significant, the magnitude of the changes would be higher if a more specific analysis was performed. Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell M, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips J, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ (2015). Afamelanotide for erythropoietic protoporphyria. N Eng J Med. 373(1):48-59.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes, this is an innovative technology with very high potential to make significant and substantial impact on EPP patients; this technology will meet the large unmet need of EPP patients and their physicians. Long-term observation study of patients in Europe by Biolcati et al 2015 indicate that improvement is maintained over at least 8 years, and there was a very high adherence rate of 74% of patients who continue with Afamelanotide (the majority of those that discontinued, i.e. 23%, did so for reasons such as finance and pregnancy). Biolcati G, Marchesini E, Sorge F, Barbieri L, Schneider-Yin X, Minder EI. (2015). Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol 172: 1601–1612

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, the technology provides an absolute step change in the management of EPP. It is a first-in-class agent (alpha-melanocyte stimulating hormone analogue). It is also the first ever licensed drug for photosensitivity (now licensed in several European countries). Patient experiences, and clinical trial results, demonstrate a step change in their care.
• Does the use of the technology address any particular unmet need of the patient population?	In my experience as an expert treating these patients, Afamelanotide is the first effective treatment for the condition EPP, thus contrasting with any other measures previously attempted. There is no effective comparison with which to compare this ground-breaking technology.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Earlier formulations of Afamelanotide involving sub-cutaneous injections showed a high prevalence of minor side effects including headache, nausea and tiredness due to the serum peak occurring with the injectable form. However these minor effects have greatly reduced with the slow release sub-cutaneous implant formulation, where the dose has also been reduced to 16mg per implant (Langendonk et al 2015). Patients have found these minor side effects highly acceptable and in several trials I have performed I have not had any patient discontinue due to side effects related to the treatment. The tanning (pigmentation) of the skin seen with Afamelanotide is accompanied by increased pigmentation of patients moles and freckles; this is expected and is managed by monitoring the patients moles. Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell M, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips J, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FPJ, Sijbrands EJG, de Rooij FWM, Lebwohl M, Naik H, Goding CR, Wilson JHP, Desnick RJ (2015). Afamelanotide for erythropoietic protoporphyria. N Eng J Med. 373(1):48-59.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The circumstances in which the trials were conducted DO reflect current UK practice. Indeed, UK centres in Manchester and Cardiff participated in the EU-USA multicentre trials as well as in previous phase II and III Afamelanotide trials in EPP.
• What, in your view, are the most important outcomes, and were they measured in the trials?	EPP is a complex and unique condition and scientific tools are not available to fully capture this condition and its treatment. I believe that important outcomes are: Increase in time spent in sunlight without experiencing pain, Reduction in number of phototoxic (painful) episodes, Reduction in severity of pain experienced, and Improvement in disease-specific quality of life. These were measured in the trials, and their good improvement within a short term period is a clinically highly significant treatment response. Patients are psychologically affected by their previous experience of severe pain, and take time to alter their behaviour. Measurement of these endpoints is complex, as increased time spent outdoors increases risk of pain, and thus trials may underestimate clinical effect. Combination of these parameters may be helpful.
• If surrogate outcome measures were used, do they adequately predict	Standardised provocation of EPP pain using laboratory lamps (to mimic sunlight exposure, whilst being able to control the conditions) was additionally performed in clinical trials and provides an indicative interim outcome. It controls for alterations in sunlight exposure conditions and for behaviour, as a standardised

long-term clinical outcomes?	challenge can be given with and without the technology, and an objective measure of increase in skin resistance is demonstrated. However, longer term outcomes would be greater than the lamp findings, and greater than the clinical outcome measures of the studies, attributable to the behavioural adjustments and increased skin resistance as sun exposure tolerance increases on the active technology.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I have performed several trials and attended research and clinical conferences where this treatment is presented and discussed, and am not aware of adverse effects subsequently coming to light.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, apart from experimental evidence that supports the clinical trial findings of efficacy and safety of the technology.
21. How do data on real-world experience compare with the trial data?	Real world experience is that Afamelanotide is more effective compared with the trial data. This is reported many times by patients and is consistent with medical observations. It is challenging for trial data to capture the full benefit gained in this condition which (i) not only has complex and unique clinical features for which (ii) there is a lack of suitable assessment tools, but also (iii) is an orphan condition with few patients available to participate in trials.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	My comment relates to the EPP patient group as a whole compared with other patient groups (and not to equity within the EPP group – where I am not aware of issues): It should be taken into account that QALY is a simplistic assessment that cannot take on board the unique complexities of this rare metabolic condition EPP, which has a lack of appropriate measurement tools. Thus without appropriate considerations, context and interpretation, this may breach the rights of the EPP patient group to equity and fairness, i.e. as compared with non-EPP patient groups with other medical conditions where QALY assessment is more appropriate.
22b. Consider whether these issues are different from issues with current care and why.	Not applicable
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- EPP is an orphan metabolic disorder with disabling impact on patients' lives due to inability to tolerate sunlight exposure
- Exposure to sunlight uniquely results in prolonged, severe and debilitating skin pain
- No effective treatment is currently available on the NHS for EPP patients
- Afamelanotide is the first effective treatment for EPP; this is demonstrated in RCT in the EU and USA as published in the top medical journal (NEJM), and in long term use studies, with greater real world benefit as trials cannot capture full benefit in this unique disorder
- Afamelanotide provides a complete step change in care for EPP patients and it is imperative to provide this treatment in the NHS without further delay, i.e.in time for the next spring season

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

Clinical expert statement

Afamelanotide for treating erythropoietic protoporphyria [ID927]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Robert Sarkany**
2. Name of organisation	**Photodermatology Unit, St John's Institute of Dermatology, Guys and St Thomas' NHS Foundation Trust**

3. Job title or position	**Head of Photodermatology and Cutaneous Porphyria Service, and Consultant Dermatologist.**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce pain, decrease photosensitivity, improve quality of life, and prevent severe bouts of photosensitivity-induced pain
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	This is a painful, distressing condition which is associated with major impact on QoL, and for which there is no effective treatment except afamelanotide, A clinically significant response would be a statistically significant improvement in QoL and a statistically significant reduction in EPP-related pain and a statistically significant normalisation of lifestyle in terms of time spent outside and in cars.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. This is a very painful, very distressing disease, associated with major psychological and QoL impacts, for which there has been no effective treatment. There have been non-evidence based claims that a variety of existing treatments (are effective): antioxidants, phototherapy etc. This is wrong -----unfortunately none of those treatments are effective in EPP. There is a great unmet need and there is no doubt that this is the first and only effective treatment.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	We review the patients annually, primarily to check liver function tests (EPP can cause liver damage) and offer genetic counselling. Some years ago we used to try phototherapy and antioxidants, but have stopped this because it has become clear (both from our clinical experience in our 80 patients, and from the lack of evidence in the literature) that they are not effective. We also offer advice re photoprotection (the visible light action spectrum means that UV protective sunscreens are ineffective), and psychological support. We do not have treatment for the bouts of pain and non-opiate analgesia is ineffective for these bouts
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	I am not aware of any formal clinical guidelines, as is often the case in rare diseases.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. The patients are almost all cared for in one of the small number of Porphyria and Photodermatology Departments. The plan of routine annual review, genetic counselling, liver function test checking are well defined. There is consensus that there is no effective treatment for the photosensitivity apart from advice about photoprotection. However there are one or two professionals who are keen on phototherapy and antioxidants despite the lack of either a significant evidence base for their efficacy. We used to use these but have stopped because of their lack of efficacy.

• What impact would the technology have on the current pathway of care?	It would increase the followup appointments from 1 clinic appointment per year, to 3 appointments in the summer for the implants, and one review clinic appointment after that. All patients should already be looked after in one of the big specialist Porphyria Units. Since this treatment would not be available in smaller Units , it would mean that all patients would be under the care of these larger specialist Units.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Current care would otherwise be unchanged ---the only change would be the 3 implants per year and the followup to monitor re the drug according to MHRA/EMA licencing conditions re monitoring.
• How does healthcare resource use differ between the technology and current care?	3 extra appointments per year to put in the implants of the drug. Nurse-led monitoring for adverse effects according to MHRA/EMA conditions
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Cutaneous Porphyria Clinics only --- some of these are Specialist Photodermatology clinics (e.g. London), others are specialist Porphyria clinics (e.g. Cardiff).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	One Clinical Nurse Specialist employed nationwide to do the monitoring and carry out the implants.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. This treatment is very effective. No other treatment is effective. It will provide transformative clinical benefits.
• Do you expect the technology to increase length of life more than current care?	Possibly by a little bit. Although I do not have evidence, chronic pain syndromes clearly cause anxiety, stress and depression, and EPP has also been shown to cause significant social isolation in published work. Anxiety, stress, depression and social isolation , as I understand it, can be associated with reduced lifespan due to increased suicide rates and increased levels of stress associated cardiovascular and other diseases.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, dramatically so.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Within the community of EPP patients, those with lower levels of fear and anxiety are likely to 'dare' to go outside following the treatment. These patients have associated spring and summer daylight exposure with prolonged (3-4 day long) bouts of severe and uncontrollable burning pain , from the age of 18 months i.e. before their earliest memory. To go outside having been given the treatment, will be easier for those with personality characteristics of lower anxiety levels and a more risk-taking and daring nature. So it is likely that most EPP patients will benefit from the drug, but it may take longer for the benefits to appear in less daring and more cautious and anxious individuals. I suspect that this effect is responsible for the more modest benefits from the drug in the clinical trials compared to the dramatic improvements we have seen in clinical practice.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As detailed above, the extra 3 appointments per summer to put in the implants, plus the monitoring data collection required by MHRA/EMA licencing conditions. This could be covered by one Clinical Nurse Specialist employed nationally.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	In our Unit, which is a large EPP Unit with around 80 patients, we would use the Clinical Trials' scoring systems to monitor for efficacy of treatment, in addition involving our (King's College London) Academic Health Psychologists to design ways of measuring behaviour and determinants of behaviour in patients

	treated with the drug i.e. to factor in the psychological variables which will affect the extent to which patients increase their going outdoors.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The key benefit is on quality of life so the QALY is a good measure. However, the measure of QoL is critical. This is a chronic pain syndrome with the complication that patients have a choice between pain (by going outside) and social isolation (by staying inside). The QoL measure has to reflect this. DLQI is the wrong measure .
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes . There is currently no effective treatment for this disease. This is a very effective treatment. This is dramatically innovative, and the most positive thing that I have seen in my 26 years working with EPP patients.
• Is the technology a 'step-change' in the	Yes it is ----- completely transformative.

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes, it meets their unmet need for an effective treatment.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects have been surprisingly small and are fairly minor . I don't think they will have a significant effect.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	They reflect current UK practice in everything else about the patients and their disease and its management. The only difference is that we do not have this drug currently available to us in clinical practice.
• If not, how could the results be extrapolated to the UK setting?	By providing the drug for use in NHS patients with EPP
• What, in your view, are the most important	Time spent outside in the spring and summer; reduction in pain experienced; improved quality of life and improved psychological indices of wellbeing. Yes they were measured in the trials though some of them are

outcomes, and were they measured in the trials?	difficult to measure and there may be confounding behavioural-psychological effects (discussed above) which might lead to the trials having produced results that underestimate the effectiveness of the drug.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surroaget measures : Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Adverse effects: none has come to light since the trial as far as I am aware.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes. The qualitative evidence from patients on using the drug has the advantage of factoring in some of the confounding psychological factors which I suspect led to the trials underestimating the therapeutic effect. The EMA considered both the trial evidence and this qualitative evidence in coming to their decision.
21. How do data on real-world experience compare with the trial data?	As above, the real-world experience is extremely dramatic. The patients I have come across have found that the drug has transformed their lives and dramatically reduced photosensitivity ------ one patient I have known for 25 years with severe EPP has increased sunlight tolerance from 5 minutes to 5 hours, another has increased from 15 minutes to 4.5 hours. I have been looking after these patients for over 25 years and

	have never come across repeated stories from patients of these dramatic increases in sunlight tolerance ---- this is completely unlike anything I have heard in a long career in caring for EPP patients.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	It is unfortunate that teenagers (and younger children) below 18 years of age, whose need is so great, are to not be allowed the treatment according to the licencing conditions.
22b. Consider whether these issues are different from issues with current care and why.	As detailed above re patients below 18 years of age.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- EPP is a severe chronic pain syndrome characterised by bouts of severe and untreatable pain, and social isolation
- There is currently no effective treatment for EPP photosensitivity: previously proposed treatments (antioxidants, phototherapy) are not effective or the effect is minimal.
- I was so convinced that Afamelanotide would not be effective that my centre did not take part in the clinical trials ---I was wrong.
- Afamelanotide has produced some dramatic (and for me entirely unexpected) therapeutic results in patients we are meeting who are taking the drug. This is entirely different to anything I have come across in 25 years of treating large numbers of EPP patients (I have 80 patients under long term followup in my clinic and have probably treated around 200 patients in the past 25 years.
- The clinical trial effects are probably underestimating the therapeutic effects due to a combination of the difficulty finding clinical endpoints in EPP, and psychological factors which may confound data about time spent outside
-

Thank you for your time.

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

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

Afamelanotide for treating erythropoietic protoporphyria

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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The authors declare no competing interests. Dr Sarkany declares no competing interests. Dr Badminton has attended a European EPP expert meeting in June 2016 with funding for travel and accommodation provided by CLINUVEL.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Joanne Lord critically appraised the health economic review, critically appraised the economic evaluation, and drafted the report; Olu Onyimadu critically appraised the health economic review, critically appraised the economic evaluation, and drafted the report; Wendy Gaisford critically appraised the clinical effectiveness review and drafted the report; Micah Rose critically appraised the health economic review, critically appraised the economic evaluation, and drafted

the report; Geoff Frampton critically appraised the clinical effectiveness review and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness review, drafted the report, project managed the assessment and is the project guarantor.

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LIST OF ABBREVIATIONS

AE	Adverse effect
BIM	Budget impact model
BAD	British Association of Dermatologists
BPA	British Porphyria Association
CBC	Complete blood count
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
DALY	Disability Adjusted Life Year
DLQI	Dermatology Quality Life Quality Index
EAR	European Assessment Report
EPAR	European Public Assessment Report
EPP	Erythropoietic protoporphyria
EPP-QoL	Erythropoietic protoporphyria Quality of life questionnaire
EMA	European Medicines Agency
EQ-5D	EuroQoL 5 Dimensions questionnaire
ERG	Evidence review group
FECH	Ferrochelatase
GBD	Global Burden of Disease
GBP	Great Britain pounds
GCP	Good clinical practice
HRQoL	Health related Quality of life
HST	Highly specialised technology
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IMP	Implant
ITT	Intention-to-treat
MD	Melanin density
MSH	Melanocyte stimulating hormone
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
PASS	Post authorisation Safety Study
PPIX	Protoporphyrin IX
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCP	Royal College of Pathologists
RCT	Randomised controlled trial
SD	Standard deviation
SF-36	Short Form survey-36
SmPC	Summary of Product Characteristics
UK	United Kingdom
USA	United States of America
UVB	Ultraviolet B

SUMMARY

Scope of the company submission

The company submission (CS) presents evidence of the clinical and cost effectiveness of afamelanotide (SCENESSE®) for adult patients with erythropoietic protoporphyria (EPP) above the age of 18 years old compared to best supportive care. In all studies afamelanotide (16 mg) was given as a subcutaneous implant. The main outcomes measured were duration of tolerance to sunlight and other forms of visible light, phototoxic reactions, health related quality of life (HRQoL) and adverse effects (AEs) of treatment.

Summary of submitted clinical effectiveness evidence

The CS presents evidence for the clinical effectiveness of afamelanotide based on a small open label phase II study (CUV010; five patients); four phase III RCTs (CUV017; CUV029: CUV030 and CUV039) comparing afamelanotide to placebo, and two observational studies on the safety and efficacy of long-term afamelanotide (one a retrospective assessment of up to eight years of the treatment of Italian and Swiss patients, the other an on-going post authorisation safety study).

All but one of the studies were sponsored by the company. Study CUV017 was based in eight EPP expert centres within Australia and Europe and included 100 patients (including three patients from the UK). Study CUV029 was based in eight EPP expert centres within Europe (including the UK) and included 74 patients (16 from the UK); study CUV030 was based in six EPP expert centres within the USA and included 77 patients and study CUV039 was based in seven EPP expert centres within in the USA and included 94 patients. Study CUV039 was the study that the European Medicines Agency (EMA) considered methodologically adequate enough to based it's licensing approval on.

Due to the lack of detail provided, the ERG is unable to make a fully informed judgement on the methodological quality of the RCTs. The methods used to generate random allocation sequences of patients to study groups were sufficient. However, it was not possible to determine from the information given whether study groups were comparable at baseline; or whether concealment of allocation was adequate; or whether there was selective reporting of outcome measures. Furthermore, although trials were double-blinded the increased skin pigmentation in participants who received afamelanotide was acknowledged to reveal treatment

allocation in some patients. The impact of this on patients' sun exposure behaviour and hence the effectiveness of afamelanotide is uncertain. The company's statistical analyses appear generally appropriate but information is lacking on how sample sizes and statistical power were estimated and on how missing data were handled. The level of patient drop-out, where reported, was low.

The company's evidence review included a narrative synthesis of the results of the studies, but no meta-analysis. The ERG considers meta-analysis would not be meaningful due to heterogeneity between the studies. Results from study CUV029 revealed a significant difference in the number of hours over the nine month study period in direct sunlight (measured between 10.00 - 15.00 hours) with no pain between patients receiving afamelanotide (median number of hours per patient, 6.0 (range 0-193)) compared to the placebo group (median number of hours per patient 0.8 (range 0-35)) p = 0.005 (primary outcome). In study CUV039 there was a significant difference in number of hours over the six month study period per patient in direct sunlight (measured between 10.00 - 20.00 hours) with no pain between study groups (afamelanotide median no of hours per patient 69.4 (range 0-651) vs placebo median number of hours per patient 40.8 (range 0-224)) p = 0.044 (primary outcome).

There was a higher number of phototoxic reactions observed in patients receiving the placebo in studies CUV029 and CUV039 though the difference between study groups was only statistically significant in study CUV029. In the phase II study (CUV010) there was a change in melanin density during the first 30 days after administration of afamelanotide, with a mean melanin density change of 124% above baseline and a small increase of 6% to 130% above baseline, following the second implantation at 90 days. The long-term retrospective observational study of Swiss and Italian patients reported an increase in melanin density that was maintained over the six year treatment assessment period.

Adverse events were mild to moderate in severity and the most common events reported in the studies included headache, nausea, gastrointestinal discomfort and migraine. Mortality was not reported in the CS; however, publications indicated that four deaths occurred during these trials (which had approximately 340 patients in total). The deaths were regarded by the investigators as definitely not related to the study treatment.

The impact of treatment on HRQoL was measured using the disease specific EPP-QoL instrument devised by the company (scores measured from 0-100, with higher scores indicating better HRQoL). [redacted], these data were used to inform the company's assessment of cost-effectiveness (see below). Quantitative results are available for studies CUV029 and CUV039. In CUV029 the scores increased over time in both study groups, although the increase was higher in the afamelanotide group at all assessment time points, with the highest score around 85 points. The differences between the groups were statistically significant at days 120, 180, and at day 240. In study CUV039 scores increased over time from baseline in both groups with larger increases in the afamelanotide group. The highest score was 77.7 points for the afamelanotide group at day 180 (scoring range 0-100, higher scores mean better HRQoL). Differences between the groups in the change from baseline were statistically significant at day 60, day 120, and day 180. By day 360 (240 days after the last implant) scores had fallen in both study groups illustrating a reduction in HRQoL, though they remained above baseline levels. The retrospective observational study of Swiss and Italian patients showed an increase in HRQoL after afamelanotide administration which was maintained up to six years of treatment observation, though HRQoL was shown to be higher in winter months than summer during this period indicating seasonal variation. The clinical significance of the changes in EPP-QoL results was unclear as minimal important differences have not been established.

HRQoL was also measured using the Dermatology Life Quality Index (DLQI) in studies CUV029, CUV030, and CUV039. Results available for study CUV039 showed that scores declined over time (thus showing an improvement in HRQoL) for both afamelanotide and placebo: 2.4 (± 4.2) and 3.1(± 4.1) respectively at day 180 compared to 10.7 (± 6.3) vs 10.4 (± 5.7) at baseline (N.B. a score of between 2 to 5 indicates a small effect on a patient's life). The decline in scores was larger in the afamelanotide group, though differences between the groups in the change from baseline were not statistically significant.

Summary of submitted cost effectiveness evidence

An evidence review was conducted by the company to identify economic evaluations of afamelanotide in adult patients with EPP. They reported that no relevant economic evaluations were identified. The ERG's search, however, identified a 2016 conference abstract reporting a relevant cost effectiveness analysis of afamelanotide for EPP. The ERG noted that the model

which was used for this study appeared to be similar to that of the model submitted by the company to NICE, and it included an exploratory sensitivity analysis using QALYs derived from SF-36 data from early clinical trials and for other 'similar' conditions. The estimated Incremental cost effectiveness ratios (ICERs) ranged from £208,000 to £1.1 million per Quality Adjusted Life Year (QALY).

The company's submitted cost effectiveness evaluation comprised a model to estimate the cost-effectiveness of treatment with afamelanotide compared with a standard treatment control for adult patients with EPP. This addressed the decision problem specified in the scope, with the exception of the measure of value for money: the model estimates incremental cost per DALY avoided, rather than the incremental cost per QALY gained expected by NICE. The company's rationale for this approach (which the ERG disagrees with – see below) is due to the lack of available robust utility data, and their view that a cost per DALY framework is more appropriate for this condition.

[redacted]

[redacted] The ERG has not identified any evidence to

contradict this. Non-compliance or discontinuation of treatment is not explicitly modelled. The model assumes that treatment continues throughout the modelled time horizon, with the same mean number of implants per patient and the same effectiveness estimates every year over the [redacted] year time horizon. The model does not include any additional disability, mortality risk or healthcare cost to reflect the impact of adverse reactions to afamelanotide. This is reasonable given the generally low incidence and mild severity of adverse events observed in the clinical effectiveness studies.

The company used individual EPP-QOL data from studies CUV029, CUV030 and CUV39 to estimate the proportions of patients in the intervention and control groups with mild, moderate and severe disease at baseline and at 120 days (assuming that the 120 day values apply for the whole year). The base case analysis uses disability weights from the World Health Organisation Global Burden of Disease (GBD) study conducted in 2010. The survey did not include EPP, or the company's preferred proxy of [redacted]. Instead, the company used a proxy of [redacted] in their base case analysis, and an alternative proxy of [redacted] in a scenario analysis. The ERG questions the relevance of these proxy conditions for EPP.

The cost per implant is reported as £12,020. This equates to [redacted] per year assuming a mean number of implants of [redacted] per year. The company estimates the administration cost of afamelanotide at [redacted] per patient per year.

The company's base case cost per DALY averted was £278,471 (see table).

Base case cost effectiveness results

	Discounted costs	Discounted DALYs
Afamelanotide	[redacted]	[redacted]
Standard care	[redacted]	[redacted]
Incremental	[redacted]	[redacted]
ICER	**£278,471 per DALY averted**	

The company conducted deterministic sensitivity analyses to explore variations in estimates of disability weights, starting age and time horizon, number of implants per year, and societal costs. The ICERs varied between £97,624 and £727,143 in these sensitivity analyses. No

probabilistic sensitivity analysis is reported. This represents a very limited exploration of uncertainty. In particular, the CS does not present any sensitivity analysis over the parameters that reflect treatment effectiveness in the model or the methods and assumptions used to derive them.

Commentary on the robustness of submitted evidence

Strengths

- The clinical effectiveness evidence base comprises four multi-centre double-blind RCTs including approximately 340 patients in total, plus a long-term retrospective observational study of 115 patients providing data on safety and efficacy up to eight years of afamelanotide use. Two of the RCTs included a small number patients from UK expert porphyria treatment centres (amongst other countries). The ERG believes that all relevant clinical effectiveness studies have been included in the CS.
- The clinical effectiveness studies measured a range of outcome measures of relevance to patients and clinicians, including: time patients are able to spend in sunlight without experiencing pain or with only mild pain; phototoxic reactions; adverse events and HRQoL (though not HRQoL of carers and family members). There do not appear to be any clinically important outcome measures that have not been included in the study programme.
- Recorded adverse events were mild to moderate in severity and the level of patient drop-out from treatment (where data are reported) was low (less than 10%).
- The company's economic model, though simplistic, is appropriate for the condition, and some, though not all, of the assumptions are reasonable.

Weaknesses and areas of uncertainty

- Full methodological details of the included clinical effectiveness studies are lacking and this prevents a full assessment of quality by the ERG. In particular, it isn't clear whether randomised study groups were comparable at baseline in all studies, or whether concealment of random allocation to study groups was adequate, indicating the potential for selection bias. It is also unclear whether there is selective reporting of outcome measures, as for most studies, protocols and clinical study reports were not supplied to the ERG (though requested). The influence on the study results of apparent unblinding

due to increased skin pigmentation in some patients who received afamelanotide is not entirely clear.

- Information is lacking on how sample sizes were estimated and on how missing data were handled in the trials.
- Meta-analysis of the studies was not conducted in the CS (though pooling of EPP-QoL results was done to inform the economic model – see below), rather, a narrative summary of the individual studies was presented. The ERG considers that meta-analysis would not be advisable given clinical and methodological heterogeneity between the studies.
- Due to concerns by the EMA about the methodological conduct of two of the RCTs (studies CUV030 and CUV029), the sole pivotal RCT to inform the decision to grant a marketing application was the CUV039 trial. The CUV039 trial was conducted in seven expert centres in the USA and therefore it does not include patients taking afamelanotide in the UK. There are differences in latitude and hence potential exposure to sunlight over the course of a year between the USA and Europe which is likely, amongst other things, to influence the amount of time patients can spend outdoors during the day (the European centres were at higher latitudes). The mean and median time that patients in the CUV039 trial were able to spend in sunlight with no or mild pain cannot therefore necessarily be generalised to England and the UK as a whole.
- Although an improvement in HRQoL was reported in the studies, the interpretation of the clinical significance of this is unclear. The EPP-QoL instrument was devised specifically for the afamelanotide study programme [redacted]. HRQoL, as assessed by EPP-QoL with results pooled for studies CUV029, CUV030, and CUV039, is the clinical outcome effectiveness measure that informs the company's cost-effectiveness analysis.
- The ERG has insufficient information about how the EPP-QoL results from the three trials, CUV029, CUV030 and CUV039 were analysed and pooled for use in economic evaluation. There is a lack of clarity over whether intention to treat (ITT) datasets were used, the number of patients included from each trial and whether the method of pooling accounted for clustering.
- The company's economic model relies on a definition of mild, moderate and severe EPP by division of the EPP-QOL scale into thirds. This is arbitrary and we cannot assess if it is consistent with the disability weights attached to these levels of severity in the DALY calculations.

- The company's use of a single time point (120 days) to represent disease severity over a whole year is simplistic and is likely to have biased DALY estimates in favour of afamelanotide. It does not account for baseline imbalance in trial arms in EPP-QoL estimates (which are amplified when extrapolated over time). In addition, we note that data at 180 days were collected in the three included trials, but not used for the economic evaluation (the largest between-arm difference in mean EPP-QOL was observed at 120 days in CUV039 and CUV029).
- The ERG notes that the analysis of uncertainty presented in the CS was inadequate. No probabilistic sensitivity analysis was reported and there was no attempt to estimate the extent or consequences of uncertainty over the effectiveness parameters and assumptions.
- Contrary to the company, the ERG believes that QALYs are a conceptually appropriate metric for quantifying the value of health effects of afamelanotide for patients with EPP, as they are for other lifelong and chronic disabling conditions and that satisfactory methods for estimating QALY gain are available. It is considered that these methods, although not perfect, are superior to the methods used by the company to estimate DALYs averted. A QALY based analysis is presented by the ERG (see Summary of additional work undertaken by the ERG below).

Summary of additional work undertaken by the ERG

The ERG made adjustments to the company's model to estimate cost-utility, generating costs per QALY. Two alternative analyses have been conducted:

- A simple QALY version of the company model by assuming utility values for mild, moderate and severe disease equal to 1 minus the disability weights used in the company's basecase proxy of [redacted]
- An ERG base case analysis, in which we estimate QALYs from mean DLQI results at 0, 60, 120 and 180 days from study CUV039 mapped to EQ-5D scores.

The simple QALY model was intended as a platform to investigate alternative scenarios and sensitivity around the company's base case. This demonstrated that the company's incremental cost per DALY averted of £278,471 (£278,386 per QALY gained after a small correction by the ERG) is likely to be an underestimate. With correction for baseline differences in EPP-QOL, the ICER rose to £454,800 per QALY gained. It rose further, to £779,657 per QALY gained, when

we assumed that treatment benefits would gradually decline over a 2 month period from month 6. Use of utility estimates from the literature for the same proxy condition as in the company base case, further increased the estimated ICER to over £1.7 million per QALY gained.

We conducted a 'best case' analysis, which combined the most favourable scenario that we had tested (our simple QALY conversion of the company's base case model), with the most favourable sensitivity analysis limits for treatment effects, disability weights and mean number of implants used for costing. This brought the ICER down to £151,212 per QALY gained. The ERG does not believe that this or any of the other ICER estimates based on our simple adaptation of the company model are plausible.

Our preferred set of analyses were based on mean DLQI data from the pivotal study (CUV039) mapped to EQ-5D utility values using a published algorithm. Results from this model were less favourable, and did not fall below £1.1 million per QALY gained in any of the scenarios that we tested. The ERG believes that this set of estimates is more plausible than the company's approach.

Budget impact in the first year varied between [redacted] and [redacted] depending on variations in the estimate of EPP prevalence in England.

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from CLINUVEL UK on the clinical effectiveness and cost effectiveness of afamelanotide for erythropoietic protoporphyria (EPP). It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the manufacturer by the ERG via NICE on 1st September 2017 (early clarification questions) and on 12th September. Sets of responses from the company via NICE were received by the ERG on 12th September, 26th September and 2nd October 2017, and these can be seen in the NICE HST committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The ERG considers that the CS provides a clear and accurate overview of the genetic disorder, erythropoietic protoporphyria (EPP, CS, pp15-17). The disease is caused by impaired function of the enzyme ferrochelatase (FECH) which disrupts the haem biosynthesis pathway, resulting in the accumulation and storage of protoporphyrin IX (PPIX), predominantly in patients' skin and liver. PPIX is a phototoxic molecule, which reacts after brief exposure to visible light (the most reactive wavelength being at 408 nm; CS, p 9). Upon exposure to light, PPIX in the capillaries underneath the skin reacts to create oxygen radicals which attack capillary walls, causing onset of erythema, oedema and an intense burning sensation which can last for days or weeks.[1] This can also lead to second degree burns (CS, p 9). During a reaction, any subsequent exposure to light, as well as heat variation, pressure and air movement, can exacerbate and prolong symptoms. Cumulative exposure to light has a 'priming' effect and after only a few minutes of daily light exposure severe phototoxicity may be triggered (CS, p 15).

EPP is described as a disease that requires lifelong and cyclical management. Phototoxicity is most predominant in the UK, from February to November each year, during the period of highest light intensity (CS, p 66). Phototoxic reactions are unresponsive to regular analgesics or

any other medication and require the recovery of damaged tissue (i.e. time) prior to their subsidence.

The CS states that "both environmental and artificial light sources (particularly modern 'energy saving' globes) can cause anaphylactoid and phototoxic reactions" (CS, p 9). Clinical experts advising the ERG commented that only a minority of patients experience phototoxic reactions resulting from exposure to artificial light sources. The clinical experts also highlighted that there is a variation in severity of disease amongst patients, where some are able to cope with light exposure for longer periods (e.g. up to an hour) before suffering any reaction. On average, however, the majority of UK patients will start to experience pain within 15-20 minutes of light exposure outdoors between early March and October.

2.2 Critique of company's overview of current service provision

The company correctly state that no NHS guidance has ever been issued for EPP and suggest that current standard care is limited to patients avoiding sunlight. Upon discussing treatment options with the ERG's clinical advisors it was noted that beta-carotene compounds (taken orally, on average eight tablets daily) seem to provide some protection for a minority of people. However, it can sometimes be hard to obtain beta-carotene in the UK and it has to be sourced from overseas (e.g. the USA). The ERG's clinical advisors also described the use of narrow-band ultraviolet beta (UVB) phototherapy (e.g. 3 x weekly for 4-6 weeks or variations of), which has, according to clinical experience and a few 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. The ERG experts state that the use of Dundee cream can also slightly increase the time patients can be exposed to sunlight. However, it tends to be reserved for particular outdoor occasions rather than being used daily. This is because large volumes need to be applied, and it can adhere to clothing. In addition, these creams have an appearance similar to cosmetic make-up and are therefore not always acceptable to some patients (e.g. younger males). They can also be difficult to get from general practitioners on prescription. Vitamin D and calcium are recommended (though patients may not always take them regularly) and this would not change if afamelanotide is prescribed.

The current treatment options discussed by the ERG experts above were not mentioned in the CS (apart from a brief reference considering beta-carotene as part of the cost effectiveness model (CS Table D3, p74)).

The ERG's clinical advisors state that there is little evidence for the above current treatments and that helping patients to manage their exposure to light is a key part of management. Patient experience of the currently available treatments is discussed in the consultee submissions to NICE (described in section 7 of this report).

2.3 Critique of company's definition of decision problem

Population

The population described in the company's decision problem is adults (CS Table A1, p. 11) which matches that specified in the final scope issued by NICE. The age range of adults is not mentioned in the decision problem section of the CS but the inclusion/exclusion criteria in the summary of methodology for the RCTs (CS table 5, pp 48 24) state adults aged between 18-70 years.

The CS states that there are 394 known patients in the UK with EPP based on published estimates (CS p 9). The CS also states separately that there are [redacted] and an estimated current total of 513 patients in England based on disease prevalence (CS, p 9). Furthermore, it is suggested that there are [redacted] patients eligible for treatment (CS, p 91), though it does not mention the proportion of patients in whom afamelanotide may be contraindicated (such those over the age of 70 years or below 18 years old, pregnant women or those with liver disease). Although this figure is higher than that previously cited, the ERG clinical experts consider that this figure is generally correct and would probably not vary by around 100 patients either way.

Intervention

The intervention in the decision problem (CS Table A1, p 11) is stated as afamelanotide (16mg), delivered as a controlled release injectable implant. Afamelanotide has a European marketing authorisation from the European Medicines Agency (EMA), granted in December 2014 under "exceptional circumstances" (CS, p 53). The European Public Assessment Report (EPAR, p 89)

[2] describes the discussions between the company and the Committee for Medicinal Products for Human Use (CHMP) regarding these circumstances, namely the fact that EPP is a rare condition and that comprehensive data on the efficacy and safety under normal conditions of use could not be generated, resulting in the granting of a marketing authorisation under exceptional circumstances.

The afamelanotide Summary of Product Characteristics (SmPC) states that the recommended dose of afamelanotide is 16mg, delivered as a subcutaneous implant (1.7 cm in length x 1.5 mm in diameter), administered every two months prior to expected and during increased sunlight exposure e.g. spring to early autumn). Three implants a year are recommended with a maximum of four per year [CS table A2, p 12]. The SmPC states that the safety and efficacy of afamelanotide has not been established for patients under 18 or over 70 years of age, or during pregnancy or lactation (SmPC, pp 3-5). It also states that long term safety data (after two years) have not been evaluated (SmPC, pp 3-4).

Comparators

The only comparator included in the scope and the decision problem is best supportive care. The CS does not explicitly define best supportive care within the decision problem (CS Table A1, p 11), but the ERG assumes that it would include the various current management options that are described above (section 2.2). The CS states that there are no alternative treatments or comparators used or in development at present (CS, p 10).

Outcomes

The outcomes specified in the NICE scope are duration of tolerance to sunlight and other forms of visible light; phototoxic reactions; change in melanin density; adverse effects of treatment; health-related quality of life (HRQoL) (for patients and carers); and mortality. These outcomes are included in the company's decision problem (CS Table A1, p11) although the CS does not explicitly report mortality and does not report HRQoL for carers of people with EPP (due to lack of relevant information). Section 3.1.5 of this report provides a description and critique of the company's assessment of the outcome measures.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The company reported a single search for clinical effectiveness evidence, economic evidence, and resource identification and valuation (CS section 9.1 and CS Appendix 1, Appendix 3, and Appendix 4). PubMed was the sole external database searched, with the date of the search up to 15th July 2017. The company justifies only searching this database and not Embase, Medline In-Process and the Cochrane Library (as required by NICE) as it is the sole supplier of afamelanotide and is aware of all clinical research undertaken on it. The ERG acknowledges that an orphan drug/first in class product is unlikely to have been evaluated outside of the company, however the expectations of a systematic literature review have not been fully met. The ERG considers that free text search terms used in the search strategy are appropriate. The quantity of references identified from the search was not recorded nor tabulated into a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart as is customary in health technology assessment reports. The ERG requested this flow-chart for transparency but the company declined due to the burden of the administrative request (clarification response question A11, 26/09/17)). The company did not conduct separate searches for literature on adverse events, however, it is likely that any available evidence on adverse events would have been identified by the company's main search and from their in-house pharmacovigilance database (CS, Appendix 2).

The company cross-checked their internal reference library against their PubMed search results. The ERG considers it would have been informative as a minimum to quote which sources were used in the weekly current awareness alerts that feed the in-house company database. The company also reported searching for ongoing trials on the National Institute of Health clinicaltrials.gov and Eudract (European Clinical Trials Database).

The ERG elected to search Embase, Web of Science, The Cochrane Library, Econlit, and the NHS economic evaluation database (NHS EED) for any additional references relating to afamelanotide. In addition, the ERG searched the following additional databases: clinicaltrials.gov, UK Clinical Trials Gateway (UKCTG), ISRCTN, and the WHO International Clinical Trials Registry Platform (WHOICTRP). The 2017 proceedings of the International

Congress on Porphyrins and Porphyrias was also checked by the ERG. The results of the ERG searches were screened to identify any additional relevant data. Only one relevant publication was identified, a conference abstract of a cost effectiveness analysis of afamelanotide [3]. The ERG discusses this study further in section 4.2 of this report.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The inclusion criteria for the company's systematic review of both published and unpublished studies are clearly stated in the CS, (tables C1 and C2, p 22-23). No exclusion criteria were stated. The inclusion criteria stated reflect the decision problem for population and intervention.

As stated above (section 3.1.1) a PRISMA flow diagram to show the numbers of records retrieved, included or excluded at each stage of the literature review was not included. It was stated that a total of 18 peer-reviewed journal articles were identified. However, there were only four citations to these retrieved articles in the subsequent paragraphs of the CS. The ERG requested a full reference list for these 18 articles, with stated reasons for any exclusions from the submission. These have now been provided (clarification response question A12, 26/09/17). However reasons for the omissions were not stated. The ERG notes that an additional three of these 18 references were cited in later sections of the CS, however the remaining 11 do not appear to have been cited anywhere in the CS.

3.1.3 Identified studies

The CS included seven relevant studies: CUV010, CUV017, CUV029, CUV030, CUV039 (see Table 1) a long-term treatment observational study, and a post authorisation safety study CUV-PASS-001 (Table 5). Some of these studies (CUV017 and CUV030), are currently unpublished although data were presented for these studies at the International Congress of Porphyrins and Porphyria 2013[4] and the 19th European Association of Dermatology and Venerology Congress, 2010 respectively.[5]

Table 1 Overview of clinical effectiveness studies in the company submission

Trial	CUV010 (Harms et al. 2009)[6]	CUV017 (unpublished)	CUV029 (Langendonk et al. 2015)[7]	CUV030 (unpublished)	CUV039 Langendonk et al. (2015)[7]
Trial design	Phase II, open label, single arm	Phase III, double blind RCT, alternating cross-over every 60 days	Phase III, double-blind RCT	Phase III, double-blind RCT	Phase III, double-blind RCT
Location	Switzerland	Europe/ Australia	Europe	USA	USA
Study duration	4 months	12 months	9 months	6 months	6 months
Number of patients	N=5 No withdrawals/drop outs	N=100 (93 treated) Withdrawal/drop outs unclear	N=76 (74 treated) Withdrawal/drop outs =5	N=77 (77 treated) Withdrawal/drop outs =5	N=94 (93 treated) Withdrawal/drop outs =6
Intervention (n in arm)	Afamelanotide (20 mg) (n=5)	Afamelanotide (16 mg) (n=93)	Afamelanotide (16 mg) (n=38)	Afamelanotide (16 mg) (n=39)	Afamelanotide (16 mg) (n=48)
Comparator (n in arm)	NA	Placebo (all patients received both treatments)	Placebo (n=36)	Placebo (n=38)	Placebo (n=45)
Primary outcome measured	• Provocation response time (PRT) under standardised laboratory controlled conditions	• Frequency of days of pain (by severity)	• Hours of direct sun exposure on days with no pain / mild pain (10:00 to 15:00 hrs) per subject (median)	• Hours of direct sun exposure on days with no pain / mild pain (10:00 to 15:00 hrs) per subject (median)	• Hours of direct sun exposure on total no of pain free days (10:00 to 18:00 hrs) per subject (median/mean)
Secondary outcomes measured	• Melanin density • HRQoL (SF-36 form) • Phototoxic reactions • Safety	• Hours per day of sunlight exposure • HRQoL (SF-36 form)	• Hours of direct sun exposure on days with no pain / mild pain (10:00 to 20:00 hours). • Mean number of phototoxic episodes per subject (+ mean	• Hours of direct sun exposure on days with no pain / mild pain (10:00 to 20:00 hours). • Time in direct sunlight when no or mild pain.	• Hours of direct sun exposure on days with no pain / mild pain (10:00 to 18:00 hours). • Days of 'some' sun exposure on days with no pain / mild pain (10:00 to 18:00 hrs) per subject (median/mean)

Trial	CUV010 (Harms et al. 2009)[6]	CUV017 (unpublished)	CUV029 (Langendonk et al. 2015)[7]	CUV030 (unpublished)	CUV039 Langendonk et al. (2015)[7]
			severity of episodes per subject) • Duration of phototoxicity (days) • HRQoL (EPP-QoL 15 form).	• HRQoL (EPP-QoL 15 form),	• HRQoL using -(EPP-QoL 15 form and revised 12 question form (post hoc)) and generic DLQI

NA = Not applicable; Dermatology Life Quality Index (DLQI)

Table 2 Overview of observational studies in the company submission

Name	Design	Number of patients	Intervention	Duration of study	Country/region	Outcomes measured
Biolcati et al. (2015)[8]	Longitudinal observation study	115	Afamelanotide 16mg	Up to 8 years	Italy, Switzerland	Primary Outcome • HRQoL (EPP-QoI) • Compliance + dropout Secondary outcome • Safety
Langendonk (2017) [9] CUV-PASS-001	Post-Authorisation Disease Registry Safety Study (incorporates European EPP Disease Registry (EEDR))	150 (as of Aug 2017)	Afamelanotide 16mg	On-going	International	Primary Outcome • Safety Secondary Outcome • HRQoL (EPP-QoL) (18 question form), • Length of severity of phototoxicity reported

- CUV010 was a four month phase II, open label, single am study carried out in Switzerland on five patients. This study compared afamelanotide (20 mg) versus placebo on the time to appearance of provoked symptoms; melanin density, phototoxic reactions and safety.[10]
- CUV017 was a 12 month phase III, crossover RCT, carried out in Europe and Australia, on 100 patients (93 treated). The study compared the effect of afamelanotide (16 mg) versus placebo on the frequency of days of pain (by severity); number of hours per day of sunlight exposure, melanin density, and HRQoL using the short form survey-36 (SF-36). The EPAR states that this trial was originally intended to be submitted as a pivotal study for marketing authorisation in 2009. However, the CHMP deemed that the crossover design was unsuitable and that pivotal, confirmatory parallel group studies should be run.[2] This study is unpublished.
- CUV029 was a nine month phase III, double blind RCT, carried out in Europe on 76 patients (74 treated). The study compared the effect of afamelanotide (16 mg) versus placebo on the number of hours of direct sun exposure on days with no pain and on days with no pain or mild pain (between 10.00-15.00 hours or 10.00-20.00 hours; number of phototoxic episodes; duration of phototoxicity, HRQoL using the Erythropoietic protoporphyria questionnaire (EPP-QoL), and adverse events.[7] HRQoL results from this study are used to inform the company's cost-effectiveness analysis. The trial was conducted between January 2010 and May 2011.
- CUV030 was a six month phase III, double blind RCT, carried out in the USA on 77 patients. The study compared the effect of afamelanotide (16 mg) versus placebo on the number of hours of direct sun exposure on days with no pain / mild pain (between 10.00-15.00 hours or 10.00-20 hours); number of phototoxic episodes; duration of phototoxicity and HRQoL using the EPP-QoL questionnaire. HRQoL results from this study are used to inform the company's cost-effectiveness analysis. This study is unpublished.
- CUV039 was a six month phase III, double blind RCT, carried out in the USA on 94 patients (93 treated). The study compared the effect of afamelanotide (16 mg) versus placebo on the number of hours of direct sun exposure on days with no pain / mild pain (between 10.00-15.00 hours or 10.00-20 hours); number of days of "some" sun exposure on days without pain or with no pain / mild pain (between 10.00-20.00 hours) and HRQoL using a 12 item revised version of the EPP-QoL and the Dermatology Quality

Life Quality Index (DLQI).[7] Some of the design characteristics of this trial (e.g. the length of treatment) were informed by experience gained from earlier trials, including CUV029. The trial was conducted between May 2012 and July 2013 with inclusion restricted to two months to allow the trial to be performed mainly during the summer months[7]). The EMA considered this trial to provide pivotal data for the assessment of efficacy of afamelanotide and was robust enough to support the marketing authorisation (however, they did not consider that studies CUV029 or CUV030 were pivotal due to concerns about their conduct; see section 3.1.6.5 of this report for further details).[2] HRQoL results from this study are used to inform the company's cost-effectiveness analysis.

The two long-term observational studies included are:

- Biolcati et al.[11] followed up 115 patients (retrospectively) treated in Italy and Switzerland who had been treated for up to eight years between 2006 and 2014, to assess HRQoL (EPP-QoL), melanin density, adverse events and compliance and dropout.
- Langendonk et al.[9] describes the post authorisation disease registry safety study (PASS) which was set up as a condition of the European licensing authorisation. Afamelanotide can only be prescribed by designated and trained porphyria centres according to a protocol (supplied as an appendix to the CS). Centres are required to monitor patients and the company to submit yearly reports. As of May 2017 104 Dutch patients have been included in the treatment programme where patients have received up to five implants (CS p 39, [9]). The European EPP Disease Registry (EEDR) collects safety and effectiveness data from European Centres in the PASS. The first safety data from the EEDR have been reported to the EMA, with subsequent annual reports to be submitted in December each year.

The CS reports details of the included studies including the location, study design, study duration, sample size, inclusion/exclusion criteria, method of randomisation and blinding, intervention and comparator, statistical tests and outcomes. The numbers of patients discontinuing treatment are reported in most studies, although it was stated to be not applicable in CUV017. The CS stated that statistical tests were reported, however the summary tables contain no details of power/sample size calculations. Participant characteristics at baseline are not given for all studies and the ERG requested clinical study reports and trial protocols from the company, though the company chose not to provide these.

No ongoing studies have been listed in the CS apart from the ongoing PASS study mentioned (CUV-PASS-001).

The ERG believes that all relevant studies have been included in the CS and all of those that have been included meet the stated inclusion criteria.

3.1.4 Description and critique of the company's approach to validity assessment

The company assessed the quality (using the NICE recommended criteria) of studies CUV029, CUV030, and CUV039 (CS, Table 7) but not studies CUV010 or CUV017. The company provided a brief critical appraisal of the long-term observational study by Biolcati et al.[11] (CS, Table 8). Table 3 below provides the company's quality assessment judgements for studies CUV029, CUV030, and CUV039 and the ERG's quality assessment judgements for these three studies, plus study CUV017 (the ERG requested the company to provide a critical appraisal of this study but the company said that this was not appropriate as it was a cross-over trial. The ERG contends that critical appraisal criteria are applicable to cross-over RCTs as well as parallel-group RCTs and has conducted a critical appraisal of this study based on the information given in the CS).

Table 3 Company and ERG assessment of trial quality

Study Name	CUV017		CUV029		CUV030		CUV039	
Critical appraisal criterion	**Judgement**							
1. Was the method used to generate random allocations adequate?	**CS:**	Not stated	**CS:**	Yes	**CS:**	Yes	**CS:**	Yes
	ERG:	Yes	**ERG:**	Yes	**ERG:**	Yes	**ERG:**	Yes
	ERG comment: The CUV017 trial was not included in critical appraisal table C7 p 41. However, in the CS [table C5 p 28], it is stated that "each patient was assigned to a treatment arm according to a computer generated randomisation list. For each study site, patients who satisfied the inclusion/exclusion criteria were allocated patient randomisation numbers sequentially and chronologically, based on the timing of their attendance at the clinic for the first study implant". This method was also used for CUV029 and CUV030 [CS page 31 and page 34], however for CUV039, the randomisation process differed. Here subjects were randomised on a site basis to maintain a geographic/climatic balance between treatment arms [CS p 36]. The randomisation method used a small block size (four) to ensure that treatment was balanced within study sites. Five individually sealed sets of computer-generated randomisation codes (each set containing 48 randomised numbers) were provided to the pharmacy. The study pharmacist chose one of the five sealed envelopes and the selected randomisation list was used to randomise the subjects in this study.							
2. Was the allocation	**CS:**	Not stated	**CS:**	Yes	**CS:**	Yes	**CS:**	Yes

Study Name	CUV017		CUV029		CUV030		CUV039	
Critical appraisal criterion	**Judgement**							
adequately concealed?	**ERG:**	Unclear	**ERG:**	Unclear	**ERG:**	Unclear	**ERG:**	Unclear
	ERG comment: The CS does not explicitly state whether procedures were followed for concealment of random allocation. The randomisation procedures used in CUV039 suggest that allocation may have been concealed, but it is not completely clear: "Five individually sealed sets of computer-generated randomisation codes (each set containing 48 randomised numbers) were provided to the pharmacy. The study pharmacist chose one of the five sealed envelopes and the selected randomisation list was used to randomise the subjects in this study" (CS page 36). For study CUV017 Table C5 [page 28] does not state whether any procedures to conceal allocation were used. It is stated however, that all sponsor, investigator site and monitor staff were blinded to the treatment code except the unblinded pharmacy monitor; pharmacy staff preparing treatments and statistician preparing randomisation. In studies CUV029 and CUV030 it is stated that the randomisaton code was kept in a sealed code break envelope. However, this appears to be reserved for emergencies in the event that the blinding needed to be broken, rather than a process for concealing the allocation of patients during enrolment.							
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	**CS:**	Not stated	**CS:**	Yes	**CS:**	Yes	**CS:**	Yes
	ERG:	Unclear	**ERG:**	Unclear	**ERG:**	Unclear	**ERG:**	Unclear
	ERG comment: Some baseline data are provided in the journal article for CUV029 and CUV039.[7] The data in this article shows a difference in the percentage of patients at baseline with Fitzpatrick type 1 skin (never tans, always burns) between the afamelanotide and placebo groups (16% vs 33%) in study CUV029. A similar difference is not observed in study CUV039 (27% vs 22%, respectively). The CS states that "Due to the limited potential sample size (i.e. orphan indication), it was not possible to actively control groups at baseline. At no point in the evaluations of these studies (including by EMA) was concern raised on this issue" [Table C7, page 41]. It is not clear to the ERG exactly what is meant by "actively control" in this context. In principle, adequate randomisation should ensure an even distribution of patient characteristics between trial arms, with any notable differences occurring due to chance. These can be adjusted for in statistical analysis of the outcome variables. The CS does not state if any adjustment was made for any instances of imbalance. Full baseline data for the other trials are not given in the CS and the ERG therefore requested these from the company (clarification response question A5, 02/10/17). The company did not supply these data but commented that there is no evidence that gender, age, skin type or the concept of race have any impact upon the safety or efficacy of afamelanotide. Expert clinical advice to the ERG suggested that it is reasonable to assume that skin type does not necessarily influence the effects of afamelanotide since the effectiveness of the treatment is unlikely to rely only on increases in melanin density.							
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not	**CS:**	Not stated	**CS:**	Yes	**CS:**	Yes	**CS:**	Yes
	ERG:	Yes	**ERG:**	Yes	**ERG:**	Yes	**ERG:**	Yes
	ERG comment: All the trials are described as being double-blind. However, in the journal publication of the CUV029 and the CUV039 trials[7] it is stated that "the increased skin pigmentation in participants who received afamelanotide partially unblinded the trial" (p 53). This is not mentioned in the CS and presumably it was encountered in the other trials. The risk of patients being unblinded to the treatment due to the tanning effect of afamelanotide was acknowledged by the							

Study Name	CUV017		CUV029		CUV030		CUV039	
Critical appraisal criterion	**Judgement**							
blinded, what might be the likely impact on the risk of bias (for each outcome)?	company (clarification question response A2, 02/10/17). They stated that this issue had been addressed by the CHMP. It was considered that the beta-carotene that was evaluated in EPP patients causes tanning with no treatment effect and therefore does not translate in a change in the EPP patient's behaviour (in terms of their willingness to expose themselves to sunlight). It is not clear to the ERG if the statement is referring to beta-carotene taken by patients in the afamelanotide trials, or patients more generally. The point seems to be that tanning effects, whether caused by afamelanotide or beta-carotene, do not necessarily influence patient sun exposure behaviour.							
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	**CS:**	Not stated	**CS:**	No	**CS:**	No	**CS:**	No
	ERG:	Unclear	**ERG:**	No	**ERG:**	No	**ERG:**	No
	ERG comment: Information on patient drop-out between study groups CUV017 was unavailable from CS table C5 (p 27-30). In the remaining three trials, all patients lost to follow up were explained in the CS (table 5 pp 30-38). The CS states that study drops outs were minimal and generally balanced between the active and placebo groups. The ERG notes that the number of patients discontinuing early was twice that in the afamelanotide group than the placebo group in study CUV029 (n=4 vs n=2), but these were small proportions of the study sample (10% vs 5% respectively).							
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	**CS:**	Not stated	**CS:**	No	**CS:**	No	**CS:**	No
	ERG:	Unclear	**ERG:**	Unclear	**ERG:**	Unclear	**ERG:**	Unclear
	ERG comment: Due to the absence of detailed study protocols (apart from CUV039 which was available as an appendix to the journal publication [7]), it was not possible to fully assess whether additional outcomes were measured in these studies. The ERG requested detailed study protocols from the company for the studies but these were not provided.							
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?*	**CS:**	Not stated	**CS:**	Yes	**CS:**	Yes	**CS:**	Yes
	ERG:	Unclear	**ERG:**	Unclear	**ERG:**	Unclear	**ERG:**	Unclear
	ERG comment: For study CUV017 CS table 5 states that the ITT population included all treated subjects who provided at least one post-dose efficacy assessment. The protocol for trial CUV039 [7] defines ITT in the same way. The ITT definition given by the company is effectively that of a "modified ITT" analysis rather than a true ITT analysis (which would require all randomised patients to be analysed). For the other studies the analysis is described as ITT but no definition is given to enable the ERG to determine whether it was a true ITT analysis. The CS highlighted in table C7 (pp 41-42) that although ITT was used for CUV029,030 and 039, it was stated in the critical appraisal section (CS p 42) that the principle of last value carried forward was not considered appropriate to the assessment of the chosen endpoints in this indication. Due to the variable nature of sun exposure and phototoxicity from day to day, using these as endpoints where the last value carried forward would not result in meaningful results. The CS reasoned that if a patient experienced a severe phototoxic reaction and dropped out with a pain scale score of 10 then that value would							

Study Name	CUV017	CUV029	CUV030	CUV039
Critical appraisal criterion	**Judgement**			
	need to be imputed for all future assessment points - would be nonsensical. The ERG agrees with this assertion.			

The ERG's judgement concur with that of the company for some of the quality assessment criteria, namely the adequacy of randomisation procedures and the procedures for ensuring blinding of patients, care providers and outcome assessors. However, the ERG notes that afamelanotide is associated with a tanning effect and that this is likely to have led to unblinding in many patients. The company state in their clarification response that, based on experience with beta-carotene in EPP patients, skin tanning does not appear to affect patients' behaviour in relation to exposure to sunlight. The ERG agrees that unblinding due to a tanning effect might not necessarily lead to systematic differences in patients' behaviour between the study groups, although it is unclear whether study investigators would be influenced by such unblinding. The ERG also agrees with the company that there were no unexpected imbalances in drop-outs between study groups (though this information is not available for study CUV017).

The ERG disagrees with the company's quality assessment for allocation concealment, similarity of the study groups at baseline, and use of an ITT analysis. It is unclear to the ERG whether random allocation was adequately concealed in the studies as the descriptions given did not explicitly mention concealment procedures. Also, due to the absence of detailed patient baseline information in the CS it is not possible to determine whether the randomised study groups were similar at the outset of study, and there was one notable imbalance in Fitzpatrick type 1 skin between the afamelanotide and placebo groups (16% vs 33%) in study CUV029 (the company asserts that skin type does not modify the effects of afamelanotide). Furthermore, although the studies were described as using ITT analyses the precise definition of ITT is not given for all studies. The ERG notes that there is much variation in definition of ITT analyses in descriptions of clinical trials and that they do not always describe a "true" ITT analysis (i.e. all randomised patients within the groups to which they were allocated) (see section 3.1.6 of this report for description and critique of the statistical procedures in the studies).

3.1.5 Description and critique of company's outcome selection

The CS states that the company proposes no variations in outcomes to the NICE scope (CS p 11). The ERG agrees that the outcomes selected by the company match the NICE scope, apart from two exceptions:

- For the NICE scope outcome "HRQoL (patients and carers)" the CS has only provided HRQoL data for patients. Following a clarification question (clarification response question A14, 26/09/17) the company confirmed that they are not aware of any published data on the impact of EPP on the quality of life of carers, though anecdotal evidence is available with reference to Food and Drug Agency Scientific Workshop transcripts (see section 7 of this report for the ERG's summary of the consultee submissions to NICE, which includes patient perspectives).
- The CS does not report mortality, which is an outcome specified in the scope.

3.1.5.1 Outcomes specified in the NICE scope

The CS reports data for the outcomes in the NICE scope as follows.

Duration of tolerance to sunlight and other forms of visible light

Outcomes reported in the CS refer to two types of light exposure among EPP patients: voluntary exposure to natural light, including sun exposure; and exposure to artificial light under standardised laboratory test conditions (in the form of a 300W Xenon Arc Lamp), which in the CS is termed "photoprovocation". The majority of light exposure outcomes reported in the CS relate to EPP patients' voluntary exposure to natural light.

Exposure to natural light

The voluntary light exposure outcomes reported by the company are shown in Table 4. In addition to the outcomes shown in Table 4, study CUV017 assessed patients' voluntary sun exposure but the CS does not specify during which hours of the day assessments were made and only brief descriptive results are given (see section 3.3 of this report). The CS also states that in the small study CUV010 (n=5), "sun exposure" was a secondary outcome, but no further information defining this, or results, are presented in the CS.

Table 4 Voluntary light exposure outcomes assessed in the studies

Outcome	Study CUV029	Study CUV030	Study CUV039
Total hours in study in direct sunlight with no pain	Assessed 10:00 – 15:00 (5h) per day (co-primary outcome) and 10:00-20:00 (10h) per day (secondary outcome)	Assessed 10:00 – 18:00 (8h) per day (primary outcome) and 10:00-15:00 (5h) per day (secondary outcome)	Assessed 10:00 – 18:00 (8h) per day (primary outcome) and 10:00-15:00 (5h) per day (secondary outcome)
Total hours in study in direct sunlight with no pain or mild pain	Assessed 10:00 – 15:00 (5h) per day (co-primary outcome) and 10:00-20:00 (10h) per day (secondary outcome)	Not assessed	Assessed 10:00 – 18:00 (8h) per day (secondary outcome)
Total hours in study in direct sunlight regardless of pain score	Not assessed	Not assessed	Assessed 10:00 – 18:00 (8h) per day (secondary outcome) (data in EPAR only)
Total days in study "in some direct sunlight" on days with no pain [a]	Not assessed	Not assessed	Assessed 10:00 – 18:00 (8h) per day (secondary outcome; also referred to in the CS as an exploratory outcome)
Total days in study "with some sunlight" on days with no pain or mild pain [a]	Not assessed	Not assessed	Assessed 10:00 – 18:00 (8h) per day (secondary outcome; also referred to in the CS as an exploratory outcome)

[a] Phrasing of outcomes (indicated here in quotation marks) as reported in the study publication[7] is inconsistent between these two outcomes – unclear whether this is a typographic error or reflective of a material difference in how the outcomes were assessed; the ERG assumes these outcomes differ only in the degree of pain experienced, not in sunlight exposure

The majority of results relating to voluntary light exposure behaviour of EPP patients are from the CUV039 study which was conducted in the USA, and from CUV029 which was conducted in Europe. As well as being of different duration, the studies differed according to the daily times when outcomes were assessed, which were 10:00-15:00, 10:00-18:00, and 10:00-20:00. The CS does not explain these differences in the timing of exposure assessments between the trials. Although the CS designates the different sunlight exposure outcomes as "primary" and "secondary" within each study, insufficient information is reported in the CS to determine whether the primary outcomes would be any more reliable than secondary outcomes in terms of their statistical power (see section 3.1.6).

The CS provides varying descriptions of light exposure, including (amongst others) "direct sunlight exposure" (e.g. CS P 32), "direct light/sunlight exposure" (e.g. CS p 32), "light/sun

exposure" (e.g. CS p 36) or "direct light/sunlight exposure" (e.g. CS p 36). The ERG requested clarification of the exposure definitions from the company via NICE (clarification response question A6, 26/09/17). The company responded stating that the studies "evaluated the excitation of protoporphyrin IX by "visible light (>408 nm)" and that "patients were asked to expose themselves to conditions of direct light/sunlight exposure, which was the best approximation that was possible at the time of the clinical programme".

Duration of tolerance to sunlight is dependent on the amount of pain caused by light exposure. For this reason, in trials CUV029, CUV030 and CUV039 the company assessed duration of direct sunlight exposure for subgroups of patients who experienced "no pain" and "no pain or mild pain". The intensity and duration of pain and exposure to sunlight and shade were recorded daily by the patients in a diary, with the time spent outdoors being recorded in 15-minute intervals. Pain was scored on a 0-10 Likert scale. The CS describes the scale only for trial CUV017, stating score 0 was used for no pain, scores of 1 to 3 for mild pain, scores of 4 to 6 for moderate pain, scores of 7 to 9 for severe pain and 10 for worst imaginable pain. The ERG notes that the cut-off for mild and moderate pain is arbitrary, not explained by the company, and differed between the trials (CUV017, CUV029, CUV039 defined mild pain as 1-3 whilst CUV030 defined mild pain as 1-4). Full details of the Likert scale used in each trial and an explanation for the cut-off discrepancy between trials were requested by the ERG from the company via NICE (clarification response question A10, 26/09/17). The company responded that a panel of biostatisticians were consulted about defining anaphylactoid reactions and phototoxic episodes. The Likert scale was "a near approximation since EPP patients describe their ordeal as "pain" while a proper medical lexicon is lacking". However, no justification was given regarding the scoring threshold used.

The company presents sunlight exposure outcomes in terms of the total hours of exposure to sunlight during the study (i.e. the first three outcomes listed in Table 1) and the days with sunlight exposure (i.e. the last two outcomes listed in Table 1). The company calculated the light exposure outcomes based on the patients' diary records of light exposure and pain scores. The CS, study publication,[7] SmPC, EPAR[2] and company's clarification response do not clearly explain how the outcomes were calculated from the diary card data.

Total hours in direct sunlight

The ERG assumes that to obtain the first outcome listed in Table 4 the company summed the patient's sunlight exposure time in each of the 15-minute study intervals that had a maximum pain score of zero, to give the total time of sunlight exposure per patient during the study with "no pain". Similarly, for the second outcome listed in Table 4 we assume that the company summed the sunlight exposure time in each of the 15-minute study intervals that had a maximum pain score of 3 (or 4), to give the total time of sunlight exposure per patient during the study with "no pain or mild pain". The third outcome listed in Table 4 would have been calculated similarly, by summing sunlight exposure time across all 15-minute intervals irrespective of the pain score of each interval. Results of these outcomes (see section 3.3) are presented as the mean and median duration of sunlight exposure per patient.

Total days in direct sunlight

The method of calculating the final two outcomes listed in Table 4 for study CUV039 is not reported in the CS or study publication[7] and is not clear to the ERG. The EPAR[2] (p. 50) implies that these outcomes were calculated for each subject by dividing the total time in the study spent in direct sunlight (without or with mild pain) by the number of days each subject was in the study. This would result in fractional outcomes <1.0 since the denominator would be larger than the numerator, but this does not agree with the format of the reported outcomes, which are expressed in days (section 3.3). The wording of these outcomes is inconsistent in the study publication (see footnote to Table 4) which adds ambiguity to the interpretation.

Photoprovocation

Photoprovocation is a test of the duration of tolerance of artificial light under standardised laboratory test conditions (in the form of a 300W Xenon Arc Lamp) in which the time taken to provoke minimal symptoms is recorded. Advantages of photoprovocation testing are that exposure conditions can be clearly controlled (which is not possible with patients' voluntary outdoor exposure behaviour and heterogeneous weather conditions), and patient exposure to the light stimulus can be ensured (i.e. behavioural avoidance of light exposure does not occur). Disadvantages of photoprovocation testing are that it is unclear how generalisable the exposure conditions are (specific areas of the body are assessed rather than all exposed skin areas); and photoprovocation does not capture patients' behavioural response to light exposure which could be an important determinant of compliance with therapy.

Photoprovocation is reported in the CS only for the small (n=5) study CUV010 (CS p 26), in which photoprovocation, carried out on the dorsal surface of the hands, was the primary outcome, but no further information defining this, or results, are given in the CS, although results are reported in more detail in a publication by Harms et al.[12]

According to publications, photoprovocation was also tested in small subgroups of patients in study CUV030[13] and study CUV039.[2 7] The photoprovocation tests were conducted on subsets of patients: n=15 in CUV030 (but only six completed testing); and n=21 in CUV039 (number completing testing not reported). However, no rationale is given in the CS or study publications for the patient subgroup selection.

The CS does not provide any explanation of why photoprovocation was conducted and the very limited descriptive results given suggest that the company does not view this as being an important outcome for the current appraisal.

Phototoxic reactions

Phototoxic reactions are reported in the CS for five studies (CUV010, CUV017, CUV029, CUV030, and the ongoing study CUV-PASS-001). Phototoxic reactions are reported for the CUV039 trial in a publication by Langendonk et al.[7] but these data are not mentioned in the CS.

The outcome relating to phototoxicity, as reported in the CS, is “pain”. The company specifies “pain” within quotation marks without defining explicitly what they mean by “pain”. However, in the NICE “Response to consultee and commentator comments on the draft remit and scope (pre-referral)” the company had stated in a comment to NICE that “…patients have an ingrained fear for an episode of anaphylactoid reaction, burns, oedema and scarring, causing an unspeakable internal ordeal often poorly – and by lack of a better word – expressed as “pain”…”. This statement suggests that the “pain” outcome reported in the CS somehow captures other aspects of phototoxicity such as burns and oedema.

The CS does not report any specific outcomes for non-pain aspects of phototoxicity (e.g. burns, oedema, rash, scarring). The ERG understands from clinical experts that pain is a significant burden to patients but it is unclear to us whether the other aspects of phototoxicity are also

important to patients relative to the pain and, if so, whether the "pain" outcome adequately captures the full burden of phototoxic effects.

Pain was assessed on the 11-point Likert scale described above (see Exposure to natural light above). In reference to trial CUV039, the afamelanotide EPAR[2] states that "the **number** of phototoxic reactions was determined by counting the number of episodes on which patients report a Likert score of 4 or more for 1 or more consecutive days. The **total severity** of an individual phototoxic reaction was determined by adding the Likert scale severity scores for all days in an individual phototoxic reaction. The **maximum severity** of a phototoxic reaction was determined by the highest daily Likert scale score that occurred during that phototoxic reaction" (p 51).

The CS states for study CUV017 that "the primary efficacy objectives were to determine whether afamelanotide could reduce the number and severity of phototoxic reactions in patients with EPP" (CS p 27). For study CUV029 the CS states that the primary objective was modified when preparing the statistical analysis plan, with the modified objective being "to determine whether afamelanotide can enable patients to expose themselves to direct sunlight during the most intense periods of sunlight during the day in spring and summer" (CS p 30). This outcome recognises that without sunlight as a causative factor no pain or phototoxic reaction is possible. For study CUV030 the CS states that "during the initial stages of analysis, and in order to determine the clinically relevant impact of afamelanotide treatment, the sequence of the study objectives was adapted to assess whether the study subjects are able to modify their lifelong conditioned behaviour. This was assessed by evaluating time spent in direct sunlight while remaining pain free or experiencing only mild pain, during spring and summer months" (CS p 34). For study CUV039 the stated objective was "To determine whether afamelanotide can enable EPP patients to expose themselves to light/ sunlight without incurring phototoxic reactions and pain" (CS p 36).

Change in melanin density

The CS states that melanin density was measured by spectrophotometry (reflectometry according to Harms et al.[12]) but no technical details of the method are reported. The change in melanin density is mentioned briefly in the CS only for the small (n=5) study CUV010. A journal publication by Harms et al.[10] gives further melanin density results for study CUV010. Change in melanin density was also assessed in the crossover study CUV017 (according to the EPAR)

and in the long-term observational study (Biolcati et al.[11] supplemental appendix) but these assessments of melanin density are not mentioned in the CS. The CS does not explain the mode of action of afamelanotide, other than that it is a melanocortin-1 receptor (MC1R) agonist, and the reliability of melanin density as a clinical effectiveness outcome is not discussed in the CS. The ERG notes that EPP can occur in some people who have dark skin[14] and that melanin density is cited in the afamelanotide EPAR as an indicator of pharmacodynamics, rather an effectiveness outcome (EPAR section 2.4.3).

Adverse events

The adverse events section (CS Table C10, pp 48-50) reproduces the list of adverse events given in the SmPC which is a summary list and is not explicit about which of the studies provided source data. The CS also provides limited information on adverse events for studies CUV010, the long-term observational study (safety reported anecdotally from the study publications[11 15]) and the ongoing study CUV-PASS-001. Detailed information on adverse events in trials CUV029 and CUV039 is available in a journal publication (Langendonk et al.[7]) but is not reported in the CS. Brief information on adverse events in trial CUV030 is given in a document by CLINUVEL 2010[16] but this is also not mentioned in the CS.

HRQoL

HRQoL was measured in all seven of the included studies, but the information provided in the CS is descriptive and very brief for most of the studies. Three HRQoL instruments were employed. These were the Short-Form 36 (SF-36) in studies CUV010 and CUV017; and the Dermatology Quality Life Quality Index (DLQI) and an EPP-specific questionnaire (EPP-QoL) in studies CUV029, CUV030 and CUV039 (CS p 71). The EPP-QoL was also employed in the long-term observational study (Biolcati et al.[11]) and in the monitoring study CUV-PASS-001 (CS Table C5). However, the CS states that the SF-36 "did not prove to be useful for the assessment because most patients reported a very high quality of life from baseline assessments onwards, a finding contrary to the published literature" (CS p 71). The CS also states that that the SF-36 and the DLQI are not suitable for the quantification of the humanistic burden of EPP and hence a new disease-specific questionnaire, the EPP-QoL, was designed by expert porphyria physicians globally together with the sponsor (CS pp 9 & 71).

According to the CS, a 15-question version of EPP-QoL was developed (CS p 71), but the publication reporting results for studies CUV029 and CUV039 (Langendonk et al.[7]) presents a

12-question version of EPP-QoL. It is not clear in the CS which version of EPP-QoL was used in each study. In several places in the CS the company mentions that the [redacted]

The CS appears inconsistent in its criticism of the DLQI, since a survey of EPP patients by Holme et al.[17] which utilised the DLQI, is cited as evidence that EPP has a marked impact on patients' quality of life (CS pp 15-16). Although DLQI is a generic instrument for assessing HRQoL impacts of skin conditions, we note that it includes a question about pain whereas the EPP-QoL does not directly (it does include a question asking patients how often they feel they are risk of developing EPP symptoms. The ERG notes that this could therefore include pain). The wording of the DQLI pain question is "Over the last week, how itchy, sore, painful or stinging has your skin been?" This appears pertinent to the nature of pain experienced by EPP patients, since the survey by Holme et al.[17] indicated that patients found the cutaneous sensation following sunlight exposure difficult to describe, with the most frequent responses being burning (85%), tingling (33%), prickling (4%) and stinging (3%). The Holme et al.[17] survey is the largest survey conducted in EPP patients and demonstrated that DLQI scores in EPP patients are higher than in other skin conditions and indicative that EPP has a substantial impact on patients' quality of life. The DLQI has been widely used and subjected to validation in a number of studies.[18] It has also been used to measure quality of life in EPP patients in other studies.[19] The ERG therefore disagrees with the company's assertion that DLQI is not necessarily suitable as a measure of HRQoL in EPP. The CS does not report any DLQI scores, although we note that DLQI scores from study CUV039 are given in the afamelanotide EPAR.[2] (we have reported these in section 3.3.5 of this report). The ERG requested standardised DLQI scores from the company via NICE (clarification response question A2, 12/09/17) but the company declined to provide these. Further discussion of the use of DLQI to inform cost effectiveness of afamelanotide for EPP is provided in section 4.3.3.2 of this report.

Mortality

Mortality is not reported in the CS but is mentioned in the journal publications[7] and the EPAR[2] for studies CUV029, CUV039 and the long-term observational study[11] (see section 3.3.7 of this report).

3.1.5.2 Outcomes not specified in the NICE scope

According to the publication, in study CUV029 only, the levels of protoporphyrin IX (in erythrocytes) were assessed at baseline and follow-up.[7] Levels of protoporphyrin IX may indicate disease severity but are not influenced by afamelanotide therapy, so this is a prognostic factor rather than an efficacy or effectiveness outcome.

Summary

The company's outcomes are appropriate for the health condition and match the NICE scope, apart from no data being provided for the HRQoL of carers and for mortality. Not all of the information regarding outcome measures is provided in the CS, with additional information being sought by the ERG from journal publications and the EPAR.

3.1.6 Description and critique of the company's approach to trial statistics

The CS does not report trial results for all of the outcomes specified in the NICE scope. Where results are presented they are often descriptive only (CS Tables C5 and C9) and do not reflect all relevant results that are available elsewhere in trial publications (e.g. Langendonk et al. report relevant outcomes for trials CUV029 and CUV039 in more detail than the CS[7]).

3.1.6.1 Overall analytical approach

For six of the studies (not including the CUV-PASS-001 monitoring study) the CS states that analysis was by ITT. However, the CS only defines ITT for the crossover trial CUV017, stating that the ITT population included all treated subjects who provided at least one post-dose efficacy assessment, and that this was planned to be the main population for all efficacy analyses (CS p 42). The protocol for trial CUV039 (not initially provided by the company but available in a supplement to a journal publication[7] defines ITT in the same way. The ITT definition given by the company is effectively that of a "modified ITT" analysis rather than a true ITT analysis (which would require all randomised patients to be analysed).

The afamelanotide EPAR (p 52)[2] notes that for study CUV039 there are three "ITT" populations, reflecting the availability of post-dose effectiveness data for different data types, i.e. diary card, photoprovocation subset and HRQoL. In CUV039 the "study completers" population included subjects who received all doses of study treatment and returned adequately completed diary card entries ("diary card population"), completed all HRQoL assessments ("HRQoL population) or had the required number of photoprovocation tests ("photoprovocation subset"). The safety

population included all enrolled subjects who were randomised and received at least one dose of study medication (afamelanotde EPAR[2]). The company did not provide clinical study reports or protocols for any studies, but we assume that the population definitions for CUV039 apply also to the other studies, CUV017, CUV029 and CUV030 (clinical study reports and protocols were requested by the ERG from the company via NICE but these were not supplied; clarification response question A3, 26/09/17).

For study CUV039 the updated (June 2013) Statistical Analysis Plan (available in an appendix to Langendonk et al.[7]) does not name the specific statistical tests that would be employed in analyses, but it states that descriptive statistics would be provided in summary tables. According to the CS and journal publication (Langendonk et al.[7]), differences between the study-drug groups were assessed with the use of the Kruskal–Wallis test with Hodges-Lehmann shift estimate of difference for primary outcomes; chi-square tests for proportions; and a Wilcoxon rank-sum test for changes in HRQoL. The Hodges-Lehmann shift estimate of the difference between two groups uses the information contained in all pairwise differences between the groups and can provide a robust estimate of the median difference between groups when the underlying distributions for the groups are symmetric about their respective medians.[20] However, the CS does not provide any explanation of the rationale for using this statistical test and whether the distributions of data were symmetric. In cases of non-symmetry the reliability of the Hodges-Lehmann shift estimate is less clear.[20] In study CUV017 a Cochran-Mantel Haenszel test for two categorical datasets obtained in a crossover design was employed (CS p 29), but the CS does not specify whether a treatment-by-period interaction was tested and if a washout period between observations from alternating afamelanotide and placebo treatments was necessary (each patient alternated between an afamelanotide or placebo implant every 60 days. The duration of the effect of an afamelanotide implant, and hence the appropriate washout period, is not clear). The ERG agrees that the tests employed by the company appear generally appropriate, but few details are reported, and the descriptive statistics provided in the CS are incomplete and inconsistent across studies and outcomes (in some cases only qualitative narrative statements of results, sometimes with p-values, are reported; in other cases mean ± SD, 95% confidence intervals (CIs) and/or median and range are reported). The ERG has obtained missing descriptive statistics that were available from the study journal publications and the EPAR[2]) (see section 3.3).

3.1.6.2 Sample size

The CS, study publications and EPAR[2] do not provide any justifications for the sample size or statistical power of the studies. The statistical analysis plan for study CUV039 (provided in a supplementary appendix to the publication by Langendonk et al.[7]) states that analysis of data from the prior CUV029 and CUV030 studies demonstrated that a significant difference in the primary endpoint could be detected with "approximately 75-100 patients", but the variance, detectable difference and statistical power values used in the sample size calculation are not specified. The eventual number of patients randomised in study CUV039 was 94 which is at the upper end of the range specified. The EPAR reports that basing the sample size on a previous phase III trial was considered acceptable by the CHMP[2].

3.1.6.3 Attrition

According to CS section 9.4.6, overall patient withdrawal rates were low across the clinical trial programme. Across the three late stage studies (CUV029, CUV030 and CUV039), 17 patients did not complete the full protocol, including three who were lost to follow up but received all study medication.

The CS does not provide any Consolidated Standards of Reporting Trials (CONSORT) charts to show patient flow through the studies although the afamelanotide EPAR [2] provides a flow chart for study CUV039. (The ERG requested charts for all the studies from the company via NICE, but the company did not provide them - clarification response question A6, 02/10/17). The CS does not mention any patient attrition for studies CUV010 (which only included five patients), CUV017, or the long-term observational study[11]. Patient discontinuations in the remaining three core studies are reported in the CS as follows (CS Table C5):

- CUV029: Four subjects discontinued from the afamelanotide arm and two from the placebo arm, with reasons reported separately by study arm.
- CUV030: The CS states "[redacted]". It is unclear whether all patients who discontinued are accounted for by this statement.
- CUV039: According to the CS, 3 subjects in each arm discontinued. Reasons for discontinuation are given, but not separately by study arm. The afamelanotide EPAR[2] reports that reasons for discontinuation from the afamelanotide arm were withdrawal of

consent (no reasons given) (n=2) and a physician's decision (n=1) (clinical reasons not related to implant); whilst 2 patients from the placebo arm were lost to follow up and 1 discontinued due to a physician's decision (serious adverse event, clinical reasons not related to implant).

For studies CUV029 and CUV039 although attrition rates per arm ranged from 5.5% to 10.5% the reasons for discontinuation do not suggest that the discontinuations would have led to systematic imbalances in prognostic characteristics of the study arms (i.e. bias). For study CUV030 it is unclear whether all the discontinuations have been reported.

The CS states that given the low numbers and the reasonably even distribution of withdrawals, these withdrawals were not considered to have had an impact on the outcome of the overall assessment of the study endpoints. The ERG agrees that the company's assertion is reasonable for studies CUV029 and CUV030 but there is uncertainty as to whether all discontinuations in CUV030 have been reported, and no information on discontinuations is available for study CUV017.

3.1.6.4 Handling missing data

The CS states that for studies CUV029, CUV030 and CUV039, ITT was used but "the principle of last value carried forward was not considered appropriate to the assessment of the chosen endpoints in this indication" (CS Table C7, p 42). The company's rationale is that "Sun exposure and phototoxicity are not endpoints where the last value carried forward would give meaningful results because both are quite variable day to day. As an example, if a patient dropped out because they experienced a severe phototoxic reaction with a pain scale score of 10, then that values [sic] would need to be imputed for all future assessment points – this would be nonsensical" (CS p 42). The ERG agrees with this assertion.

The CS, in describing study CUV039 (CS p 37), states that analyses were therefore performed on a best and worst cases imputation, as described in the statistical analysis plan. The ERG agrees that this imputation approach is appropriate. However, the company does not report for any studies or for any individual study arms whether the results presented in the CS and in the journal publication (Langendonk et al.[7]) are for the best-case or the worst-case imputation.

According to the CS, in study CUV039 "compliance of diary completion was very high. There were 185 out of 15608 diary days (1.2%) with missing Likert pain scores, and 296 diary days

(1.9%) with missing information about time outdoors. Last observation carried forward for missing phototoxicity or "pain" scores on days after a "pain" score of greater than 2 was applicable to only four subjects, for a total of 6 diary days" (CS p 37). Although not explicit, this appears to suggest that relatively few imputations would have been necessary, affecting 4/93 of the randomised subjects (4%) in study CUV039 (data are not reported by study arm). Corresponding information for the other studies is not given in the CS. The EPAR (p 71) states that (for post-hoc analyses of secondary outcomes) sensitivity analyses using the ITT diary card population produced similar results to the study completers diary card population.

In summary, the company's approaches to statistical analyses appear generally appropriate but information is lacking on how sample sizes and statistical power were estimated and on how missing data were handled. However, rates of attrition appear low for patients and for diary card data and it appears unlikely that attrition would have led to bias.

3.1.6.5 Additional criticisms by the European Medicines Agency

The EPAR[2] reports that a Good Clinical Practice (GCP) inspection was conducted of studies CUV029 and CUV030 as a result of changes to their analysis plans and the lack of clarity regarding sample size. The conclusion of the inspection was that the main efficacy data from these two studies were not considered robust and they could not be used to inform the marketing authorisation of afamelanotide. The key criticisms were: (1) that the design of the patient diary for capturing the data as needed for the analysis of endpoints related to duration of sun exposure was not suitable; (2) there was a change to the statistical analysis plan of study CUV030 after data had been analysed; (3) improper statistical planning and data handling for both trials; and (4) verification of the databases and of relevant events such as database lock / unlock was not possible. The inspection of study CUV039 concluded that it was compliant with the GCP hence its status as the sole pivotal study informing the marketing authorisation.

The GCP inspection and it's results are not mentioned in the CS though the company did acknowledge in their response to a clarification question that studies CUV029 and CUV030 were not used within the CHMP's efficacy assessment for the reasons explained within the EPAR (clarification response question A3, 02/10/17).

The ERG considers that criticisms of the EMA need to be taken into account in the interpretation of the results of these studies. This is particularly pertinent given that EPP-QoL results from

study CUV029 and CUV030 (pooled with those of CUV039) are used in the company's assessment of cost-effectiveness (discussed further in section 4.3.3.2 of this report).

3.1.7 Description and critique of the company's approach to the evidence synthesis

A narrative review is provided, with results of the included studies provided individually in tables, though the level of detail given is superficial and inconsistent across the studies. The interim NICE highly specialised technology (HST) company submission template states that the review should summarise the overall results of the individual studies with reference to their critical appraisal. However, there is no structured critical summary or comparison of the results across the trials in the CS.

A meta-analysis was not provided, with the authors stating that "it is not considered appropriate for the appraisal of SCENESSE®, due to the lack of scientific tools, alternative therapies and the extensive evaluation of the product in clinical trials compared to placebo (standard of care)" (CS p 52). It is not clear what the company means in this statement and the ERG does not agree that there is a lack of scientific tools for meta-analysis, since the outcomes analysed by the company would in principle be amenable to statistical pooling using orthodox methods. The ERG's view is that, in principle, a meta-analysis comparing afamelanotide with placebo plus standard of care (thus in keeping with the NICE scope) could be possible. However, due to clinical heterogeneity between the trials (e.g. duration of treatment; country/region and associated differences in outside light exposure) a meta-analysis would not be meaningful. Further, there are differences in the definitions of outcomes between trials which would which make meta-analysis potentially inappropriate (e.g. Hours of direct sun exposure on days with no pain / mild pain (10:00 to 15:00 hours) per subject in one study (CUV029), versus the same outcome with a time period of 10:00 to 18:00 hours in another study (CUV039)).

3.2 Summary statement of company's approach to systematic review

Table 5 provides the ERG's quality assessment of the company's review of clinical effectiveness.

Table 5 Quality assessment of CS review (Centre for Reviews and Dissemination (CRD) criteria)

CRD Quality Item; score Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question? Yes – brief criteria are reported in CS Tables C1, p22 (published studies) and C2, p23 (unpublished studies). Only criteria for inclusion are given, with no specific exclusion criteria reported. The criteria do not conflict with the decision problem and the NICE scope. The company state that the literature searches were conducted by a single author, and that the clinical sections of the CS were written by a single author and reviewed by others (clarification response question A8, 02/10/17). It is not clear whether inclusion criteria were applied by a single reviewer or by more than one reviewer.
2. Is there evidence of a substantial effort to search for all relevant research? No – only PubMed and a couple of trials registers were searched, and cross-referenced to the company's internal literature library. However, given the orphan nature of the drug indication and it being a first-in-class drug it is unlikely that there would any other relevant studies that the company would not be aware of (see ERG report section 3.1.1).
3. Is the validity of included studies adequately assessed? Yes – the criteria in the NICE HST template for company submissions is used, but only for some of the studies. The RCTs CUV029, CUV030 and CUV039 are appraised jointly in a single table (CS Table C7, p41). However, the RCT CUV017 and small study CUV010 are not appraised at all (CUV010 is wrongly included in the summary table for RCTs (Table C5, p 24) - it is a single arm study with a very small number of patients and it does not contribute data to the economic model). A critical appraisal of the observational study by Biolcati et al[11] is given in Table C8 (p42) but the level of detail is very superficial and many of the items declared as not applicable. The ERG asked the company to provide full quality assessments of these studies (clarification response question A1, 02/10/17) but the company declined to do so, stating that this was not appropriate as they were not traditional RCT design studies. The ERG considers that all studies should undergo critical appraisal, regardless of design, using appropriate criteria.
4. Is sufficient detail of the individual studies presented? No – Full results for the clinical studies are not given – only selected outcomes. For example, EPP-QoI scores, which were collected in trials CUV029, CUV030, CUV039 are not given in the CS. The CS does state in various places that due to the requested format of the data, effect size information (contained in study report tables) cannot be provided, and that further information can be provided on request. The ERG requested the full clinical study reports but the company did not supply these stating that they had submitted all data from the studies to the CHMP (clarification response question A3, 26/09/17). However, the ERG does not have access to such data.
5. Are the primary studies summarised appropriately? No – The CS provides a study-by-study description of study characteristics and results, but does not provide a critical summary of the results across the studies (e.g. what the collective evidence is for each outcome in turn). The justification for not doing meta-analysis given is not very clear (see section 3.1.7 above).

The CS does not state that the review of the clinical effectiveness literature was systematic (there are no instances of the term 'systematic review'). The review stated the inclusion criteria and undertook critical appraisal of some but not all of the included studies. As stated earlier, a limited number of databases were searched for clinical effectiveness studies, however, it is unlikely that there would be any studies that the company is not aware of. The level of detail provided on the characteristics and results of the studies provided is limited, and there is no overall systematic critical summary of the clinical effectiveness of afamelanotide for EPP.

3.3 Summary of submitted evidence

The following sub-sections provide the results of the clinical effectiveness review for each of the outcomes included in the decision problem, as collated by the ERG from the CS and, where necessary, from the study journal publications and the EPAR.

3.3.1 Voluntary natural light exposure results

Outcomes relating to the duration of tolerance to light exposure are reported in the studies (CUV017, CUV029, CUV030 and CUV039), with the most detailed data being for study CUV039. Further detailed results for light tolerance outcomes are given by Langendonk et al.[7] for studies CUV029 and CUV039 and in the afamelanotide EPAR[2] CUV039. The results for studies CUV029 and CUV039 drawn together from the CS, publication and EPAR are shown in Table 6. Only brief results for studies CUV017 and CUV030 are available and these are summarised in the text below and in Table 7

Table 7. These results include the primary outcomes of the trials, though light exposure data is not used as an input parameter in the company's economic model.

Table 6 Duration of tolerance to sunlight in studies CUV029 and CUV039 (Diary Card population)

Outcome[a]	Study CUV029 (Europe)		Study CUV039 (USA)	
	Afamelanotide N=38	Placebo N=36	Afamelanotide N=46	Placebo N=43
Total hours in study in direct sunlight with no pain, mean per patient ± SD; median per patient (range)	Daily assessment 10:00-15:00 (5h) (co-primary outcome)		Daily assessment 10:00-15:00 (5h) (secondary outcome)	
	20.4 ± 40.5; 6.0 (0-193)	5.6 ± 9.3; 0.8 (0-35)	71.2 ± 89.2; 39.6 (0-419)	41.6 ± 45.3; 31.8 (0-199)
	Difference between groups p=0.005 CS states p=0.006		*Difference between groups 13.1 hours (95% CI -1.3 to 28.0); p=0.092*[b]	

	Daily assessment 10:00-20:00 (10h) (secondary outcome)		**Daily assessment 10:00-18:00 (8h) (primary outcome)**	
	Not reported; [redacted]	Not reported; [redacted]	115.6 ± 140.6; 69.4 (0-651)	60.6 ± 60.6; 40.8 (0-224)
	Difference between groups p=0.007		*Median difference between groups 24 hours (95% CI 0.3 to 50.3); p=0.044*	
Total hours in study in direct sunlight with no pain or with mild pain, mean ± SD; median (range)	**Daily assessment 10:00-15:00 (5h) (co-primary outcome)**		**Daily assessment 10:00-18:00 (8h) (secondary outcome)**	
	Not reported; [redacted]	Not reported; [redacted]	141.1 ± 165.1; 80.0 (0.5-825)	74.6 ± 67.5; 51.0 (1.25-251)
	Difference between groups p=0.043			
	Daily assessment 10:00-20:00 (10h) (secondary outcome)			
	Not reported; [redacted]	Not reported; [redacted]		
	Difference between groups p=0.026		*Median difference between groups 26.8 hours (95% CI -0.3 to 57.5); p=0.053*	
Total hours in study in direct sunlight regardless of pain score, mean ± SD; median (range)	Not reported	Not reported	**Daily assessment 10:00-18:00 (8h) (secondary outcome)**	
			145.0 ± 164.1; 83.5 (0.5-825)[b]	81.8 ± 71.2; 65.3 (3.5-278.5)[b]
			Difference between groups 26.1 hours (95% CI -2.3 to 57.3); p=0.066[b]	
Total days in study "in some direct sunlight" on days with no pain, mean ± SD; median (range)	Not reported	Not reported	**Daily assessment 10:00-18:00 (8h) (secondary outcome)[c]**	
			80.5 ± 48.9; 85.5 (0-167)	51 0.7 ± 37.3;[d] 54.0 (0-124)
			Difference between groups 29 days p=0.005[e]	
Total days in study "with some sunlight" on days with no pain or mild pain, mean ± SD; median (range)	Not reported	Not reported	**Daily assessment 10:00-18:00 (8h) (secondary outcome)[c]**	
			93.9 ± 51.0; 97.0 (2-185)	64.0 ± 40.6; 61.0 (3-145)
			Mean difference between groups 32.0 days (95% CI 9.0 to 54.0); p=0.004	

[a] The CS and journal study publication are not explicit that the reported sunlight exposure times are cumulative over the full study period; this is clarified in the afamelanotide SmPC (p. 9) and EPAR (p. 58). Time differences between groups are as reported in the CS, journal publication and EPAR and according to the EPAR are based on the Hodges-Lehmann shift estimate. Unless stated, the CS does not specify whether stated differences between groups are medians or means.
[b] sourced from the EPAR (not reported in the CS or study journal publication)
[c] The CS (p. 36) states this was an exploratory analysis
[d] data for mean ± SD are as written in the study journal publication (typographic error)
[e] source: EPAR (p. 70)

In both CUV029 and CUV039 studies patients in the afamelanotide group experienced a greater mean and median total number of hours in direct sunlight with no pain (Likert scale score of 0).

In CUV029 for the primary outcome (sunlight exposure between 10:00 and 15:00 hours) the median number of total hours per patient in direct sunlight with no pain was 6 (range 0-193) compared to 0.8 (0-35) for afamelanotide and placebo groups respectively (p=0.006) after nine months. As a secondary outcome (sunlight exposure between 10:00 and 20:00 hours) the median number of hours in direct sunlight with no pain was [redacted] versus [redacted] respectively (p=0.007). In study CUV039 for the primary outcome (sunlight exposure between 10:00 and 18:00 hours) the median number of hours per patient in direct sunlight with no pain was 69.4 (range 0-651) versus 40.8 (0-224), p=0.04 after six months. For the secondary outcome of sunlight exposure between 10:00 and 15:00 hours the median number of hours in direct sunlight with no pain was 39.6 (range 0-419) versus 31.8 (range 0-199), p=0.09 after six months. The journal publication suggests that the difference between the two trials in sunlight exposure without pain may be in part due to higher latitudes of the European centres compared with the US centres. Thus patients in the US would, on average, have greater potential for sunlight exposure during the year.[7]

Results for the outcome of total hours per patient in direct sunlight with no pain or with mild pain (Likert scale score of 0-3) were also more favourable for afamelanotide than placebo patients, with statistically significant differences between study groups in both studies CUV029 and CUV039 (
Table 6). In study CUV039, additional outcomes for sunlight exposure per patient expressed in terms of the total days in sunlight with no pain, or with no pain or mild pain, also favoured afamelanotide over placebo, with the differences being statistically significant, although the ERG is unsure how these outcomes were calculated (see section 3.1.5.1).

The EPAR (p 72)[2] states there were 15 patients, in trial CUV039, who experienced more than 60 minutes of direct sunlight exposure per day, of which 12 were receiving afamelanotide and 3 receiving placebo (i.e. 26% of the afamelanotide group and 7% of the placebo group).

Duration of tolerance of sunlight was a secondary outcome in the crossover study CUV017. The CS states that significantly more sun exposure occurred in patients receiving afamelanotide (p=0.0136), suggesting that afamelanotide facilitated more outdoor activity compared to placebo (CS p 29). The CS mentions (CS p 44) that this analysis refers to the number of days of exposure categorised as <1 hour, 1 to 3 hours, 3 to 6 hours and >6 hours per day, but no further

information is given so it is unclear which data comparison the p-value refers to. The ERG requested the CSR for study CUV017 from the company but this was not provided.

According to a company announcement (CLINUVEL 2010[16]) for study CUV017, "Clinically relevant daily exposure of longer than one hour per day symptom-free was recorded by the trial physicians (CRFs) at the end of each 60 day treatment. In assessing the duration of sunlight exposure per patient, there was significantly more sun exposure in patients receiving SCENESSE® ($p<0.0001$)." However, no outcome data are provided and it is unclear which analysis this p-value refers to.

Duration of tolerance to sunlight was a primary outcome in study CUV030. The results as presented in the CS are shown in

Table 7. Patients receiving afamelanotide achieved a significantly greater duration of exposure to direct sunlight during the study without incurring pain than those receiving placebo.

Table 7 Duration of tolerance to sunlight in study CUV030

Outcome	Afamelanotide N=39	Placebo N=38
Total hours of direct sunlight exposure per patient on pain-free days, median (range)	**Daily assessment 10:00 to 15:00 (5h)**	
	8.88 (0-48.3)	0.75 (0-70.3)
	Difference between groups p=0.011	
	Daily assessment 10:00 to 20:00 (10h)	
	16.0 (0-126.3)	1.25 (0-106.3)
	Difference between groups p=0.006	

In summary, the available evidence for EPP patients' tolerance to direct sunlight based on voluntary exposure in studies CUV017, CUV029, CUV030 and CUV039 consistently demonstrates a favourable effect of afamelanotide over placebo in prolonging patients' duration of sun exposure. The clinical significance of these findings is difficult to ascertain since there is no universally accepted measure of how much additional sunlight tolerance is beneficial to patients; this is likely to vary on a patient-by-patient basis given the heterogeneous nature of EPP in which some patients are affected more profoundly than others, and patients vary in the extent to which they may need to be outdoors where they are exposed to sunlight.

3.3.2 Photoprovocation results

In study CUV010 (n=5), photoprovocation was carried out before afamelanotide treatment and repeated at days 30, 60, 90 and 120 on the dorsal surface of the hands. The mean photoprovocation response time increased at day 30 to 347%, day 60 to 595%, day 90 to 663% and day 120 to 1077% of that recorded at baseline (CS, p 26). The CS states that except for the most sensitive individual, all patients reached the maximum photoprovocation response time of 15 minutes during some point of the study. These results indicate that afamelanotide improved the patients' tolerance of the artificial light stimulus. However, the CS does not discuss the clinical interpretation of these findings or their generalisability or limitations. A graph of photoprovocation times reported by Harms et al. indicates there was considerable heterogeneity of responses even within the small sample of five patients.[12]

In study CUV029, photoprovocation was assessed in a small subset of patients, however the exact number of patients and the results were not reported.[7] In study CUV030, 15 patients were given provocation on the dorsal surface of the hands and lower back but only six (40%) completed testing which was "attributed to the rigors of the phototesting protocol".[13] Only descriptive results are reported, stating a "positive trend" (not explained) in the first 60 days but lack of a detectable effect at days 90 or 120 when fewer patients were available for testing.[13] For study CUV039, the EPAR notes that the photoprovocation testing subset of patients (n=21) was located at one of the USA study centres.

The study publication by Langendonk et al. provides a table of results for photoprovocation to the dorsum of the hand and the lower back in study CUV039.[7] The results are presented as the change from baseline in minimum symptom dose, expressed in J/cm^2 of light energy and they show that higher doses were tolerated by afamelanotide patients than placebo patients, both on the hand and back, with the differences being statistically significant from 90 days after baseline onwards. However, limitations of these results are that tolerance appeared to be higher in the afamelanotide group than the placebo group at baseline; sample sizes were small (dorsum of hand n=10; lower back n=11) and only limited clinical interpretation of the findings is provided by the study authors.[7] The EPAR notes that due to an error several patients received a lower light exposure dose than intended and this was corrected for using an unexplained 'mathematical adaptation' (not mentioned in the study publication). According to the EPAR, the company

observed that the median response to photoprovocation in the afamelanotide group appeared to follow a cyclical pattern which would be consistent with the expected pattern of change in melanin density, although melanin density was not measured in the study.

Overall, the limited evidence available on photoprovocation indicates that afamelanotide improves patients' tolerance to artificial light in controlled settings but the wider clinical significance of these findings is unclear, and the data are heterogeneous and of uncertain generalisability due to the small sample sizes tested. Photoprovocation data is not used as an input parameter in the company's economic model.

3.3.3 Phototoxic reactions

The CS reports information on phototoxic reactions in two studies (CUV017 and CUV029) principally referring to the frequency or severity of pain experienced. More extensive results for phototoxic outcomes in study CUV029 and also in study CUV039 are reported in the study publication by Langendonk et al.[7] and in the EPAR.[2] Phototoxicity was specified as a secondary outcome in each study. It is not used as an input parameter in the company's economic model.

For the cross-over study CUV017 (CS, pp 29-30) the CS states "the distribution of frequency of days on which patients experienced pain in the various pain severity categories is consistent with the mean scores and was different between the active and placebo groups (p=0.0042)". In CUV017, placebo patients experienced "more moderate and severe pain (p=0.0009)" and "individual daily pain scores" (p=0.0017) were significantly lower following afamelanotide treatment than when patients were receiving placebo. A publication referring to study CUV017 (CLINUVEL 2010[16]) states that "pain scores in patients willing to modify behaviour by continuous exposure to daily (sun)light showed a positive trend toward a reduction in average pain score following active drug treatment (p=0.1654)". These statements are the only information available to the ERG on phototoxicity outcomes in study CUV017.

For study CUV029 the CS tabulates quantitative results for three phototoxicity outcomes (number of phototoxic episodes per subject, overall sum of the severity score per patient, and the overall maximum severity per subject) (CS, p 33). These data are included below in Table 8 and Table 9, together with other phototoxicity outcomes results which are reported by Langendonk et al.[7] and the afamelanotide EPAR.[2]

Table 8 Phototoxic reactions in studies CUV029 and CUV039

Outcome	Study CUV029 (Europe)		Study CUV039 (USA)	
	Afamelanotide N=38	**Placebo N=36**	**Afamelanotide N=46**	**Placebo N=43**
Number of phototoxic episodes per subject, mean ± SD; median (range)	2.0 ± 2.8; 1.0 (0-11)	4.1 ± 5.1; 2.0 (0-20)	2.0 ± 3.3; 1.0 (0-15)	3.3 ± 6.8; 1.0 (0-35)
	Difference p=0.04		*Difference p=0.602*	
Number of phototoxic reactions during study	77	146	Not reported	Not reported
	Difference p=0.04			
Duration of phototoxic reactions, days, mean ± SD; median (range)	Not reported	Not reported	3.2 ± 6.0; 1.0 (0-34)	6.6 ± 16.8; 1.0 (0-98)
			Difference p=0.50	
Duration of longest phototoxic reaction, days, mean ± SD; median (range)	1.5 ± 1.8; 1.0 (0-7)	3.8 ± 7.4; 2.0 (0-37)	1.3 ± 1.9; 1.0 (0-12) [a]	1.7 ± 2.1; 1.0 (0-10) [a]
	Difference p=0.08		*Difference p=0.519* [a]	
Duration of phototoxicity, days, mean per patient ± SD; median per patient (range)	3.7 ± 5.6; 1.0 (0-23)	10.0 ± 18.3; 3.0 (0-90)	Not reported	Not reported
	Difference p=0.04			
Sum of Likert score for severity of phototoxic reactions during study, mean per patient ± SD; median per patient (range) [b]	[redacted]	[redacted]	16.3 ± 33.2; 4.0 (0-196)	34.1 ± 86.7; 6.0 (0-507)
	Difference p=0.020		*Difference p=0.44*	
Overall maximum severity per subject (Likert score) across all phototoxic episodes, mean ± SD; median (range)	[redacted]	[redacted]	3.5 ± 3.1; 4.0 (0-8) [a]	3.9 ± 3.3; 5.0 (0-9) [a]
	Difference p=0.010		*Difference p=0.544* [a]	
Patients with severe phototoxic reactions, n (%)	25 (66)	28 (78)	Not reported	Not reported
	Difference p=0.25			

[a] Sourced from the EPAR (not reported in the CS or publication)
[b] The Likert scale ranged from 0 (no pain) to 10 (worst imaginable pain)

Table 9 Pain severity in studies CUV029 and CUV039

Outcome (n= total days recorded in patient diaries)	Study CUV029 (Europe)		Study CUV039 (USA)	
	Afamelanotide n=9742	Placebo n=9601	Afamelanotide n=8055	Placebo n=7368
Number (%) of diary days with no pain (Likert score 0)	8914 (92) [a]	8463 (88)	7156 (89)	6245 (85)
Number (%) of diary days with mild pain (Likert score 1-3)	687 (7)	777 (8)	753 (9)	840 (11)
Number (%) of diary days with moderate pain (Likert score 4-6)	124 (1)	298 (3)	127 (2)	293 (3)
Number (%) of diary days with severe pain (Likert score 7-10)	17 (<1)	63 (<1)	19 (<1)	44 (<1)

[a] p<0.001 for comparison with placebo – other comparisons in the table were not statistically significant

Overall, patients in both study arms had infrequent phototoxic reactions during the studies. In the European study (CUV029), however, the number of phototoxic reactions recorded during the study for those receiving afamelanotide was approximately half that recorded compared to the placebo group (77 vs 146; mean per patient 2.0 ±2.8 vs 4.1 ± 5.1, respectively, p=0.04).[7] In the US study (CUV039), although not statistically significant, phototoxic reactions were slightly higher in the placebo group (46 vs 43; mean per patient 2.0 ± 3.3 vs 3.3 ± 6.8 p=0.60).[7] The company suggested that sun avoidance behaviour in the US trial may have been a contributory factor to the lack of difference in phototoxic reactions between treatment groups in this study (EPAR, pp 68-69[2]).

In addition to the phototoxic reactions reported above, the EPAR provides tables showing the distribution of daily and maximum pain scores calculated post hoc (EPAR, p 73). Given that the planned analyses on phototoxicity outcomes did not identify statistically significant differences, these post hoc data have not been reproduced here.

3.3.4 Melanin density

A change in melanin density (MD) following administration of afamelanotide, although only reported in the CS for study CUV010, was stated to be a secondary endpoint for CUV017.[2] In addition, the observational study by Biolcati et al.[11] also reported this outcome.

The EPAR highlighted that early pharmacokinetic studies demonstrated that both 16 mg and 20 mg doses increased MD (quantified by spectrophotometry) by 33%.[2] However in the crossover trial, CUV017, it was demonstrated that the increase in MD in clinically relevant skin areas was smaller, ranging between 15-20% on the forehead and 6-12% on the cheeks' skin, which indicated a non-homogeneous pigment distribution.[2]

In CUV010, MD measured as a secondary outcome, was seen to increase during the first 30 days after administration at all tested anatomical sites with one exception in one patient (CS, p 26). Further data from this study showed a mean melanin density increase of 124% of the baseline level at day 30, which slightly decreased by day 60 (121%).[10] This study also showed that a rise in MD after the second implant (at day 90) to 130% of initial MD was only slightly higher than at Day 30. The absolute difference in MD between treatment days (measured on days 30, 60, 90 and 120 at 6 anatomical sites) was stated to be significantly different to baseline (P = 0.004) (CS p 26). In addition, three patients with high sunlight exposure had a stronger MD increase at day 120 (1.084–1.824 MD units) than the other two patients (0.085 and 0.765 MD units).[10]

In the long term observational study, MD, measured in the Swiss cohort only, was reported in units (where one MD unit corresponds roughly to the difference in skin colour between two skin types in the Fitzpatrick scale of skin types).[11] The increase in MD is compared to MD before the first exposure to afamelanotide. It was reported that MD rose by about 0.4 units during months 1 and 2 and by about 0.7 units during months 3 and 4. Between the fifth month and the sixth year, MD remained stable between 0.7 and 1.0 units.

Melanin density was not used as an input parameter in the company's economic model.

3.3.5 Health Related Quality of Life (HRQoL)

3.3.5.1 EPP-QoL results

As mentioned earlier, the EPP-QoL instrument was used in studies CUV029, CUV030, CUV039, the long-term observational study by Biolcati et al.[11] and the on-going post authorisation safety study CUV-PASS-001. Pooled EPP-QoL data from studies CUV029, CUV030, CUV039 are used by the company to inform their assessment of cost-effectiveness in their model (discussed further in section 4.3.2 of this report). Limited quantitative EPP-QoL data for the respective studies are reported in the CS and the company declined to supply further data requested by the ERG (clarification response question A1, 12/09/17). Quantitative results are available for two of the studies (CUV029, CUV039), which were reported in the trial publication.[7] These are reproduced in Table 10.

The EPP-QoL score ranges from 0 to 100 (transformed from the original scoring scale), with higher scores indicating a better quality of life. The results for study CUV029 are reported as absolute scores at study visits (up to day 270), whilst in study CUV039 they are reported as change from baseline up to day 180, with absolute scores given for day 360 (240 days after the last dose). The baseline EPP-QoL scores differed between the two trials, with lower scores in study CUV039 indicating a study population with a lower HRQoL.

In study CUV029 there was a minor imbalance in scores at baseline between study groups (mean difference of 3.70). In this study the scores increased over time in both study groups, though the increase was higher in the afamelanotide group at all assessment time points, with the highest score around 85 points and with mean differences between groups ranging from around 7.9-15.2 points across the time points. The differences between the groups were statistically significant at days 120, 180, and 240.

Table 10 EPP-QoL results

Trial and questionnaire score	Afamelanotide			Placebo				Difference[a]					
Study CUV029 (Europe)	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*P value*	*Mean*	*SD*	*SMD*	*SE*	*95% CI*	
Baseline score at day 0, before dose 1	39.00	25.80	37	35.30	23.70	34	0.39	3.70	24.82	0.15	0.24	-0.32	0.62
Score at day 60, before dose 2	68.00	19.10	37	60.10	22.00	35	0.09	7.90	20.56	0.38	0.24	-0.08	0.85
Score at day 120, before dose 3	78.80	16.20	37	63.60	23.90	35	0.005	15.20	20.31	0.75	0.24	0.27	1.23
Score at day 180, before dose 4	84.60	12.60	35	73.50	24.30	35	0.03	11.10	19.36	0.57	0.24	0.10	1.05
Score at day 240, before dose 5	84.80	10.70	34	73.10	24.10	34	0.01	11.70	18.65	0.63	0.25	0.14	1.11
Score at day 270, final visit	79.70	16.10	32	67.20	25.70	34	0.06	12.50	21.59	0.58	0.25	0.09	1.07
Study CUV039 (USA)[b]	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*P value*	*Mean*	*SD*	*SMD*	*SE*	*95% CI*	
Baseline score at day 0, before dose 1	26.6	19.9	47	26.2	19.4	43	NR	0.40	19.66	0.02	0.21	-0.39	0.43
Score at day 60, before dose 2	70.6	24.2	47	49.6	29.8	43	NR	21.00	27.02	0.78	0.22	0.35	1.21
Score at day 120, before dose 3	76.9	22.0	46	55.8	30.2	42	NR	21.10	26.23	0.80	0.22	0.37	1.24
Score at day 180	78.1	24.9	46	63.0	26.2	43	NR	15.10	25.54	0.59	0.22	0.17	1.02
Score at day 360 (follow up visit)	38.4	27.0	44	45.4	29.6	40	NR	-7.00	28.27	-0.25	0.22	-0.68	0.18

[a] Descriptive statistics for the difference between study groups were calculated by the ERG using a published method,[21] [b] results reproduced from the EPAR.[2] SE = standard error; SD = standard deviation; SMD = standardised mean difference; NR = not reported.

Scores in both groups reduced slightly between day 240 and the final visit at day 270. The score improvements observed over time in both the afamelanotide group and placebo groups of study CUV029 would indicate a change from moderate to mild EPP according to the company's EPP-QoL score thresholds (whereby for the purposes of economic modelling the EPP scores are stratified as 'mild' – 66.7 to 100; 'moderate' – 33.4 to 66.6, and severe' – 0 to 33.3 – see section of the CS 10.1.9, p 59). However, caution is advised in this interpretation as these thresholds and any minimal important clinical differences have not been clinically justified by the company.

[redacted]

In study CUV039 scores increased over time from baseline in both groups with larger increases in the afamelanotide group. The highest score was 51.1 points for the afamelanotide group at day 180. Differences between the groups in the change from baseline were statistically significant at day 60, day 120, and day 180. By day 360 (240 days after the last implant) scores had fallen in both study groups illustrating a worsening of HRQoL, though they remained above baseline levels. The score at this time point was slightly higher in the placebo group (mean difference -7 points) suggesting better HRQoL than for afamelanotide patients. This observation is not discussed in the CS or the journal publication.[7]

The CS reports brief results for the untransformed EPP-QoL scores from study CUV039 (CS Table C5, p 38). The total score range is from -10 (best possible HRQoL) to 35 (worst imaginable HRQoL) and therefore the desired scoring direction is the opposite of the transformed scoring version. Median change from baseline for the afamelanotide group was between 1.6 and 1.9 times that of the placebo group, with statistically significant differences in favour of afamelanotide at days 60, 120 and 180 (p values not provided).

Overall the results from studies CUV029 and CUV039 show that HRQoL increases following implant and is maintained over time as implants are replaced every 60 days. However, the clinical significance of the increases observed is unclear as no clinically justified interpretation of changes in EPP-QoL scores is available. Once implants have been withdrawn there is deterioration in HRQoL over time; however, the rate at which HRQoL reduces following implant removal is uncertain and is an issue explored in the ERG cost-effectiveness analysis (section 4.4).

The CS reports brief narrative EPP-QoL results for study CUV030, stating that at each time point the mean change from baseline for the afamelanotide group was approximately twice that of the placebo group ($p<0.05$) (CS, p 35). The ERG notes that it is not possible to know how comparable the study groups were at baseline as the baseline values are not reported.

Long-term EPP-QoL results

The EPP-QoL instrument was also administered to patients in the long-term observational study of 115 patients who received afamelanotide for up to eight years.[11] Patients in the Swiss cohort of this study completed the original version of the questionnaire containing 18 questions (n=161 questionnaires completed). In the Italian cohort patients completed a version with three questions removed (n=460 questionnaires completed). For both cohorts data from the original and revised questionnaires were presented.[11] The mean number of implants per year was 4.4 ± 1.6 in the Swiss cohort and 2.6 ± 1.6 in the Italian cohort. In the Swiss cohort prior to afamelanotide the mean HRQoL score was 32 ± 22% of maximum (revised questionnaire 31 ± 24%). In the first six months of treatment, it rose to 74 ± 17% (74 ± 17%) and remained between 69% and 91% (66% and 84%) of maximum during the HRQoL observation period of six years.

In Italy, questionnaires were not given before afamelanotide was administered; data were available for assessment time points between the second month and the fifth year of treatment. The mean HRQoL score remained stable at between 73% and 80% (revised questionnaire 74% and 80%) of maximum with a slight increase in year five, to 85% (83%). The mean HRQoL treatment scores were stated to be similar between the two cohorts, with larger variation between assessment time points observed in the Swiss cohort. Seasonal variations in EPP QoL scores were also reported. The mean HRQoL score in winter (December to February) was higher (approximately 84%) than during summer (June to August), where it dropped to 75% in July. The difference between the months was statistically significant (P=0.037). It is mentioned that more questionnaires were available for the summer period than the winter period due to more patients requesting implants at that time of year. However, the number of questionnaires analysed from each season is not given. Also, the publication does not state which of the two cohorts these data apply to. Overall, data from this study show that HRQoL increases markedly following afamelanotide administration (as observed from the Swiss cohort) and is maintained over time (observed in both cohorts). However, there were seasonal variations, with HRQoL higher during winter months.

The only EPP-QoL information available for the PASS study is a statement that there was a trend towards improved patient quality of life (CS Table C6, p 40).

3.3.5.2 DLQI results

As stated earlier, the DLQI was administered to patients in the CUV029, CUV030, and CUV039 studies. However, the CS does not report any results for these studies. The ERG requested these data but the company declined to provide them citing their perceived inappropriateness of the DLQI for assessing quality of life in EPP (clarification response question A2, 12/09/17) (see section 3.1.5 of this report for the ERG discussion of the DLQI). The ERG was able to identify DLQI data from the EPAR for study CUV039 (Table 11).

Table 11 DLQI results in study CUV039

		Afamelanotide	**Placebo**
DLQI total score at visit 1 (Day 0)	N	47	43
	Mean (SD)	10.7 (6.3)	10.4 (5.7)
DLQI total score at visit 2 (Day 60)	N	47	43
	Mean (SD)	4.7 (5.7)	6.4 (6.0)
DLQI total score change from baseline at visit 2 (Day 60)	Mean (SD)	-6 (5.9)	-4 (5.5)
	P value	0.214	
DLQI total score at visit 3 (Day 120)	N	46	42
	Mean (SD)	2.8 (4.2)	4.1 (4.8)
DLQI total score change from baseline at visit 3 (Day 120)	Mean (SD)	-7.8 (6)	-6.5 (6.2)
	P value	0.589	
DLQI total score at visit 4 (Day 180)	N	46	43
	Mean (SD)	2.4 (4.2)	3.1 (4.1)
DLQI total score change from baseline at visit 4 (Day 180)	Mean (SD)	-8.1 (6.2)	-7.3 (5.6)
	P value	0.799	

Scale 0 = no effect on QoL, >20 = extremely large effect on QoL.

The DLQI scoring range is 0-30 with a score of 0 indicating no effect on QoL, and a score of 30 indicating an extremely large effect on QoL. 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. The EPAR states that "there were no clinically relevant or statistically significant differences between groups in quality of life at any time point when assessed by the DLQI questionnaire" (p 60). The ERG notes that for general inflammatory skin conditions (e.g. psoriasis, eczema) a change in DLQI score of at least four points is considered clinically important.[23] The largest change observed for afamelanotide was around eight points which is double the recognised minimal clinically important difference for general skin conditions.

3.3.5.3 SF-36 results

The CS reports that the SF-36 instrument was used in study CUV017 but does not provide any quantitative results. The CS states that the baseline SF-36 results were "higher than expected, with the mean across all patients of the eight quality of life scales and the physical and mental component scores being above the population average score of 50" (CS p 29). The suggested explanation in the CS is that patients are likely to have adapted their lives to live with the condition without significantly affecting their HRQoL. The ERG requested SF-36 results from the company but they declined to provide them (clarification response question B1, 12/09/17). The EPAR states that in study CUV017 results "showed no improvement in QoL during and after treatment with Scenesse" (CS p 85) but no further detail is presented.

3.3.6 Adverse events

An overall list of adverse events (AE) that occurred in afamelanotide patients is provided in the CS, as reproduced from the SmPC (CS Table 10, p 48-49). However, the CS does not identify which AE arose in each of the individual included studies, except for providing a list (without numbers) of the most frequent AE that occurred in the small (n=5) study CUV010 (these were: nausea, tiredness and headache within the first 24 hours after the first implantation; CS, p 27). Details of the AE that occurred in studies CUV029 and CUV039 are reported in the study journal publication[7] and are summarised in Table 12.

Table 12 Adverse events for trials CUV029 and CUV039

Type of AE (according to MeDRA (v14.0) Preferred term)	**EU trial (CUV029)**		**USA trial (CUV039)**	
	Afamelanotide N=38	Placebo N=36	Afamelanotide N=48	Placebo N=45
Adverse events that occurred during the study period, n	189	166	272	216
Patients with any adverse event that occurred during study period, n (%)	34 (89)	32 (89)	45 (94)	39 (87)
Serious adverse events, n	1	0	3	2
	Severity of adverse events that occurred during the study period, n (%)			
Mild	19 (50)	17 (47)	17 (35)	14 (31)
Moderate	12 (32)	14 (39)	25 (52)	23 (51)
Severe	3 (8)	1 (3)	3 (6)	2 (4)
	Most frequent adverse events that occurred during the study period, n (%)			
Headache	13 (34)	14 (39)	19 (40)	13 (29)
Neopharyngitis	8 (21)	8 (22)	6 (12)	10 (22)
Nausea	7(18)	6 (17)	9 (19)	8 (18)

MeDRA = Medical Dictionary for Regulatory Activities

Adverse events collated from studies CUV010, CUV017, CUV029, CUV030, and CUV039, are presented in the EPAR (Table 8, p 92)[2] and are summarised in Table 13. The combined study results (which include 231 patients) reveal that the five most common AE were nausea, headache, migraine, nasopharyngitis and back pain.

Table 13 The five most common adverse events in studies CUV010, CUV017, CUV029, CUV030, and CUV039 (reproduced from EPAR Table 8, p 92)

Type of AE (according to MeDRA (v14.0) Preferred term)	MeDRA (v14.0) System/Organ Class	Number of patients (number of events)					
		Afamelanotide n=231			Placebo n=220		
		Total	Related to drug study	Not related to drug study	Total	Related to drug study	Not related to drug study
Headache	Nervous system disorders	87[a] (259)	54 (161)	46 (98)	75[a] (251)	39 (116)	50 (135)
Nausea	Gastrointestinal disorders	60[a] (106)	53 (93)	11 (13)	36[a] (54)	25 (31)	17 (23)
Nasopharyngitis	Infections and disorders	41 (46)	0 (0)	41 (46)	36 (43)	0 (0)	36 (43)
Back pain	Musculoskeletal and connective tissue disorders	23 (34)	4 (4)	19 (30)	21[a] (43)	4 (7)	18 (36)
Migraine	Nervous system disorders	13[a] (38)	6 (22)	8 (16)	15 (32)	4 (8)	11 (24)

[a] numbers do not sum to the specified total number of patients (data are as reported in the EPAR)
MeDRA = Medical Dictionary for Regulatory Activities

The ERG notes that slightly different adverse events are listed in the CS under “Interpretation of clinical evidence” (CS, p 52). The CS states “The adverse events occurring in 12% of all EPP patients consist mostly of 1. transient headaches (first 48 hours); 2: nausea; 3: gastrointestinal discomfort (infrequent); 4: transient darkening of the epidermis” (CS, p 52).

Longer term data on adverse events

Although the first dataset from the ongoing safety PASS study is still to be reported, longer-term data from the two longest treatment programmes (8 years), operating at EPP expert centres in Switzerland and Italy, have been presented by Biolcati et al.[11] This study, which reports on a total of 115 EPP patients (treated with 1023 implants) revealed that the most frequent adverse events (treatment related and unrelated) were nausea, headache, administration site conditions and fatigue (CS, p 51). Within this study, it was highlighted that two patients noted the appearance of new melanocytic naevus, appearing 2.5 and 5 years after the first dose of afamelanotide. One of them was removed and showed no signs of malignancy.[11]

Serious adverse events

In total, 31 serious adverse events were reported with afamelanotide in the clinical trial programme (EPAR summary of the five clinical trials as above), all of which were considered unlikely or definitely not related to study drug (EPAR, p 93).[2] Early data from the PASS study (23 June 2016 – 31 May 2017) identified four serious adverse events, of which three were unrelated to treatment (CS, p 40).

3.3.7 Mortality

The CS does not report mortality. For trials CUV029 and CUV039 the study journal publication states there was no mortality.[7] The EPAR (p 93) states "Four deaths were reported during clinical studies with the afamelanotide implant, all of which were regarded as definitely not related to study treatment by the investigators," although the EPAR is not explicit about which studies are being referred to.[2] For the long-term observational study the publication by Biolcati et al. [11] states that one patient died of heart failure, but does not specify whether this was treatment-related.

3.3.8 Sub-group analyses results

The NICE scope and company's decision problem do not specify any subgroups to be included. Some of the company's analyses involved subgroups of the randomised population (e.g. where tolerance to light exposure was analysed according to different pain severity subgroups) and these are considered above.

3.3.9 Mixed treatment comparison results

The company did not conduct a mixed treatment comparison. The ERG considers this appropriate, given that the NICE scope specifies the comparison should be between afamelanotide and best supportive care. Insufficient evidence is available to form a network to support such a comparison. Accordingly, the CS focuses on studies that directly compared afamelanotide against placebo (which is a proxy for best supportive care).

3.4 Summary of clinical effectiveness

The CS presents an evidence review of four RCTs and three observational studies of afamelanotide, most of which were sponsored by the company. The decision problem as defined by the company is consistent with the NICE scope of the appraisal. Although the searches for evidence were limited to a small number of databases, due to the orphan nature of the drug and the rarity of the condition it is unlikely that any additional relevant studies have not been included.

Some of the afamelanotide clinical effectiveness studies remain unpublished and limited detail on these and also on the published studies is provided in the CS. Clinical study reports and study protocols for all studies have not been made available to the ERG and therefore a full independent assessment of the methodological characteristics and results of the studies has not been possible for this appraisal. Although the company has conducted placebo-controlled RCTs, in such a poorly understood rare condition the ERG has concerns about the methodological quality and potential risk of bias of the studies. It is not possible to ascertain whether randomisation was adequately concealed and whether study arms in all trials were balanced at baseline. In one of the studies (CUV029) there were twice the number of patients with Fitzpatrick skin type 1 in the placebo group compared to the treatment group. The significance of this is not discussed in the CS. Unblinding is known to have occurred in some patients, yet the impact of this on the results is uncertain. The ERG also notes that the EMA expressed concerns about the conduct of two of the RCTs and only one of them (CUV039 conducted in the USA) was considered of sufficient validity to support the marketing authorisation. The ERG's quality assessment of this RCT identified potential risks of bias in this study (as in the other studies), but given its status as the pivotal trial the ERG has used it to inform it's cost-effectiveness analysis (see section 4 of this report).

The available evidence shows that afamelanotide is associated with clinical effectiveness benefits, in terms of increasing the amount of time patients can spend in sunlight without incurring pain, or incurring only mild pain; a reduction in phototoxic episodes; and a statistically significant reduction in duration of phototoxic episodes (the latter observed in CUV029 but not in CUV039). Adverse events were generally mild in severity. Statistically significant improvements are reported in the HRQoL measurements, although the clinical significance of this is unclear. The instrument used (EPP-QoL) has been designed specifically to measure the impact on EPP,

with highly specific questions about impact of the condition on ability to undertake daily activities inside, around and outside the home, choice of clothing, and mode of transport outside. [redacted] and it does not include a question about pain, which is one of the most debilitating aspects of the condition. This is an important consideration as EPP-QoL results are the sole outcome from the clinical effectiveness studies that directly informs the company's cost-effectiveness analysis.

The ERG suggest that caution is exercised in the interpretation of the results of the clinical effectiveness studies for the reasons stated above.

4 COST EFFECTIVENESS

4.1 Overview of company's approach to economic evaluation

The company conducted a review of published economic evaluations (CS section 11, pp 62 to 63), but did not find any relevant studies. However, the ERG search identified one relevant study in a published conference abstract,[3] which we describe in section 4.2 below (p 66). The company produced a model-based economic evaluation comparing afamelanotide to standard care in adults with EPP, using Disability Adjusted Life Years (DALYs) as the measure of benefit (CS section 12, pp 64 - 80). They argued that a Quality Adjusted Life Years (QALY)-based model would be inappropriate for EPP. We describe and critique the company's approach to economic evaluation in section 4.3 below (p 69). Additional ERG analyses are presented in section 4.4 (p 91), including: a simple adapted version of the company's base case model with QALYs as the measure of benefit; an ERG base case analysis with QALYs; and exploration of uncertainty around the company and ERG base cases, with probabilistic sensitivity analysis (PSA) and deterministic sensitivity and scenario analyses.

4.2 Description and critique of company review of economic evaluations

The company identified a published systematic review of economic evaluations of ultra-orphan drugs with marketing authorisation in Europe, published in 2015 by Schuller et al.[24] This review did not identify any economic evaluations of EPP. The company included terms to identify economic evaluations in their PubMed search (see section 3.1.1 above, p 22), but reported that this did not identify any economic evaluations. However, the ERG search for additional evidence found an abstract published in 2016 by Thompson et al.[3] which we consider relevant to this appraisal.

The abstract by Thompson and colleagues reported a cost-effectiveness analysis of afamelanotide for EPP that was presented at the ISPOR 21st Annual International Meeting, held in Washington in May 2016, with authors from ICON, a consultancy based in the UK and an author from CLINUVEL.

*[redacted]

The abstract reported on an economic model that appears to be very similar to the model submitted to NICE, with both sharing the following characteristics:

[redacted]

- Levels of EPP symptoms categorised as mild, moderate or severe
- Proportion of patients by level of severity based on trial quality of life scores
- Disability Adjusted Life Years (DALYs) were the primary measure of benefit

But, unlike the company submission, Thompson et al. also presented a sensitivity analysis using QALYs derived from 'preliminary SF-36 data from early clinical trials' and from other 'similar' conditions.

Broadly, one might think of one DALY averted (a year of life adjusted for the level of disability experienced during that year) as similar to a one QALY gained (a year of life adjusted for the level of quality of life experienced during that year). QALYs are calculated as the area under a weighted survival curve and DALYs as the area above a similar curve. Thus, one wants to maximise QALYs and minimise DALYs. There are, however, differences in the conceptualisation of the weighting factors (disability versus health-related quality of life) and in the methods by which these weights are obtained. See section 4.4.1.1 for more formal definitions and discussion of the differences and relative merits of QALYs and DALYs.

Results from the Thompson et al. DALY model are summarised in 14. They reported a base case estimate of 1.87 DALYs averted over a lifetime (discounted) with afamelanotide compared with standard care, with a range from 0.72 to 2.50 in sensitivity analysis with alternative sources for DALY weights.

[redacted] The Thompson et al. base case incremental cost-effectiveness ratio (ICER) was £373,000 per DALY averted, which was higher than that reported in the company submission: £278,471 per DALY averted (CS Table D9, p 82).

[redacted]. Thompson et al.[3] stated that "the model showed sensitivity to the number and cost of each dose". We further note that the ICER in the Thompson et al.[3] model must also have been sensitive to the source of disability weights, as illustrated in 14.

14 Base case DALY model results from Thompson et al. abstract

Afamelanotide vs. standard care	Base case	Lower limit for DALYs	Upper limit for DALYs
DALYs averted	1.87	0.72	2.50
Incremental cost *	£697,510 *	£697,510 *	£697,510 *
ICER: £ per DALY averted	£373,000	£968,764 *	£279,004 *

* Figures inferred by ERG from results reported by Thompson et al.[3]

Thompson et al. cited an ICER of £401,000 per QALY gained from a sensitivity analysis using the condition hereditary angioedema (swelling under the skin) as a proxy for EPP, and a range from £208,000 to £1.1 million per QALY in sensitivity analyses using alternative sources for utility weights. We note that, assuming the same incremental cost as in the Thompson et al.[3] DALY analysis, these cited ICERs suggest a base case discounted lifetime gain of 1.7 QALYs, with a range from 0.6 to 3.4 QALYs. This illustrates that DALYs averted are of a similar magnitude to QALYs gained, but that they cannot be assumed to be equal.

At the clarification stage of the HST appraisal process, additional information was requested on the methods, parameters and results of the Thompson et al. model. The company declined to provide this information, arguing that:

[redacted]

[redacted]"

(Company response to clarification question B1, p 6, 12/9/17)

The ERG disagrees with this position. We believe that QALYs are a conceptually appropriate metric for quantifying the value of health effects of afamelanotide for patients with EPP, as for other lifelong and chronic disabling conditions; that satisfactory methods for estimating QALY gain are available; and that these methods, though not perfect, are superior to the methods used by the company to estimate DALYs averted. We present this case in section 4.4.1.1. Further, we note that the HST committee does need to make a judgement about the plausible range of incremental cost per QALY gained to assess whether afamelanotide for EPP represents good value to the NHS, in relation to other uses of NHS funds and measured in a way that is consistent with other NICE health technology assessments. We therefore highlight the above QALY-based ICER estimates and present our own estimates and exploration of uncertainty around them in section 4.4.

4.3 Description and critique of the company's economic evaluation

4.3.1 NICE reference case

The ERG assessment of whether the submitted economic evaluation met the NICE Reference Case requirements is presented in Table 15. As the company did not present cost effectiveness using incremental cost per QALY, they failed to comply with the NICE Reference Case,[25] the interim methods guide for HSTs,[26] or the final scope for this appraisal.[27]

Table 15 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	
Comparator: As listed in the scope developed by NICE	Yes	
Perspective on costs: NHS and PSS	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	Estimate of societal costs presented as sensitivity analysis.
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	No	The outcome measure used in model (12 item version of EPP-QOL) does not include all direct health effects for patients (no direct questions on distress, anxiety or impact on work).

Type of economic evaluation: Cost utility analysis with fully incremental analysis	No	The economic evaluation uses DALYs, which are not utilities.
Synthesis of evidence on outcomes: Based on a systematic review	No	The review reported in the CS is not described as a systematic review. However, it is unlikely that there would be any studies that the company is not aware of.
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	Whilst a full lifetime horizon is not adopted, sensitivity analyses extending the horizon have no effect on ICERs.
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	No	The company used DALYs as the primary measure of benefit.
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	EPP-QOL used in the submission to define severity of disease was derived from patients
Source of preference data: Representative sample of the UK population	No	DALY weights not derived from a representative UK sample.
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	There are no QALYs, but the DALYs are the same weight regardless of other characteristics.
Discount rate: 3.5% pa for costs and health effects	Yes	
Notes: ? = uncertain; N/A=not applicable		

4.3.2 Model structure and assumptions

The company model is described on pages 64 to 81 of the CS, with further discussion of how health effects were measured and valued on pages 57 to 61 of the CS. The model was designed to estimate the cost-effectiveness of treatment with afamelanotide compared with a standard treatment control for adult patients with EPP. It addresses the decision problem specified in the scope, with the exception of the measure of value for money: the model estimates incremental cost per DALY avoided, rather than the incremental cost per QALY gained expected by NICE.[27] The company stated that the rationale for this decision was **"**the extreme paucity of robust utility data**"** and **"**the fact that a cost per DALY framework provides a better fit for the condition and treatment provided**"** (CS, pp 64-65). As stated above, we disagree with this conclusion.

[redacted]

The model entails a number of key assumptions:

Survival

[redacted]. The company states that with the exception of liver failure (estimated to affect 2-5% of patients), EPP has no known effect on life expectancy (CS, p 66). The ERG has not identified any evidence to contradict this claim. Available evidence from afamelanotide trials and observational studies does not suggest any impact on mortality (section 3.3.7 of this report, p 64).

Starting age and time horizon

[redacted] Although not a lifetime horizon, the company correctly explains that the ICER is independent of the time horizon, given their assumptions that cost and disability effects are constant over time and that treatment does not affect survival (CS, p 69). The company demonstrated this by conducting a scenario analysis with a starting age of 18 and a time horizon of 60 years (CS, p 80).

Change in costs or effects with age

[redacted] This might seem strong, but we have not identified any evidence of changes in quality of life, effectiveness or costs with age or years of treatment. Holme et al. did not find a relationship between quality of life (measured by DLQI) and age in 176 adults with EPP.[17] In the longitudinal study of 115 EPP patients in Italy and Switzerland treated with afamelanotide for up to eight years, it was found that mean quality of life (measured by EPP-QoL) was stable after the first year of treatment.[11]

Treatment compliance and continuation

Non-compliance or discontinuation of treatment is not explicitly modelled. It is not clear whether the effectiveness estimates used in the model (CS Table C12, p 59) implicitly account for non-compliance in the clinical trials by including all randomised participants, regardless of whether or not they had an implant or, if so, how many (see discussion of ITT analysis in section 3.1.6) above). The mean number of implants per patient per year assumed for costing purposes does seem to allow for 'real-life' non-compliance, as it is based on an average of expanded access and commercial distribution (CS, p 66).

Looking over a longer period, the model assumes that treatment continues throughout the modelled time horizon, with the same mean number of implants per patient and the same effectiveness estimates every year over the [redacted] time horizon. Evidence on long-term trends is inevitably limited, but what there is suggests that most patients will continue to ask for implants as reported within the observational data on 115 patients in Italy and Switzerland, of whom around three quarters were continuously treated for 6 to 8 years.[11] Of those who discontinued, half stopped in the first year and 90% within three years. A more interesting issue from an economic perspective is whether patients who experience limited benefit from implants stop having them. If so, this would suggest that the real-life cost-effectiveness might be better than that estimated by the model. One of the clinical experts who we consulted has suggested that patients who do not feel that they are benefiting from afamelanotide might well decide not to continue, due to the need for travel and discomfort and inconvenience of having the implants. However, in the absence of an objective measure of response it would be difficult to define an explicit stopping rule.

Adverse effects

The company model does not include any additional disability, mortality risk or healthcare cost to reflect the impact of adverse reactions to afamelanotide (CS, p 70 and p 78). This is reasonable, given the current evidence from the clinical trial programme and observational cohorts, where reported adverse events were mild in severity (transient nausea, headache, administration site conditions and fatigue (CS, p 51. See section 3.3.6 of this report for a summary of adverse events).

In summary, the ERG agrees that the basic model structure, although simple, is appropriate for evaluation of afamelanotide in DALY terms. With simple adjustments, it can be adapted to estimate QALYs (see section 4.4). However, the robustness of both DALY and QALY versions of the model depends on how the average annual disability/ utility losses and net healthcare costs are estimated.

4.3.3 Model parameters

The company model has four sets of input parameters, described in the following sections:

- **Disability weights**: 0 to 1 index for mild, moderate and severe disease (a higher number represents greater disability). The weights were assumed to be equal with and without treatment and constant over time.
- **Disease severity:** proportions of patients with mild, moderate and severe EPP. This distribution differed between treatment arms – reflecting the effectiveness of afamelanotide at reducing severity compared with usual care - but was assumed to be constant over time.
- **Mortality rates**: annual probabilities of death by age, [redacted]
- **Resource use and costs**: healthcare costs calculated from the mean number of implants per year and drug acquisition, administration and monitoring costs. Costs of EPP-related productivity were also estimated and included in a scenario analysis.

4.3.3.1 Disability weights

The company's base case analysis uses disability weights from the World Health Organisation Global Burden of Disease (GBD) study conducted in 2010, reported by Salomon et al.[28]. This was a large international survey to elicit judgments from the general public about health losses

associated with multiple causes of disease and injury. The survey did not include EPP, or the company's preferred proxy condition of [redacted]. So instead, the company used a proxy of [redacted] in their base case analysis (Table 16).

Table 16 Disability weights (from CS Table C11, p 58)

Severity	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]

1 Salomon et al. (2012)[28]
[redacted]

The company explained their choice of proxy on page 58 of the CS. They stated that the effects of EPP are similar to [redacted], one of the DSM-IV class of [redacted], defined as: [redacted]". The company argued that, although the reasons differ, the behavioural impact of EPP can be likened to that of [redacted]. Fear of painful phototoxic reactions has a psychological impact and people with EPP learn to avoid high light exposure at an early age, hence restricting their ability to participate in a variety of social, occupational and other activities. We recognise this as a description of the psychological and functional impacts of EPP,[17 30-32] and acknowledge some similarity with the functional impacts of [redacted]. However, an obvious difference is the direct effect of phototoxic reactions for people with EPP (section 3.3.3, p 52).

However, even if the nature of the effects of a proxy condition were broadly similar to those of EPP, it does not mean that the magnitude of effects or definitions of severity are comparable. The GBD 2010 disability weights for mild, moderate and severe [redacted] were elicited using short lay descriptions provided to respondents (Table 17). We consider below whether these are descriptions are compatible with the definitions of severity used to analyse the afamelanotide clinical trial data.

Table 17 Lay descriptions of [redacted] (GBD 2010)[28]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The company used an alternative proxy of [redacted] in a scenario analysis, with disability weights reported by [redacted] (Table 16).[redacted] The company did not explain the reasons for choosing [redacted] as an alternative proxy, although they stated that in their clinical research, people with EPP had been likened to people suffering with [redacted] (CLINUVEL data on file). The ERG cannot judge the validity of this claim. We note, however, that the 'disability weights' in the [redacted] are actually utility decrements that could have been used to calculate QALYs: they were derived from SF-6D scores (utilities) from a sample of 71 adult men with [redacted] minus the mean SF-6D score for males in the general population (population norms) in the same age group.

4.3.3.2 Treatment effects

The company used individual EPP-QoL data from studies CUV029, CUV030 and CUV39 to estimate the proportions of patients in the intervention and control groups with mild, moderate and severe disease at baseline and at 120 days (CS Table C12, p 59). Levels of severity were defined by an equal division of the 0 to 100 EPP-QoL scale: 'severe' (0 to 33.3); 'moderate' (33.4 to 66.6); and 'mild' (66.7 to 100). The EPP-QoL severity distributions and mean disability weights by treatment and time point (for [redacted] proxies) are shown in Table 18 below. The model actually only makes use of the 120 day results and assumes that these values apply for the whole year. Thus in the base case model (with the [redacted] proxy),

[redacted] DALYs are lost per year of life under standard care and [redacted] with afamelanotide: [redacted] DALYs are assumed to be avoided per person per year of treatment.

Table 18 EPP-QoL categories and disability weights by treatment

		Baseline		120 days	
		Afamelanotide	**Standard care**	**Afamelanotide**	**Standard care**
Proportions by EPP-QoL severity[a]					
'Mild'	0 to 33.3	[redacted]	[redacted]	[redacted]	[redacted]
'Moderate'	33.4 to 66.6	[redacted]	[redacted]	[redacted]	[redacted]
'Severe'	66.7 to 100	[redacted]	[redacted]	[redacted]	[redacted]
Mean disability weights[b]					
[redacted] proxy		[redacted]	[redacted]	[redacted]	[redacted]
[redacted] proxy		[redacted]	[redacted]	[redacted]	[redacted]

[a] Distribution of EPP-QOL scores by thirds of scale, CUV029, CUV030 & CUV039 (CS Table C12 p 59)
[b] Mean disability weights calculated from EPP-QOL distribution and proxy weights (CS Table C11 p 58)

The ERG has the following serious concerns about the source of these effectiveness estimates and the way in which they are used in the model:

Choice of outcome measure: 12 item version of EPP-QoL

The company describe their rationale for developing the EPP-QoL on pages 58-59 of the CS. They argue that other quality of life measures in their trial programme (the generic SF-36 and dermatology-specific DLQI) had proved inadequate to reflect the "humanistic burden of EPP", and so they undertook development of a new EPP-specific measure, in consultation with a number of clinical experts (CS, p 58 and p 71). Methods used in this development process are not reported: for example, it is unclear how items were generated, tested and selected for inclusion in the questionnaire. Biolcati et al. mention three versions of the EPP-QoL, containing 18, 15 and 12 questions.[11] They state that the latter was developed following a psychometric validation study by Oxford Outcomes. The results of this validation study have not been reported. The EMA stated that the clinical research organisation "were not able to fully validate the questionnaire but did review the scoring algorithm" (EPAR, p 64 [2]). In response to a clarification question, the company [redacted] (clarification response 12/9/17, question A1). The clinical trials used to inform the

model (CUV029, CUV030 and CUV039)

[redacted]

(CS, p 71).

Given the lack of information about the development and validation of the EPP-QoL, [redacted], the ERG has serious concerns about use of the EPP-QoL to drive the economic model. 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] See section 4.4.1.2 for further discussion about the relative merits of the EPP-QoL and DLQI for use in the economic model.

Definition of disease severity

The CS did not address the clinical relevance of defining disease severity by thirds of the EPP-QoL scale. We acknowledge the lack of accepted definitions of disease severity for the EPP-QoL, but note that the validity of the DALY estimates does depend on using compatible definitions of severity for the disability weights (Table 17) and for clinical outcome data (Table 18). Thus, for example, we need to know whether the scale of psychological and functional impact for patients scoring between 66.7 and 100 on the EPP-QoL scale is similar in severity to the GBD description

[redacted]

". The company has stated that [redacted] (CLINUVEL clarification response 12/09/17, question B2). But this contention is not supported by evidence. The ERG therefore concludes that it is uncertain if the disability weights used in the company model are consistent with the outcome data used in the model.

Use of data from CUV029 and CUV030

The company has provided limited information about the methods and results of studies CUV029 and CUV030. We have not had access to their study protocols, statistical analysis plans or clinical study reports (section 3.1.3, p 23 above). Although selected results from CUV029 were reported by Langendonk et al.[7], the protocol and analysis plan were not included in the online appendices. We also note that following GCP inspection of CUV029 and CUV030, the EMA concluded that they could not be relied on for the benefit-risk assessment (EPAR, p 39 and pp 83-84,[2]). The EMA used CUV039 as the pivotal study, to provide evidence of efficacy

and detailed methods and results are available for that trial in the EPAR document in addition to the 2015 Langendonk publication.[27] We therefore believe that it would be more robust to use results from CUV039 alone to inform the cost-effectiveness model.

Statistical analysis

The CS provides little information about the methods of statistical analysis used to derive the effectiveness estimates for the model (CS Table C12, p 59). It is simply stated that "The individual patient data for EPP-QoL scores was provided and the baseline/120-day data were used to stratify the results into three EPP-QoL groups". Thus we do not know whether ITT datasets were used, and if so what definition of ITT was employed (see section 3.1.6, p 40). We do not know the number of patients from each of the three studies included in the analysis and so it is not possible to estimate confidence intervals around the proportions cited. It is also unclear how the data from the three trials were pooled. In particular, it is unclear whether the method of analysis correctly reflected clustering of patients within trials, using a two-step or one-step approach suitable for ordinal data.[33,34] This is potentially important, given heterogeneity in study location and possibly patient characteristics (section 3.1.3 above). The company did not explain these issues in response to clarification questions (response to clarification questions 26/09/17 Question A5).

Extrapolation over time

Finally, we believe that the company's use of a single time point (120 days) to represent disease severity over a whole year is simplistic and likely to have biased DALY estimates. It ignores the following features of the data:

- There was a degree of imbalance between the trial arms at baseline, with a greater proportion of control patients in the severe EPP-QoL state at the start of the trials than afamelanotide patients: [redacted] vs [redacted] respectively (Table 18). We cannot assess whether this difference was statistically significant, but note that a small imbalance in disability at baseline can be amplified as DALYs are extrapolated over a long time horizon. As there was no correction for baseline severity in the model, this may have introduced bias in favour of afamelanotide.
- The company stated that they used day 120 as the follow up point because this was the longest follow-up interval available in all trials. However, it appears from the summary of included studies in section 9.4 of the CS that EPP-QoL was also collected at 180 days in all three trials; CUV029 (p 33), CUV030 (p 35) and CUV039 (p 38). We cannot assess

the effect of using 120 days rather than 180 days for the economic analysis, as we do not have the 180 day results. However, we note that for both CUV029 and CUV039, the largest between-arm difference in mean EPP-QoL was observed at four months.[27] This can be seen in Figure 1 below (top panel).

- A large reduction in severity was evident between baseline and 120 days in the control group as well as in the intervention group (see Table 18). For comparison, the mean EPP-QoL results for all time points in studies CUV029 and CUV039 are shown in Figure 1 below.[27] This shows a pattern of improvement in both groups over the first 6-8 months, followed by a return close to baseline by 12 months in CUV039. The reasons for the initial improvement in the control group might be related to a placebo effect (although some degree of unblinding was likely in these studies); improved monitoring and standard treatment for all trial participants; seasonal effects (recruitment occurred in May and June in the US CUV039 study); and/or a 'regression to the mean' effect (if patients were more likely to consult a specialist and hence be recruited to a trial, at times when their quality of life was worse than usual).
- Whatever the cause of these trends, it does not appear that the four-month snapshot of quality of life is representative of the whole year. We conclude that the company's analysis is likely to have overestimated the benefit of treatment whether quantified in DALY or QALY terms.

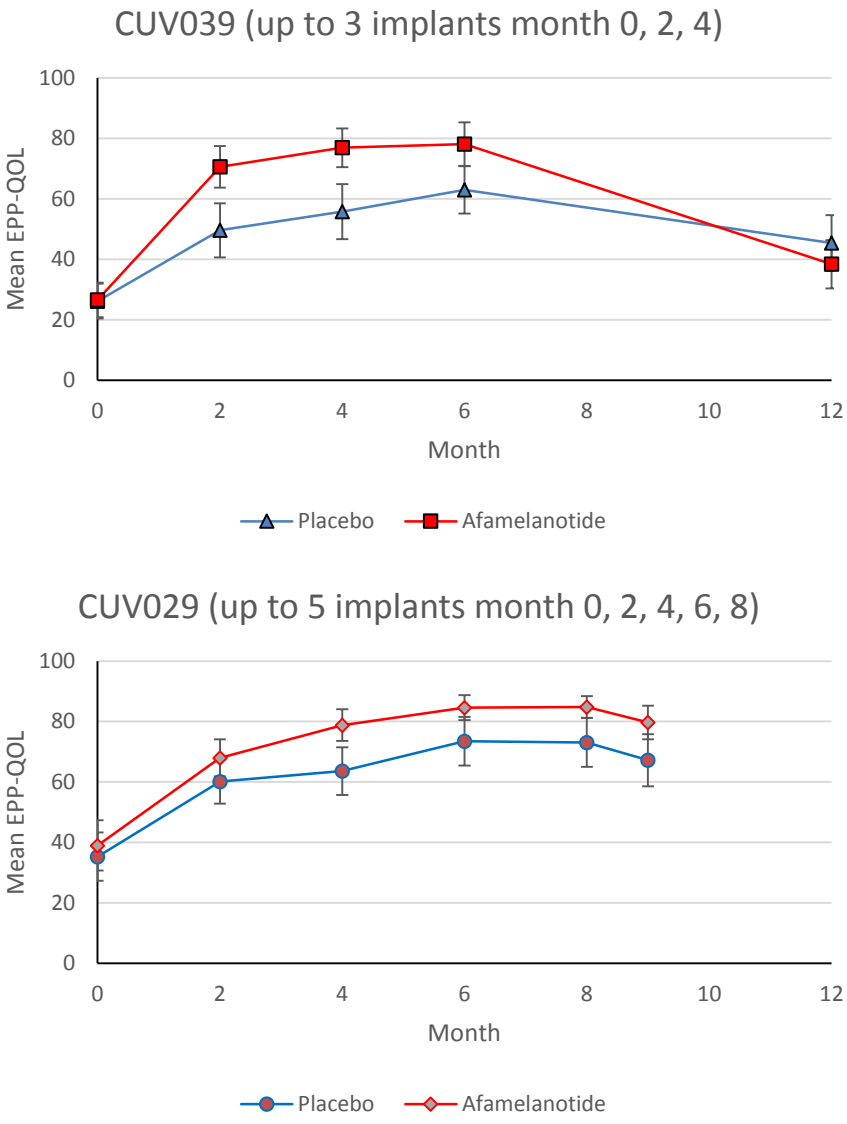

Figure 1 Mean EPP-QoL for studies CUV029 and CUV039

Source: CUV029 data from Langendonk et al. 2015 (Table 4, p 56)[7]. CUV039 data from EPAR (Table 23, p 64)[2], Error bars show 95% confidence interval estimated by ERG, using large sample method based on reported numbers of observations and standard deviations.

4.3.3.3 Mortality rates

Annual probability of death by age for both treatment groups was taken from UK National Life Tables (ONS) (www.ons.gov.uk/ons/taxonomy/index.html?nscl=Life+Tables#tab-data-tables). It appears that 2010-12 figures were used, rather than the most recent estimates based on data from years 2012 to 2014. Rates were averaged for males and females, assuming a 50:50 gender mix at all ages. This is not realistic, but will not affect the cost-effectiveness results.

4.3.3.4 Resource use and costs

The company model includes costs for drug acquisition and administration, laboratory tests, and follow-up appointments with the patient's care team. A list of unit costs is provided in Table D3 (CS p 74). Table D4 (CS, p 75) summarises assumptions about staff time for implant injection visits. Other assumptions that govern resource use that were not reported in the CS were derived from the model. We present a summary of annual resource use and costs using the company base case assumption of [redacted] implants per year in Table 19. Note that the estimated costs of implants and administration do not accord with those reported in Table D6 of the company submission (CS, p 77).

Table 19 Summary of annual costs

Resource	Unit cost	Quantity per year			Cost per year	
		Afamelanotide	Standard care		Afamelanotide	Standard care
Medication						
Implant	£12,020	[redacted]	-		[redacted]	-
Vitamin D & calcium	£0.04	365	365		£15	£15
beta-carotene	£0.05	0	0		£0	£0
					[redacted]	£15
Administration						
Implant injection	£203.75	[redacted]	-		[redacted]	-
Final visit of year	£136.25	1	-		£136	-
					[redacted]	£0
Laboratory tests						
ETP	£2	2	1		£4	£2
Plasma porphyrin	£2	2	1		£4	£2
CBC	£2	2	1		£4	£2
Ferritin	£2	2	1		£4	£2
Liver functioning	£1	2	1		£2	£1
					£18	£9
Follow up						
Dermatology screen	£170	2	1		£340	£170
Photoprovocation	£135	1	1		£135	£135
					£475	£305
					[redacted]	**£329**

ETP - erythrocyte total protoporphyrin; CBC – complete blood count

Number of implants

The cost of treatment is largely governed by the mean number of implants per patient per year. The SmPC recommends three implants per year, up to a maximum of four. The costs in the company base case analysis are based on a mean of [redacted] implants per patient per year (CS Table D5, p 76), with the proportions of patients receiving zero to four implants cited as 'CLINUVEL data on file'. In response to a clarification question, the company explained that their estimates are based on 'real world' use: [redacted] (clarification response, 02/10/17). For cross validation, we checked the number of implants that the company model reported from the long-term follow-up study by Biolcati et al. (Table 20).[11] However, it should be noted that the Swiss centre allowed patients to have up to six implants per year, which is more than the capped value of four in the SmPC.

Table 20 Number of afamelanotide implants per year

Number of implants	N	Mean	SD
Company base case		[redacted]	
Swiss centre[a]	53	[redacted]	[redacted]
Italian centre[a]	120	[redacted]	[redacted]
Weighted average (Swiss & Italian)[a]	173	[redacted]	

[a] Biolcati et al. 2015

The mean number of implants can be changed in the company model. This changes the cost outputs but not the estimated effects. Thus the model generates the same number of DALYs avoided per patient treated, regardless of how many implants those patients were assumed to be using. In reality, treatment effectiveness is likely to be tied to the number of implants a patient receives. We note that if the mean number of implants costed in the company base case model ([redacted]) is not commensurate with average use underlying the effectiveness evidence, the results will be biased. CUV030 and CUV039 allowed up to three implants for patients in the intervention group, and CUV029 up to five implants. However, the mean number of implants per patient used in these three trials is not publicly available, and not reported in the CS. The CS includes a scenario analysis varying the mean number of implants per patient per year (CS Table D15, p 87). This analysis is helpful for understanding how the ICER might have been underestimated, if the company base case estimate of [redacted] implants is less than average use in the clinical trials. In additional ERG analysis, we also explicitly model how effectiveness (QALYs

gained), in addition to cost, is likely to change if the maximum number of implants per patient per year is varied (See section 4.4 below).

Drug acquisition costs

The cost per implant is reported as £12,020. Assuming a mean number of implants of [redacted] per year, this equates to [redacted] per year.

The model also assumed ongoing use of vitamin D and calcium for all patients, whether treated with afamelanotide or not. These costs cancel out of the incremental cost calculations. The company assumed that no patients received beta-carotene in either arm. We were advised by our clinical experts that routine beta-carotene use is uncommon, as it has questionable efficacy and causes orange pigmentation of the skin. Given this and the low cost of beta-carotene, its level of use is not an important issue for this appraisal.

Administration costs

In addition to drug acquisition costs, afamelanotide requires an appointment to inject each implant and a final visit after the last implant of the year. The company used estimates from Erasmus University to quantify the staff time required for each injection visit (CS Table D4, p 75). For each implant injection visit, this included: 15 minutes from the principal physician, 30 minutes from one consultant, 15 minutes from a second consultant and an hour from a nurse. The final visit of the year was assumed to require 15 minutes from the principal physician, 15 minutes each from two consultants, and one hour of nurse time. Based on PSSRU estimates of the cost per hour a medical consultant (£135) and band 5 nurse (£35)[35] and assuming [redacted] implants per year, the company estimates the administration cost of afamelanotide at [redacted] per patient per year. Experts consulted by the ERG believed that the resource use for injection visits may be higher than would be seen in UK practice. Thus the cost of administering the implants might be an overestimate.

Monitoring costs

The company included the cost of two full body skin examinations for patients on afamelanotide, as recommended in the SmPC. They assumed that patients on standard care would have one fully body skin examination per year. Each screening visit was assumed to take one hour of consultant and one hour of nurse time, costing £170 (at Personal Social Services Research Unit (PSSRU) estimates of the cost per hour). Experts consulted by the ERG thought that patients with EPP would not all be having an annual full dermatological scan under current NHS practice. They also suggested that the assumed staff time per visit was excessive.

The company also assumed that patients would have one photoprovocation test per year, whether or not they were using afamelanotide, at a cost of £135 (one hour of consultant time). Experts consulted by the ERG questioned whether this was necessary or acceptable.

Laboratory resource use and costs consisted of the following tests: erythrocyte total protoporphyrin (ETP), plasma porphyrin, complete blood count (CBC), ferritin, and liver functioning. The company assumed that under current practice patients have one of each test per year, and that with afamelanotide two tests per year would be needed. Costs for these tests were derived from NHS Reference Costs, in line with NICE guidance.

Costs of implementation

Conditions of marketing specify that the company should provide an educational training package for physicians, comprising face to face training material, educational video, SmPC and registry information sheet.

Productivity

The base case analysis only includes NHS costs. But the company highlights that EPP has an effect on employment, choice of profession, productivity and earnings: "a proportion of EPP patients is known to be unemployed, others are limited in their productivity, some have full employment, and others have taken up nocturnal employment" (CS, p 80)[17 31 32]. They explored the possible societal costs of EPP and assumptions about how they might be alleviated in a scenario analysis.

4.3.4 Cost effectiveness results

Results from the company model are presented section 12.5.1, of the CS (pp 81-82). For the base case analysis an incremental cost per DALY avoided of £278,471 is reported (see Table 21). The company notes that the incremental cost of [redacted] is largely driven by the cost of the afamelanotide implant, assuming a mean use of [redacted] implants per person per year and a cost per implant of £12,020. They note that the other costs included in the model have a small impact on total costs. The incremental benefit was [redacted] DALYs averted.

Table 21 Base case cost effectiveness results

	Discounted costs	Discounted DALYs
Afamelanotide	[redacted]	[redacted]
Standard care	[redacted]	[redacted]

Incremental	[redacted]	[redacted]
ICER	**£278,471 per DALY averted**	

4.3.5 Assessment of uncertainty

The approach to sensitivity analysis is described in section 12.4 (pp 79-81) of the CS, and the results are reported in section 12.5.11 (pp 86-88). The company reported on four deterministic sensitivity analyses, which we discuss below, changing:

- the disability weights;
- the starting age and time horizon;
- the number of implants per patient per year that are costed; and
- the perspective, from NHS to societal.

The CS does not include a probabilistic sensitivity analysis (PSA).

This represents a very limited exploration of uncertainty. In particular, the CS does not present any sensitivity analysis over the parameters that reflect treatment effectiveness in the model or the methods and assumptions used to derive them. As discussed in section 4.3.3.2 (p 75) above, we believe that there is substantial uncertainty over the robustness of these parameters and assumptions.

4.3.5.1 Disability weights

The base case used a proxy of [redacted], with disability weights from the GBD 2010 survey (Table 22). The company tested two variations on this analysis, in which the disability weight for mild disease was changed from 0.03 in the base case, to 0.04 (Scenario 1) and 0.02 (Scenario 2). In each case, the ratios of the weights for moderate to mild disease (4.97) and severe to mild disease (3.51) were fixed at the base case values. A third scenario tested the effect of using the [redacted] estimates of disability weights for [redacted].[29]

Table 22 Scenario analysis: disability weights

Disability weight	[redacted]			[redacted]
	Base case	**Scenario 1**	**Scenario 2**	

Mild	0.030	[redacted]	[redacted]	[redacted]
Moderate	0.149	[redacted]	[redacted]	[redacted]
Severe	0.523	[redacted]	[redacted]	[redacted]
Incremental cost	[redacted]	[redacted]	[redacted]	[redacted]
Incremental DALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£ per DALY averted)	£278,471	£208,854	£417,707	£727,143

This analysis illustrates the sensitivity of the ICER to changes in the disability weights. Using weights for the proxy condition of [redacted] has the largest impact, because the gradient of the weights between mild, moderate and severe disease is less steep. Thus the benefit of reducing the proportion of patients with moderate or severe disease with the use of afamelanotide is lower. We note that the [redacted] estimates for [redacted] were derived from SF-6D scores, so are really utility decrements. This means that the ICER for the [redacted] scenario (£727,143) can be interpreted as an incremental cost per QALY gained.

4.3.5.2 Starting age and time horizon

The base case is for a cohort modelled from the age of [redacted]). The company presented a scenario analysis for a younger cohort, from the age of 18 to 78 years (60 year horizon).

Table 23 Scenario analysis: age and time horizon

	Base case (age 38 to 73)	Age 18 to 78
Incremental cost	[redacted]	[redacted]
Incremental DALYs	[redacted]	[redacted]
ICER (£ per DALY averted)	£278,471	£278,471

Although the incremental costs and DALYs are higher in this scenario than in the base case, reflecting the longer time horizon, the ICER is unchanged. As noted in the CS (p 69), the insensitivity of the ICER to the time horizon is a necessary result of model assumptions:

[redacted] These assumptions also mean that the ICER is insensitive to starting age. In reality there may be differences in the effects or costs of treatment at different ages, for example if younger patients are better able to make changes to their lifestyle. But there is insufficient evidence to model such possible effects.

4.3.5.3 Number of afamelanotide implants

The base case is costed, assuming a mean of [redacted] implants per person per year. The company tested the effect of changing this assumption: assuming a mean of 3 or 4 implants per year. The company notes that as the change is modelled, it only changes the cost of treatment, not the treatment effect. Thus with more implants per person, the incremental cost and ICER are higher (and conversely, with fewer implants the incremental cost and ICER are lower).

Table 24 Scenario analysis: number of implants

	Base case: [redacted] implants per year	3 implants per year	4 implants per year
Incremental cost	[redacted]	[redacted]	[redacted]
Incremental DALYs	[redacted]	[redacted]	[redacted]
ICER (£ per DALY averted)	£278,471	£378,561	£503,672

We interpret this analysis as demonstrating uncertainty over the ICER related to potential over or under-estimation of the mean number of implants that were associated with the clinical effectiveness results used to drive the model (from studies CUV029, CUV030 and CUV039).

4.3.5.4 Inclusion of societal costs

The base case analysis is conducted from an NHS perspective. In this scenario analysis, the company explored the possible effect of afamelanotide on earnings for people with EPP. This was based on the following assumptions:

- Mean weekly wage: £518 (source cited as a website that was not available)
- Retirement age of 62 (OECD)
- Proportion of mean wage without treatment: 50% (assumption)
- Proportion of mean wage with treatment: 67% year 1; 83% year 2 and 100% year 3+ (assumption).

Table 25 Scenario analysis: societal costs

	Base case: no societal costs	Scenario analysis: increase from 50% to 100% of mean wage over 3 years
Incremental cost	[redacted]	[redacted]
Incremental DALYs	[redacted]	[redacted]
ICER (£ per DALY averted)	£278,471	£172,302

Alternative assumptions about the gap in mean weekly earnings with and without treatment were also tested (see Table D15, CS p 87). However, these were not explained and we were unable to replicate them.

We acknowledge the occupational effects of EPP and their importance to patients and their families. Estimates of productivity costs are not usually taken into consideration in NICE appraisals, but they can be presented alongside a reference case analysis when appropriate. We note the high degree of uncertainty over the company's scenario analysis. Evidence of improving employment, productivity or earnings is not available from the clinical trial programme or long term follow up, up to eight years in the analysis presented by Biolcati et al.[11] Although they do present anecdotal evidence, citing cases where individuals reported being able to take up educational and occupational activities that they did not think they could do without treatment.[11] (see section 0 for the ERG's discussion of the impact of afamelanotide beyond direct health benefits).

4.3.6 Model validation

4.3.6.1 Internal consistency

The company states that internal validation of the model was conducted by a senior health economist not involved in the initial model build (CS section 12.7.1, p 89). No further information is given about how this validation was conducted.

The ERG conducted a series of checks on the model:

- We checked that all of the input parameters in the model were consistent with the numbers cited in the CS and also in the root source of evidence when possible.
- We visually checked the formulae throughout the model, to ensure that they were correctly connected to input parameters and the chain of calculations through the model.
- We replicated some aspects of the model, including the disability weight and cost calculations.
- We tested the reproducibility of the analyses reported in the CS, including the base case and sensitivity/scenario analyses.
- We ran a series of 'stress tests' on the model, checking that changes to input parameters had the expected results.

These tests did not identify any serious data entry or coding errors and we believe the model to be internally consistent. One small rounding error meant that the proportions of patients with

mild, moderate and severe disease in the company's model did not sum to 100% (at baseline for the afamelanotide arm, and 120 days for standard care, see Table C12 p59 CS). We corrected this in our additional analysis by rounding up the proportions of patients assumed to have mild disease. This led to a very small change to the company's base case ICER: from £278,471 per DALY averted to £278,386 per DALY averted.

4.3.6.2 External consistency

The company stated that "to our knowledge, this is the first economic evaluation of EPP attempted, therefore it was not possible to validate to external evidence sources." (CS page 89).

As stated earlier, the ERG identified a published abstract that reported some results from a model of afamelanotide for the treatment of EPP in adult patients (Thompson et al).[3]

[redacted] Other than this abstract we have not identified any other models or evidence sources that would provide a means of external validation.

4.3.7 Summary of ERG critique of company model

We consider that the structure of the submitted model is appropriate. It entails some strong simplifying assumptions:

[redacted] This is reasonable given current evidence.

However, we do have serious concerns about the way in which effectiveness was estimated and valued in the form of DALYs:

- There is insufficient information about the development and validation process of the EPP-QoL scale. It also appears that the items and scoring system may have been revised after initial analysis of trial results, which introduces risk of bias.

- The definition of mild, moderate and severe disease by division of the EPP-QoL scale into thirds is arbitrary and we cannot assess if it is consistent with the disability weights attached to these levels of severity in the DALY calculations.
- We do not know if [redacted] is an appropriate proxy condition for EPP. There are similarities in some of the psychological and functional impacts, but it is not clear if the magnitude and levels of severity are comparable. The same applies to the alternative proxy condition of [redacted]
- We have insufficient access to information about the EPP-QoL methods and results of studies CUV029 and CUV30 to be able to assess their quality or check the results.
- We also have insufficient information about how the results of the three trials, CUV029, CUV030 and CUV039 were analysed and pooled. There is a lack of clarity over whether ITT datasets were used, the number of patients included from each trial and whether the method of pooling accounted for clustering or randomisation.
- Results from a single time point (120 days) were used to estimate DALYs incurred over the whole year. The company stated that they chose 120 days as this was the longest time point available from all three trials, but the CS indicated that EPP-QoL data was also collected at 180 days. Results from two trials, to which we had access, suggest that the choice of 120 days rather than 180 days would have favoured afamelanotide as there was a larger difference between groups at that time. The use of a single time point also ignored information about how EPP-QoL changed during follow-up and failed to correct for baseline imbalance in EPP-QoL severity, which would have favoured afamelanotide.

We also have some questions about the cost estimates used. These were very largely driven by an assumption about the mean number of implants per person per year. This figure was estimated from 'real world' data, and it is not clear whether this was consistent with use in the clinical trials. If not, this would be a source of bias.

Finally, we note that the analysis of uncertainty presented in the CS was inadequate. In particular, there was no attempt to estimate the extent or consequences of uncertainty over the effectiveness parameters and assumptions. Given the discussion above, we think this could be considerable. There was also no PSA.

4.4 Additional work undertaken by the ERG

4.4.1 Overview and rationale for additional analyses

We developed two alternative versions of the company model as platforms to explore alternative assumptions and parameter uncertainty:

- A simple QALY version of the company model, applying utility estimates for mild moderate and severe disease for the company's proxy of [redacted] (section 4.4.2.1)
- An ERG base case analysis, in which we estimated QALYs from mean DLQI results at 0, 60, 120 and 180 days from CUV039 mapped to EQ-5D scores (section 4.4.2.2)

The key features of these analyses are summarised in Table 26, with further discussion below.

Table 26 Key features of company base case and ERG models

	Company base case	Simple QALY version	ERG base case
Value for money	Incremental cost per DALY averted	Incremental cost per QALY gained	
Source of clinical data	CUV029, CUV030 and CUV039 (method of pooling not specified)	No change	CUV039
Outcome measure	EPP-QoL 12 item	No change	DLQI
Effectiveness statistics	Proportion of sample by thirds of EPP-QoL scale at 120 days: intervention and control groups	No change	Between-group differences in mean change from baseline DLQI at 60, 120 and 180 days
Method of extrapolation	Assumed fixed within year and between years	No change	Standard care modelled assuming linear change between observations, with return to baseline at 12 months. For afamelanotide we assumed: linear onset of benefit over two months after the first implant of the year and linear loss of benefit over 2 months after last implant of year. Assumptions tested in scenario analysis.

Valuation	Disability weights from GBD 2010 for proxy of [redacted][28]	Utilities assumed as 1-GBD disability weights and scenario with utilities for proxy [redacted]	Utilities mapped from DLQI to EQ-5D from registry data for moderate to severe psoriasis [37]
Mean implant use	[redacted] per person per year (not related to effectiveness)	No change	No change for costing, but effectiveness data based on maximum of 3 implants per year (as in CUV039), and scenarios with up to 2 or 4 implants per year.
Uncertainty	Limited deterministic sensitivity analysis	Additional scenario analysis and deterministic sensitivity analysis, as well as probabilistic analysis	

4.4.1.1 Rationale for use of QALYs

Mathematically, DALYs and QALYs are similar. Both are calculated in relation to a weighted survival curve, with DALYs being the area above the curve (the healthy life that is lost) and QALYs the area below the curve (the imperfect quality life that remains). In economic evaluation, we are interested in the area between two weighted survival curves: one with the intervention of interest and one with an appropriate comparator. This area would be identical for DALYs avoided and QALYs gained, except that the meaning and method of estimation of the weights used to adjust survival differs. For DALYs the construct of interest is 'health loss', whereas for QALYs it is 'welfare loss'.[28] Welfare (or 'utility') is affected by health, but is also subject to other influences. This conceptual difference leads to different methods of eliciting weights. The GBD 2010 disability weights were based on a survey in which respondents were asked to make a series of judgements about which lay descriptions of states they considered to be 'healthier'. In contrast, the weights used to calculate QALYs are derived from trade-off questions designed to elicit preferences, in which the welfare is indirectly elicited by asking what sacrifices people would accept for defined improvements health. For example, the UK tariff for scoring the EQ-5D was based on survey in which respondents were asked how many years of life they would give up to avoid impairments (time trade-off). The scales of measurement do

also differ: DALY weights lie between 0 (no disability) and 1 (maximum disability); while QALY utility weights can be less than 0 if the state is considered worse than death.

The company believes that DALYs are more appropriate than QALYs for quantifying the effects of treatment for people with EPP. They argue that QALYs are conceptually inappropriate because of the way that people with EPP adapt to their condition:

> "Individuals with EPP are left to modify their natural behaviour by leading an indoors-based life deprived or starved of light sources (Lecha et al. 2009), while seeking ways to manage their anxiety of long-lasting burns. As a result, the ability to lead a 'normal' life in the community is severely impacted. Such impacts include choice of education at an early age, social development and interactions, access to further education and ultimately employment (Holme et al. 2006; Biolcati et al. 2015a)." CS, p 65.

Adaptation is common for people with lifelong or chronic conditions and has implications for evaluation of interventions as; patients may rate their pre-treatment health status or value it more highly than might be expected by people without the condition; the response to treatment may be lower or slower than expected, as learned behaviour can be difficult to change. The company suggested that such effects might explain poor results with the generic SF-36 quality of life questionnaire. In study CUV017, participants' SF-36 scores were higher at baseline than expected (higher than population norms) and showed no marked trends over time associated with treatment dose (CS, pp 29-30).

The phenomenon of adaptation and resulting 'disability paradox', have been cited as reasons for preferring an extra-welfarist or non-utilitarian approach (like DALYs) for public policy appraisal.[38] However, there are various possible explanations for adaptation that have different implications for the moral basis of using adapted patients' ratings of quality of life to inform allocation public resources.[39] For example, patients may make a higher than expected assessment of their health state or quality of life because of cognitive denial or lowered expectations, or because of more positive activity adjustment and altered conceptions of health. From an economic point of view, the use of a common metric to value health improvements across different conditions and patient groups is necessary to make judgements about the opportunity cost of new technologies. NICE has reached a considered position that QALYs should be the primary measure of effectiveness for use in economic evaluations.[40] This applies

in the HST programme, so in appraising value for money the committee is expected to consider incremental cost per QALY gained.[26]

In addition to conceptual arguments, the company make a more practical argument that QALYs could not be used because of the lack of robust utility data (CS, p 64). We disagree with this judgement and present two sources of utility estimates below:

- published utility values for the company's chosen proxy of [redacted]; and
- a published equation to map from the DLQI to EQ-5D utilities.

Although less robust than a generic utility instrument, such as the EQ-5D, or direct utility measurement by people with EPP, we believe that mapping from the DLQI is superior to the use of disability weights (or utilities) for proxy conditions. It is illogical to argue that QALYs cannot capture the unique and nuanced effects of EPP and then argue that DALYs from a common illness ([redacted]) can capture the effects of EPP, or that an illness that has very little in terms of symptoms in common ([redacted]) can also adequately capture the disease.

For comparison, we also present a simple QALY version model of the company model (Scenario 1.0), with utilities for mild, moderate and severe disease defined by subtracting the GBD disability weights from 1. This is a simplistic approach, but provides a baseline for comparison of our other analyses.

4.4.1.2 Rationale for use of DLQI

The appropriateness of the DLQI and EPP-QoL questionnaires for EPP is central to the interpretation of the clinical effectiveness and cost-effectiveness evidence. There was a difference in the results of the pivotal study CUV039 with EPP-QoL and DLQI: changes over time and between groups were mostly statistically significant with the former but not the latter (see section 3.3.5 of this report for HRQoL results). This might have been related to the different items included in the questionnaires and/or to their framing. We summarise arguments below.

Face validity of content and framing

See Table 27 for a summary comparison of the content of the DLQI and EPP-QoL (15-item version used in CUV039 and 12-item version used for scoring). For copyright reasons we cannot reproduce the full questionnaires, but they can be downloaded online.

- The DLQI questionnaire is available from the Cardiff University Department of Dermatology website, along with instructions for use and related references: see http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/.
- The 15-item version of the EPP-QoL is included in the protocol for study CUV039 published in the online material for the 2015 Langendonk et al. journal paper (http://www.nejm.org/doi/full/10.1056/NEJMoa1411481).[7] The 12-item version is also available in Table S1 in the supplementary appendix to this paper.

The DLQI contains 10 questions on the impact of skin problems over the last week on symptoms, feelings, daily activities, social and leisure activities, work and study, personal relationships and treatment, each measured on a four point scale from 'very much' to 'not at all'. The EPP-QoL has 15 (12) questions about the impact of EPP over the last two months on symptoms, daily activities, social and leisure activities, on a similar four point scale. The wording of several EPP-QoL questions relates specifically to effects on a sunny day and on outdoor activities. It includes additional questions on transport and the ability to be spontaneous, but excludes questions about feelings and personal relationships. Three items were removed in the 12-item version of the questionnaire used to score the study results: frequency of the need to seek out shade or to wear protective clothing; and impact on work or study. Unlike the DLQI, the EPP-QoL includes a direct question on well-being ('much better' to 'worse') and one on improvement in quality of life ('very much' to 'not at all').

The face validity of the two questionnaires and appropriateness for economic evaluation is unclear. The EPP-QoL asks about EPP-specific symptoms, which is important if people with this condition would not recognise the DLQI description of 'itchy, sore, painful or stinging' skin as applying to their symptoms. But the EPP-QoL (12-item version) excludes questions on feelings and ability to work or study, which are important aspects of life. The company argues that anxiety and depression are significant features of EPP, but then omit them from the questionnaire. 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. The EPP-QoL does ask directly about well-being and quality of life. But we are concerned about the framing of the quality of life question (Q. 14), which does not allow for the possibility of deterioration. This is likely to have introduced 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.

Table 27 Comparison of questions from DLQI and EPP-QoL

Concepts[a]	DLQI questions[b] Over the last week, how much has skin affected...	EPP-QoL questions[c] Over the last two months, how much has EPP affected...
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]
Feelings	Q2. Embarrassed or self conscious	
Daily activities	Q3. Going shopping, looking after home or garden Q4. Clothes you wear	Q10. Going shopping, looking after home or garden on sunny day Q4. Choice of clothes on sunny day ~~Q9. Frequency not wearing protective clothing on sunny day~~ [d] Q15. Transportation method or seating preference
Social and leisure activities	Q5. Social or leisure activitites Q6. Sport	Q6. Social or leisure activities on sunny day 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
Work and study	Q7. Prevented or problem with work or study	~~Q2. Capacity to go to work or school~~ [d]
Personal relationships	Q8. Problem with partner, close friends or relatives Q9. Sexual difficulties	
Treatment	Q10. Treatment problems, e.g. making home messy or taking time	
Overall		Q1. Well-being Q14. Quality of life

[a] Adapted from key concepts for DLQI from analysis by Ali et al. 2017.[41]

[b] DLQI: http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/

[c] EPP-QoL: 15-item version, CLINUVEL Protocol CUV039, Appendix 5 page 51-51. Available as online supplement to Langendonk et al. 2015.[7]

[d] Item deleted in 12-item version of EPP-QOL, Langendonk et al. 2015, Table S1 p5 online supplement.[7]

Responsiveness of DLQI in EPP

Whilst the DLQI has been criticised for inadequately measuring the effect of some skin conditions,[18] the study by Holme et al. (2006), a British study that is the single largest study to measure quality of life in EPP patients, does not support this claim in an EPP population.[17] This study found that DLQI showed marked gradations in the severity of HRQoL for patients with EPP in the UK. Rather than not capturing the severity of the disease, it was the first study to show the difficulties that EPP patients face using a HRQoL instrument, the DLQI. Table 28 shows the distribution of DLQI severity categories from Holme et al.[17] It can be seen that the range of quality of life in UK EPP population ranged from fairly normal quality of life, to severely impaired, with the majority of patients in the 'very large effect' category. Patients with severe DLQI scores have a very poor quality of life.[22]

Since 2007, there have been algorithms available to map DLQI to EQ-5D.[37 41-44] We applied two available algorithms to the Holme et al. results to estimate the distribution of EQ-5D utility scores in this UK EPP population (Table 28). It shows a wide range of utility: from values close to population norms for patients with no or small DLQI effects, to values between 0.3 or 0.4 for patients with severe effects. For context, Table 29 presents utility scores for a range of other disease areas using reputable UK sources.

Table 28 Mapping DLQI to EQ-5D in a UK EPP population

Severity	N[1]	Proportion [a]	Score (assume centre)	EQ-5D[b]	EQ-5D[c]
No effect (DLQI ≤ 1)	6	3.41%	0.5	0.8679	0.9433
Small (DLQI 2-5)	15	8.52%	3.5	0.8091	0.8668
Moderate (DLQI 6-10)	32	18.18%	8.0	0.7209	0.7522
Very large effect (DLQI 11-20)	92	52.27%	15.5	0.5739	0.5611
Severe (DLQI 21-30)	31	17.61%	25.5	0.3779	0.3063
Total	176	100.00%	14.4	0.5962	0.5900
Mean			14.0	0.6033	0.5993
Best possible			0	0.8777	0.9560
Worst possible			30	0.2897	0.1916

[a] N and proportions are derived from Holme et al. (2006), the assumed central points of each severity and the mapping are the work of the ERG[17]

[b] Norlin 2012 (whole population), EQ-5D = 0·8777 – 0·0196 DLQI[37]

[c] Currie & Conway 2006 EQ-5D = 0.956–0.0255 DLQI[43]

Table 29 Comparison of utility scores

Disease	EQ-5D score	Mapping (Yes/No)	Study
Metastatic breast cancer	0.685	Yes	Lidgren 2007[45], NICE TA424
Heart attack/angina	0.628	No	Ara & Brazier[46] [a]
Arthritis / rheumatism / fibrositis	0.597	No	Ara & Brazier[46] [a]
Fabry Disease with ESRD and heart complications	0.584	No	Rombach 2013[47], Migalastat (NICE HST4)

EPP Erythropoeitic protoporphyria; EQ-5D Euroqol five dimensions questionnaire; DLQI Dermatology quality of life index; KDQOL-36 Kidney disease quality of life 36; ESRD End-stage renal disease

[a] Patients with comorbidities

On balance, the ERG considers that the DLQI is a more robust choice for use in the economic evaluation than the EPP-QoL. This judgement is based on the lack of information about the development and validation process for the EPP-QoL. We are also seriously concerned that questions were removed from the EPP-QoL without adequate explanation, and the scoring system may have been revised after initial analysis of trial data, which poses a risk of bias. Despite some criticisms of the unidimensionality of the DLQI and the under-representation of emotional aspects of some skin conditions, it has been extensively studied and evidence for its validity, reliability and responsiveness is available.[18] Further, we consider that the Holme et al. study has shown that the DLQI is capable of detecting the severe impact that EPP has on patients' lives.[17] There are also mapping algorithms that allow estimation of EQ-5D utility values from DLQI scores. In particular, we note that the algorithm developed by Currie and Conway, has been validated in an independent dataset of 3542 people with a range of skin conditions.[41] [43] We use this algorithm in our base case model described in section 4.4.2.2 below.

4.4.1.3 Rationale for use of trial data

The third set of issues that we examine in additional ERG analysis relate to our criticisms of the company's use of trial data, as summarised in section 4.3.7 above.

First, we use our simple QALY version of the company model (Scenario 1.0) to test the impact of adjusting for baseline differences between the study arms and possible attenuation of treatment effects after the last implant of the year. These analyses use the estimated proportions of patients with mild, moderate and severe disease (as defined by thirds of the EPP-QoL scale) at baseline and 120 days pooled data from CUV029, CUV030 and CUV039 (Table C12 p59 CS). The company just used the 120 day results in their analysis, assuming that these values would remain unchanged within and between years. We tested two alternative

scenarios: adjusting the distribution of severity for baseline differences (Scenario 1.1); and assuming a linear loss of the treatment benefit between 180 days and the end of the year (Scenario 1.2).

Our second approach is more of a departure. The ERG base case model (Scenario 2.0) uses effectiveness data from CUV039 only – to address our concerns about the lack of information about the methods and results of trials CUV029 and CUV030 and about the company's methods of pooling data from the three trials. We also change the outcome measure used to drive the model to the mean DLQI mapped to EQ-5D utility values. We present three scenarios modelling alternative assumptions about how the estimated utilities from observed data might change over time: assuming immediate onset of treatment benefit after the first implant of the year (Scenario 2.1); assuming slower loss of treatment benefit after the last implant of the year (Scenario 2.2); and a combination of fast onset and slow loss of treatment effect (attenuation) (Scenario 2.3). In our base case model we assume a maximum of 3 implants per year, to match the effectiveness data from study CUV039. We also present two scenarios modelling changes to the maximum number of implants per year: two implants (Scenario 2.4) and four implants (Scenario 2.5).

We also introduce an exploration of uncertainty over the effectiveness data for both sets of analysis, with deterministic as well as probabilistic sensitivity analysis. Thus each scenario is accompanied by three sets of sensitivity analyses, investigating the effect of uncertainty over the key cost-effectiveness drivers: treatment effectiveness; weights used to adjust life years (disability weights and utilities); and mean utilisation of implants per year, which drives the costs.

4.4.2 ERG methods

4.4.2.1 Simple QALY model

We adapted the company model to calculate QALYs alongside DALYs. The simplest version of this model (Scenario 1.0) uses utilities for mild, moderate and severe EPP estimated from the GBD disability weights for the same proxy as in the company's base case model (utility = 1 – disability weight). This is intended to provide a platform to examine changes to the company's base case model and as a comparison for our preferred model. All parameters were the same as in the company base case (see Table 30).

Table 30 Simple QALY model: Input parameters

Parameters	Standard care	Afamelanotide	Source
Severity at baseline			
Proportion in mild category	[redacted]	[redacted]	CS Table C12 p 59
Proportion in moderate category	[redacted]	[redacted]	CS Table C12 p 59
Proportion in severe category	[redacted]	[redacted]	CS Table C12 p 59
Severity at 120 days			
Proportion in mild category	[redacted]	[redacted]	CS Table C12 p 59
Proportion in moderate category	[redacted]	[redacted]	CS Table C12 p 59
Proportion in severe category	[redacted]	[redacted]	CS Table C12 p 59
Sample size			
Total CUV029, CUV030 & CUV039	119[b]	125[b]	CS p33, p35, p37
Disability weights (GBD 2010)			
[redacted] proxy (mild)	[redacted]		Salomon 2012
[redacted] proxy (moderate)	[redacted]		Salomon 2012
[redacted] proxy (severe)	[redacted]		Salomon 2012
Utility estimates	*Mean (95% CI)*		
Mean EQ-5D mild (intercept)	[redacted]		[redacted]
Decrement for moderate	[redacted]		[redacted]
Decrement for severe	[redacted]		[redacted]
Implant utilisation		*Mean (SE)*	
% of maximum implants per year, used for costing (mean = [redacted])		[redacted]	CS Table C12 p 59

[a] Rounding changed to ensure total sums to 100%

[b] ERG assumption that all patients who received study drug (not ITT) were included in the company analysis of EPP-QoL by severity

We conducted three scenario analyses on this model:

Scenario 1.0: Company base case, adapted to calculate QALYs as well as DALYs

Scenario 1.1: Same as Scenario 1.0, except the mean disability weight per year with afamelanotide was adjusted for the difference in severity (vs. standard care) at baseline.

Scenario 1.2: Same as Scenario 1.1, except the benefit of treatment (mean difference in utility with afamelanotide vs. standard care) was assumed to attenuate after the last implant of the year. We assumed a linear decline between month six and eight.

Scenario 1.3: Same as Scenario 1.0, except utilities for the company proxy condition were taken from a published source. We used estimates for [redacted] The survey included EQ-5D questionnaires, with utilities calculated with the UK Tariff. Regression modelling was used to estimate mean utilities and additional decrements for moderate and severe symptoms.

Error! Reference source not found. to **Error! Reference source not found.** illustrate how estimates of mean utility over one year for these four scenarios. Note that for Scenario 1.0 (**Error! Reference source not found.**) the mean utilities at month 4 are equal to 1 minus the disability weights in the company's base case model: [redacted] for standard care and [redacted] for afamelanotide (Table C13 p59 CS). The QALY gain per year is calculated as the area between the standard care and afamelanotide curves.

Figure 2 Simple QALY Scenario 1.0: company base case

Figure 3 Simple QALY Scenario 1.1: adjusted for baseline

Figure 4 Simple QALY Scenario 1.2: adjusted for baseline and attenuation

Figure 5 Simple QALY Scenario 1.3: utilities for proxy condition from literature

For sensitivity analysis we varied three sets of parameters:

- **Effects**: Note that sample sizes or measures of uncertainty were not reported around the severity distributions in Table C12 (CS p 59). For PSA, we used Dirichlet distributions for the four severity distributions, based on assumed sample sizes (all patients randomised and treated, as reported in section 9.4.1 of the CS). For deterministic sensitivity analysis we changed the proportion of patients treated with afamelanotide with mild disease at 120 days to between 60% and 90% (holding the ratio of patients with moderate to severe disease and other effectiveness parameters constant).
- **Weights**: For our scenarios with utilities calculated from proxy disability weights (1.0, 1.1 and 1.2), we used the same assumptions as the company (scenario 1 and 2 in Table D15 p87 CS). This entailed changing the disability weight for mild disease from [redacted] in the base case to [redacted] and [redacted], holding the ratios of mild to moderate and moderate to severe weights constant. We did not include the disability weights in the PSA. For Scenario 1.3, we fitted a beta distribution for the utility estimate for mild disease, and gamma distributions to the two decrement parameters. In deterministic sensitivity analysis, we varied the two decrement parameters between lower and upper 95% confidence limits.
- **Implants**: The mean number of implants costed per patient per year was based on the company's assumption ([redacted] per year). To include uncertainty over this parameter in the PSA, we assumed a beta distribution for the proportion of an assumed maximum number of implants that patients would actually receive ([redacted]). A standard error around this mean (0.049) was estimated from the implant utilisation reported for the Italian cohort (n=120) in the Biolcati et al. observational cohort (assumed maximum of three implants per year). For deterministic sensitivity analysis, we varied this parameter between 0.667 and 1.000, yielding a range of between two and four implants per year.

4.4.2.2 ERG preferred model

In our analysis:

- We used mean DLQI results from study CUV039 (at 0, 60, 120 and 180 days).[2]
- We first modelled mean DLQI through the year for the control group, starting from the observed baseline value and using change from baseline values to estimate mean DLQI

at 60, 120 and 180 days.[2] This approach enables correct propagation of uncertainty in the PSA, without treating repeated measures as independent variables.

- Then we modelled the DLQI curve for afamelanotide, using the between-group mean differences in DLQI at each time point. This retains patient randomisation in the trial, and builds in correlations between the control and intervention curves in the PSA.
- Utilities were estimated by mapping from the estimated mean DLQI values at each time point, using the mapping algorithm reported by Currie and Conway 2007.[43]
- We assumed a mean of three implants per person per year in our base case analysis (the maximum for the intervention group in study CUV039 and as recommended in the SmPC).
- We made the same assumptions about percentage utilisation as in the simple QALY model. Thus, we assumed that on average patients would use [redacted] of the maximum permitted number of implants per year, giving a mean of [redacted] implants per year for costing. This provides consistency with the company's assumptions based on 'real life' utilisation rates. We would have preferred to use the utilisation rate from CUV039, the same source as the effectiveness data, but data on the mean number of implants per patient was not available to us.

Input parameters for our preferred model are reported in Table 31 below.

Table 31 ERG preferred model: Input parameters

Parameter	Mean	SE	Source
DLQI standard care (placebo group)			
Baseline: day 0	10.4	0.87	EPAR (Table 18 and 20, pp 61-79)
Change: day 0 to day 60	-4.0	0.84	
Change: day 0 to day 120	-6.5	0.96	
Change: day 0 to day 180	-7.3	0.85	
Treatment effect (afamelanotide vs. placebo)			
Mean difference: day 0 to day 60	-2.0	1.20	EPAR (Table 18 and 20, pp 61-79)
Mean difference: day 0 to day 120	-1.3	1.30	
Mean difference: day 0 to day 180	-0.8	1.25	
EQ-5D mapping			
Maximum utility, DLQI=0 (Intercept)	0.878	0.039	Currie and Conway
Utility loss per unit increase in DLQI (slope)	0.020	0.004	
Implant utilisation			
% of maximum implants per year, used for costing (mean = [redacted])	[redacted]	[redacted]	CS Table C12 p 59

For the base case analysis (**Scenario 2.0**), we made the following assumptions about how utilities would be expected to change between modelled time points:

- **Baseline utility**: both groups were assumed to start with the same utility.
- **Onset of treatment effect**: there is a gradual increase in utility for the afamelanotide group over a two month period after the first implant of the year.
- **Effect with subsequent implants**: the treatment effect changes gradually between subsequent timepoints, with further increases in utility after the second and third implants.
- **Attenuation of treatment effect**: the relative treatment effect (mean difference between arms) gradually declines over a two month period after the last implant of the year (from day 180 to 240). Thus, the estimated utility for afamelanotide and standard care converge over two months.
- **End of year**: We assumed that both groups return to their baseline values at the end of the year, with no persistence of effect between years. This assumption is supported by EPP-QoL data at 360 days in study CUV039, which showed a mean change from baseline that was slightly lower in the afamelanotide group than in the placebo group

(not statistically significant) - see Figure 1 on page 80 above.[2] (We note that DLQI was not collected at 360 days in CUV039).

- This pattern is assumed to repeat in subsequent years, yielding the same mean QALY gain with treatment (vs. standard care) every year over the time horizon.

The resulting estimates of utility over a year are illustrated in Figure 6. Note that the observed datapoints (with adjustment for baseline) are shown with solid circles and squares, and assumed changes between these points by solid lines. The empty points and dotted lines represent ERG assumptions over extrapolation after the last DLQI observations at 6 months.

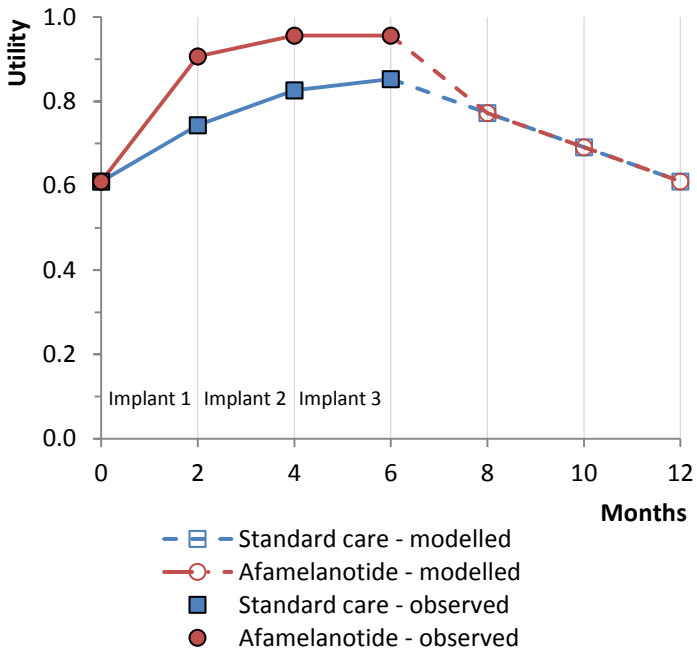

Figure 6 ERG Scenario 2.0: ERG base case

We conducted a set of three scenario analyses on our base case model to explore the effects of different assumptions about the speed of onset of treatment benefits after the first implant of the year and the speed of decline after the last implant of the year:

Scenario 2.1 Fast onset of effect (immediate) after the first implant of the year, with the observed mean difference in DLQI for afamelanotide vs. control at day 60 applied throughout the first two months. The rationale for this scenario is

bioavailability and pharmacodynamics information reported in the EPAR, which showed a peak of melanin density at day 15 (+0.68 from baseline) (CUV028 group 2, Table 4, p 44).[2] We note however that there is uncertainty about the plausibility of this scenario, because of uncertainty over how quickly a change in plasma levels translates to physical protection against light, how that translates to behaviour change (taking the risk of more sun exposure) and subsequently better utility.

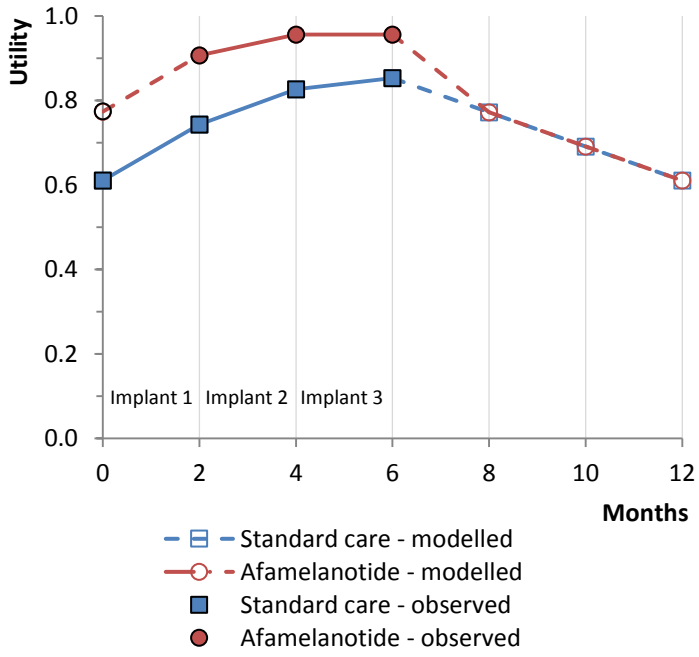

Figure 7 ERG Scenario 2.1: fast onset of effect

Scenario 2.2 Slow attenuation of effect (over six months). This illustrates a slower decline in treatment benefit after the last treatment of the year than in our base case, with a linear loss of the DLQI mean difference over six months (from day 180 to 360). Pharmacodynamic information from the EPAR (Table 4 p 44) shows that mean melanin density was starting to decline by day 60 (+0.38)).[2] Again, there is uncertainty over the plausibility of this scenario.

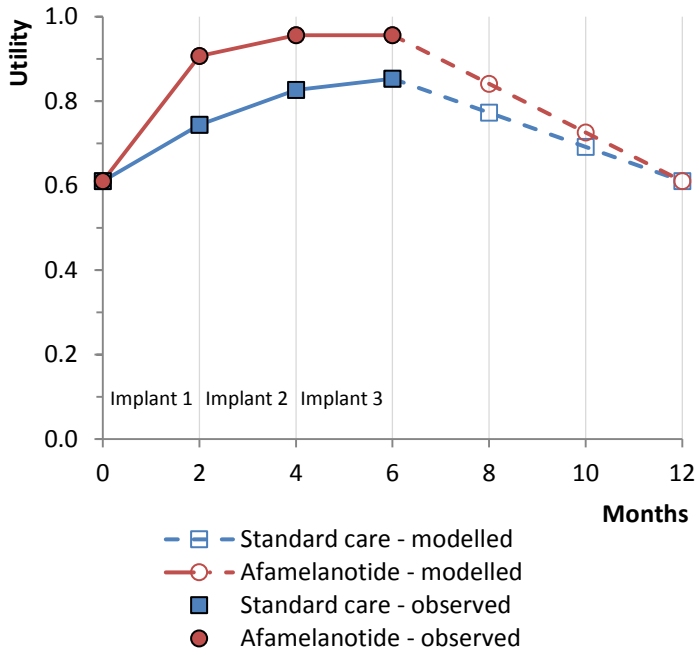

Figure 8 ERG Scenario 2.2: slow attenuation of effect

Scenario 2.3 Fast onset and slow attenuation, combining the assumptions in scenarios 2.1 and 2.2, with an immediate onset of benefit after the first implant of the year and gradual loss of benefit over six months after the last one. This is the most favourable variation on the ERG QALY model that we tested, producing the largest QALY gain (and lowest ICER).

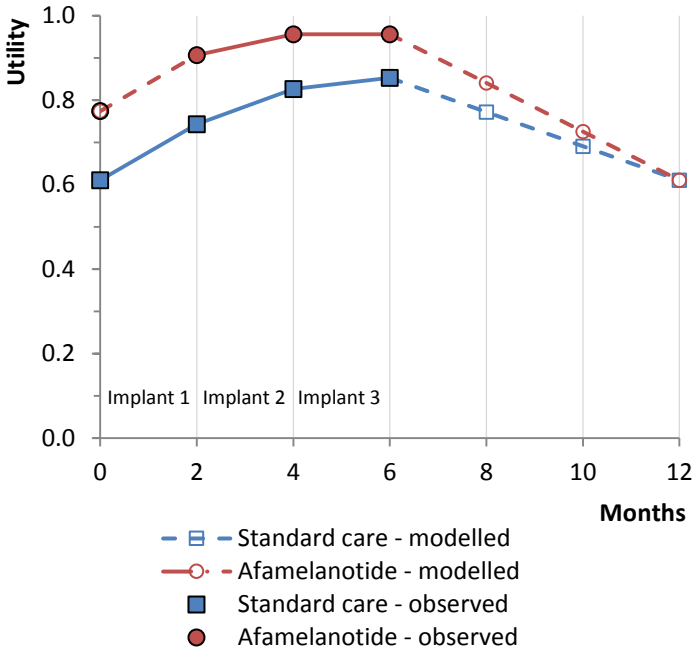

Figure 9 ERG Scenario 2.3: fast onset and slow attenuation

Our final pair of scenarios are designed investigate the impact of changing the maximum number of implants per patient per year:

Scenario 2.4 Assumes a maximum of two implants per year. Similar to our base case, there is a gradual loss of effect after the last implant, with utility in the afamelanotide arm declining to match that in the standard care arm over a two month period. These assumptions reduce the incremental effect, but also the incremental cost. Note that the same assumption about the mean proportion of implants that patients use is the same as in our base case ([redacted]), so a mean of only [redacted] implants is included in the cost calculations for this scenario.

Scenario 2.5 Assumes a maximum of four implants per year. Here we assume that the treatment effect at eight months is the same as that observed at six months, with attenuation of this effect over the next two months. And only

[redacted] ([redacted]) of the maximum four implants are included in the cost calculations.

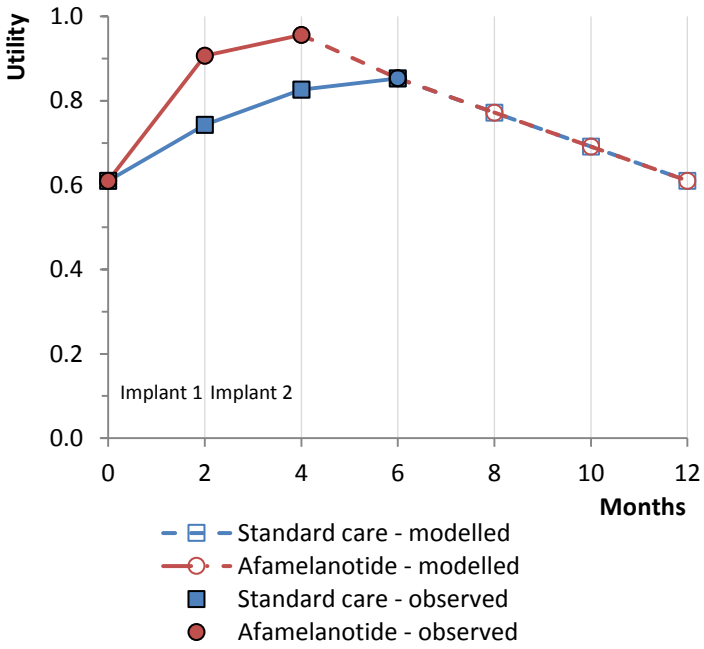

Figure 10 ERG scenario 4: fewer implants (up to 2 per year)

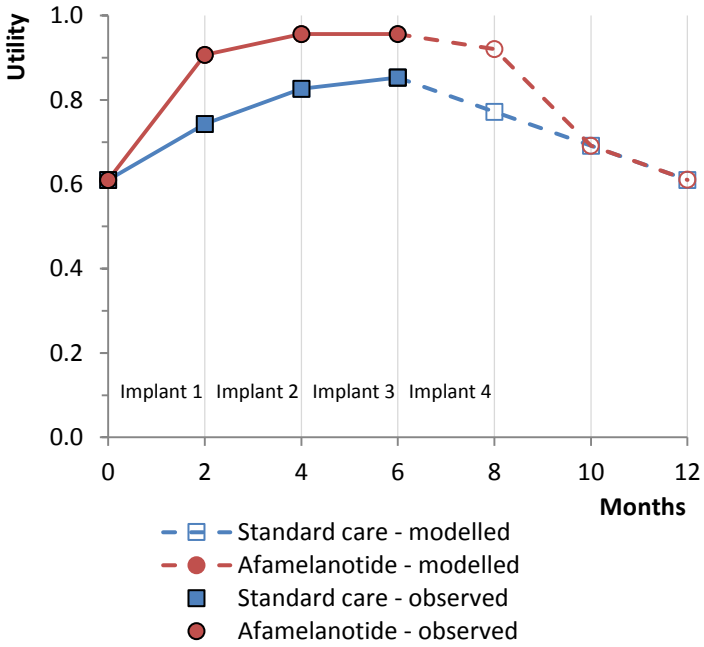

Figure 11 ERG scenario 5: more implants (up to 4 per year)

4.4.3 ERG results

4.4.3.1 Simple QALY model

Results from our simple QALY model are presented in

Table 32. The ICER for the simplest QALY adaptation of the company's model is £278,386 per QALY gained. Note that the small difference between this and the company's base case ICER of £278,471 is purely due to the small rounding error in the effectiveness data which we corrected (see 4.3.6.1 above). Otherwise the models are identical. Scenarios 1.1 and 1.2 shows that the company's ICER would have been higher had they adjusted for baseline differences between study arms in EPP-QoL scores, and if they had made assumptions about attenuation of treatment benefit for the part of the year when the patients' did not have implants. The final scenario in this simple model shows that using estimates of utilities from the literature for the company's proxy condition yielded a much smaller QALY gain, and hence higher ICER.

Table 32 Simple QALY model results

Treatment	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SCENARIO 1.0: company base case					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	*£278,386*
SCENARIO 1.1: adjustment for baseline					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	*£454,800*
SCENARIO 1.2: adjustment for baseline and attenuation of effect					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£779,657
SCENARIO 1.3: utilities for proxy condition					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£1,726,802

The ERG does not believe that any of these scenarios are plausible because they rely on an analysis of trial data that was post hoc and not transparent, the definitions of mild, moderate and severe disease were arbitrary and not related to the levels of severity in the disability weights/ utilities, which were also derived for a non-EPP population ([redacted] proxy).

ERG preferred model

Results for the ERG preferred version of the model are shown in Table 33. It can be seen that our base case was much higher than the company's base case, at £1.6 million per QALY gained. This result was similar to scenario 1.3, which used utility estimates from the literature rather than the simple estimates based on GBD disability weights. The ICERs were lower in scenario analyses exploring the impact of more favourable assumptions about the speed of onset after the first implant of the year and attenuation after the last implant of the year. However, our most favourable scenario (2.3) still yielded an ICER of over £1.1 million per QALY gained. Similarly, the ICER remained high when we modelled changes to the maximum number of implants per patient per year.

Table 33 ERG preferred model results

Treatment	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SCENARIO 2.0: ERG base case					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£1,605,478
SCENARIO 2.1: fast onset					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£1,290,678
SCENARIO 2.2: slow attenuation					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£1,343,359
SCENARIO 2.3: fast onset and slow attenuation					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£1,115,671
SCENARIO 2.4: maximum 2 implants per year					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£1,337,494
SCENARIO 2.5: maximum 4 implants per year					
Standard care	[redacted]	[redacted]	-	-	-
Afamelanotide	[redacted]	[redacted]	[redacted]	[redacted]	£1,785,957

The ERG believes that this model is preferable to our simple QALY adaptation of the company's DALY model. It relies on published data from the pivotal trial (CUV039) analysed in accordance with a pre-defined plan, and explicitly accounts for changes in quality of life across 12 months,

adjusting for baseline differences and changes under standard care. The utility estimates are derived from quality of life assessments by EPP patients, using a validated mapping algorithm from the DLQI to EQ-5D. There is uncertainty over which method of extrapolating between observed data points is more realistic. However, our scenario analysis demonstrates that the ICERs do not fall below £1,100,000 per QALY.

Deterministic sensitivity analysis

For each scenario, we used deterministic sensitivity analysis to examine the impact of changing three sets of input parameters: treatment effects; the disability or utility weights; and the mean number of implants per year that were costed. The results for the simple QALY model and ERG preferred model are shown in Table 34 and Table 35 respectively. It can be seen that in no case did the ICER fall below £150,000 per QALY.

The deterministic sensitivity analysis results are also shown in the Tornado graphs below Figure 12). These illustrate that the analyses based on GBD disability weights (Scenarios 1.0, 1.1 and 1.2) are much more favourable than those based on utility weights. They also illustrate the very wide range of uncertainty around the ERG preferred model ICERs. This is caused by the small magnitude of the mean differences in DLQI, which yielded very small estimates of incremental QALYs at the lower confidence limits.

Table 34 Simple QALY model: ICERs for lower and upper parameter ranges

Scenario	Effects[a]		GBD disability weight (mild)		Mean implants per year	
	Lower	Upper	Lower	Upper	Lower	Upper
	60.0%	90.0%	0.02	0.04	2	3
1.0	£221,520	£405,664	£208,790	£417,579	£253,371	£378,444
1.1	£320,421	£933,075	£341,100	£682,200	£413,934	£618,266
1.2	£549,293	£1,599,556	£584,743	£1,169,486	£709,600	£1,059,884
	Effects[a]		Disutilities (moderate; severe)[b]		Mean implants per year	
	60.0%	90.0%	(0.021;0.047)	(0.045;0.093)	2	3
1.3	£1,299,022	£2,889,993	£1,249,637	£2,542,183	£1,571,639	£2,347,455

[a] Proportion mild (120 days with treatment)
[b] Disutility vs. mild (moderate; severe)

Table 35 ERG preferred model: ICERs for lower and upper parameter ranges

Scenario	Effects[a]		Utility loss[b]		Mean implants per year	
	lower	Upper	lower	Upper	lower	Upper
	(-0.4;-0.0;-0.0)	(-4.9;-4.8;-4.5)	0.018	0.033	2	3
2.0	£552,284	£17,543,596	£1,198,119	£2,263,826	£1,461,217	£2,182,524
2.1	£457,817	£11,963,277	£963,194	£1,819,939	£1,174,704	£1,754,578
2.2	£438,286	£17,539,848	£1,002,508	£1,894,222	£1,222,651	£1,826,193
2.3	£376,615	£11,961,534	£832,591	£1,573,167	£1,015,422	£1,516,669
	Effects[a]		Utility loss[b]		Mean implants per year	
	(-0.4;-0.0;-0.0)	(-4.9;-4.8;-4.5)	0.018	0.033	1.3	2
2.4	£500,501	£11,766,004	£998,131	£1,885,952	£1,218,005	£1,815,451
	Effects[a]		Utility loss[b]		Mean implants per year	
	(-0.4;-0.0;-0.0)	(-4.9;-4.8;-4.5)	0.018	0.033	2.7	4
2.5	£534,044	£23,318,720	£1,332,805	£2,518,313	£1,625,012	£2,429,736

[a] Mean difference DLQI change (day 60;120;180)
[b] Utility loss per unit increase in DLQI

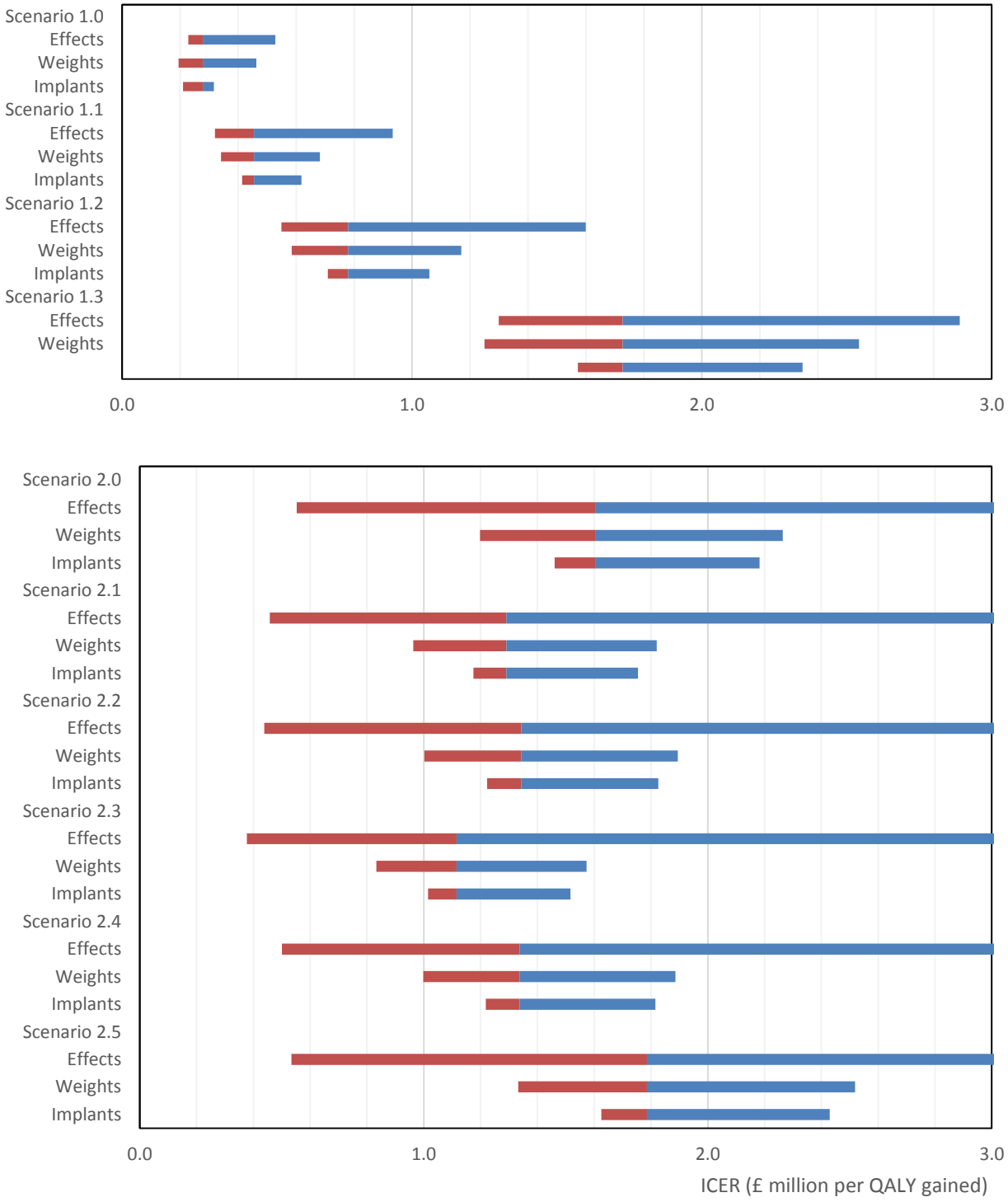

Figure 12 Tornado graphs for ERG scenarios

Probabilistic sensitivity analysis (PSA)

For all scenarios, the probability that afamelanotide was cost-effective at a threshold of £100,000 per QALY gained was 0%. When the threshold was increased to £150,000, the probability of cost-effectiveness remained negligible in all scenarios. We present three cost-effectiveness acceptability curves (CEACs) below. The company and ERG base cases are shown in Figure 13 and Figure 14 respectively, and reinforce the conclusion that these scenarios are unlikely to be cost-effective at a threshold of £150,000 per QALY gained.

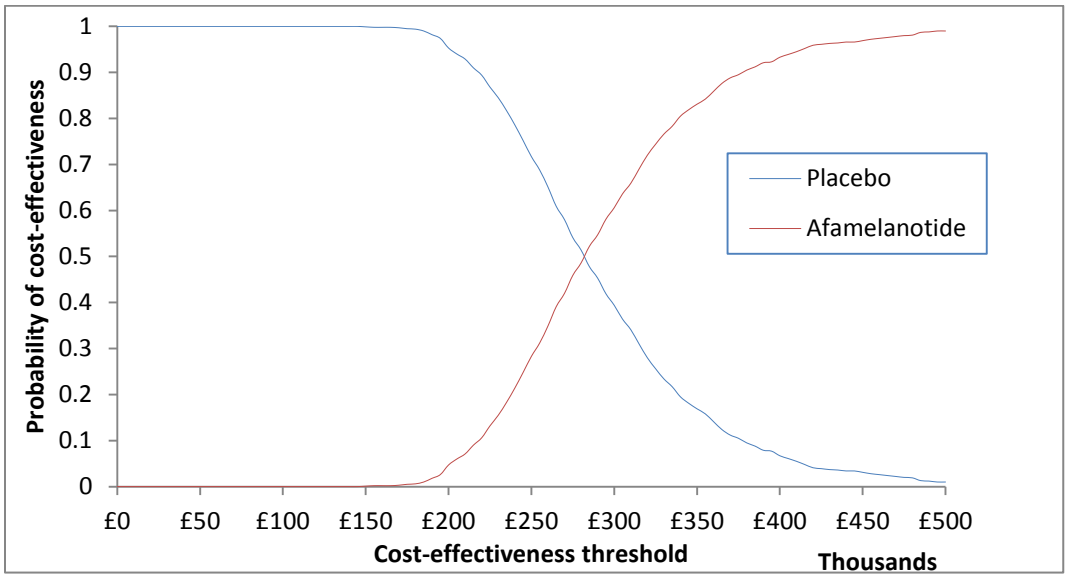

Figure 13 CEAC for Scenario 1.0 (company base case)

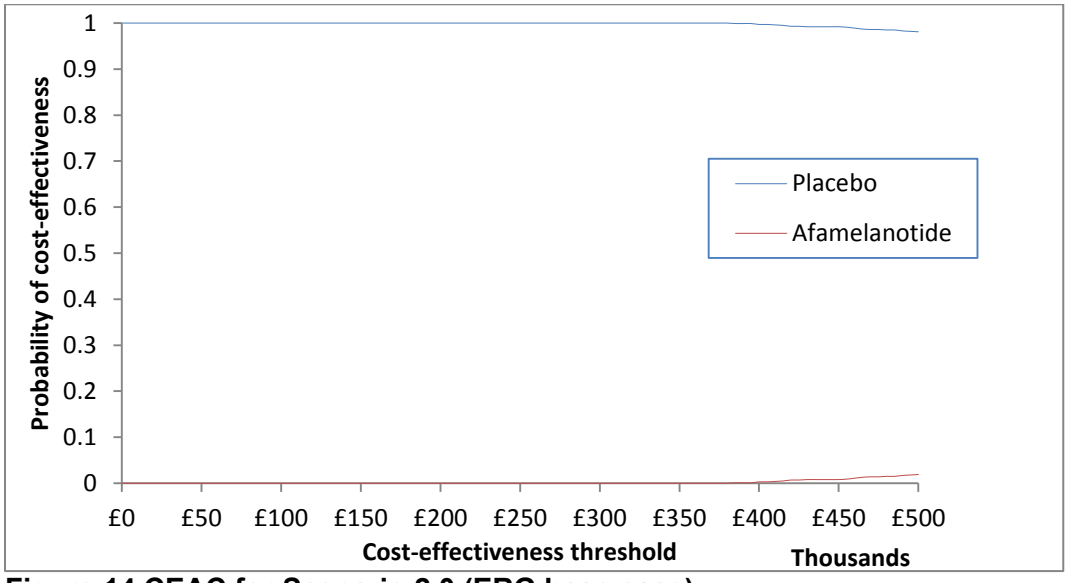

Figure 14 CEAC for Scenario 2.0 (ERG base case)

Best case analysis

Finally, we present the results of a best case PSA (Figure 15). This uses Scenario 1.0 (the QALY version of the company base case model), together with the most favourable limits for the three key sensitivity analyses: the upper limits for treatment effect and disability weights, and the lower limit for the mean number of implants per person per year used for costing. The best case scenario yielded an ICER of £151,212 per QALY gained. However, the ERG does not believe that this is a plausible scenario.

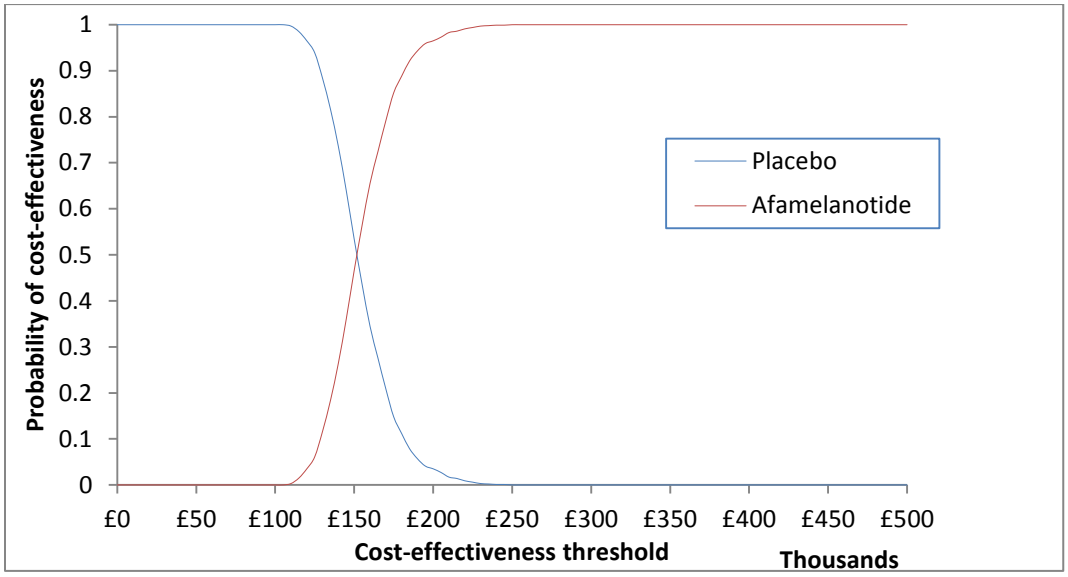

Figure 15 CEAC for best case scenario
(Company base case with upper limit for treatment effect and weights, and lower limit for number of implants)

5 Cost to the NHS and PSS

5.1 Base case budget impact

The company's model of budget impact is driven by three parameters (CS p 91):

- **EPP prevalence**. For the company's base case, 513 EPP patients were assumed to be eligible for treatment in England. This is higher than that previously cited, but clinical experts consulted by the ERG think that this figure is generally correct, or would not vary by more than 100 higher or lower (see section 2.3 above).
- **Uptake of afamelanotide**. The company assumed an uptake of [redacted] in the first year and [redacted] annually for the remaining four years.
- **Annual costs,** which are largely a function of the number of implants per patient per year. The company assumed that eligible patients would receive an average of [redacted] implants per year, in order to "[redacted]" (p91 CS).

The ERG notes that there are errors in the company's estimates of the budget impact over a five year period (section 13.7 of the CS). This seems to stems from them maintaining only [redacted] implant injection visits to administer [redacted] implants. We have corrected this to reflect that administering [redacted] implants will require [redacted] visits. Our corrected results are presented in Table 36.

Table 36 Corrected company budget impact estimated over the next 5 years

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2 Company and ERG sensitivity analyses

The CS does not report sensitivity analysis for the budget impact. We explored the budget impact, varying prevalence and the mean number of implants per year. The results of our sensitivity analysis are reported below in Table 37.

Table 37 Five year budget impact, varying prevalence and mean number of implants

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
EPP prevalence						
300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
400	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
600	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean implants per year						
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

6.1 Impact on employment and income

The CS states that due to the lack of available EPP data, is it assumed that the majority of costs and savings of afamelanotide would be incurred within the NHS (CS section 14.1, p 93). No costs or savings to other government bodies or patients themselves are reported, though a sensitivity analysis which includes societal costs (which assumes an increase from 50% to 100% of mean wage over three years of afamelanotide treatment) is provided in the CS (see section 4.3.5.4 of this report). Although there is little empirical evidence on impacts of afamelanotide beyond direct health benefits, information from the NICE consultees and ERG clinical experts highlight the negative impact EPP has on patients' lives, including reduced study opportunities, job security and career development (see section 7 of this report for a discussion of consultee submissions). For example, as travel to a place of work or study can be difficult some patients can only engage in employment indoors, or undertake night work to avoid travelling during daylight hours. The CS mentions that a proportion of EPP patients are known to be unemployed, others are limited in their productivity, some however have full employment, whereas others have taken up nocturnal employment (CS section 12.4.2, p 80), though it should be noted that these proportions are not quantified in the CS.

The British Porphyria Association (BPA) submission to NICE suggests that patients with more severe EPP are unable to work under office lights and would therefore be restricted to working at home. The BPA also mentions a survey (reference not given) by an EPP patient organisation in the Netherlands which found that: 91% percent of patients changed careers because of EPP; 40% percent of patients reported losing a job because of EPP; 46% percent of patients took several (multiple consecutive) sick-days after an EPP-attack in the last five years and that 35% percent of patients can only work with adjustments (such adjustments are not defined). The BPA suggest that these figures are also applicable to the UK and the ERG agrees that this is a reasonable inference.

The BPA also states that patients tend to face economic dependence on the welfare state, along with the psychological burden that state dependence brings. They comment that "restricted options and preventative measures required to take part in other normal activities often adds hundreds, if not thousands of pounds sterling to the cost of living for both patients

and their families" (BPA submission, p 4-5). In summary, due to a reduced capacity to study and work, the socio-economic status of EPP patients and their families can be assumed to be lower overall, to the general population.

The afamelanotide RCTs included in the CS did not specifically measure the impact of treatment on ability to work or study, although the 18-item version of the EPP-QoL instrument does include an item assessing patient capacity to go to work or school (Question 12[11]) (this question appears to have been omitted from later revised versions of the EPP-QoL instrument). The long-term observational study of 115 EPP Swiss and Italian patients by Biolcati et al.[11], provided selected anecdotes from afamelanotide treated patients on their increased ability to study and to take employment and the financial benefits that this provided. It is reasonable to assume that the effects of treatment in terms of the ability to spend longer time in sunlight without pain, as described in section 3.3 of this report, will improve patients' education and employment opportunities and thus their income. Increased employment would also reduce demand on welfare benefits. However, there is no available data to quantify these impacts at present.

It is not clear what adjustments an employer would need to make (and therefore what the associated costs would be), to enable an EPP patient to attend the workplace. The ERG suggest that these could potentially include external/internal window screens, provision of suitable lighting, air conditioning facilities (e.g. to regulate the temperature without opening windows) and provision of car parking adjacent to building entrances/exits.

6.2 Impact on patient costs

The CS does not state any costs that patients would incur that would not be reimbursed by the NHS (CS section 14.3). However, to receive afamelanotide patients would need to travel to a specialist porphyria centre. Given the small number of centres in the UK that can potentially offer the treatment (the CS estimates that up to eight expert centres across the UK would provide treatment if recommended for the NHS), many patients would have to travel long distances to receive their implants and to be monitored (as required under the PASS protocol). These patients would therefore incur travel and potential accommodation costs, as well as potential loss of earnings from time away from work. The frequency of visits would depend on the number of implants required during the year. This frequency may vary between patients according to their specific needs, though it would not exceed four per year in line with the

marketing authorisation. These would be in addition to twice yearly monitoring appointments as required by the EMA (PASS protocol).

However, the British Association of Dermatologists (BAD) and BPA consultees in their submissions and expert clinical advice to the ERG, suggest that patients would not consider additional monitoring attendances as onerous or inconvenient, particularly compared to those associated with existing treatments such as UVB therapy which have a higher frequency of treatment appointments over a short time period.

6.3 Impact of the technology on delivery of the service

Administration of afamelanotide, if approved, in specialist centres in the UK was considered by both Royal College of Physician (RCP) and BAD consultees (in agreement with ERG clinical experts) to be feasible. However, it was noted by both BAD and RCP consultees that additional costs, in terms of time to train medical /nursing health professionals to administer the implants and provide additional follow up appointments would also need to be considered. The CS mentions that as part of the risk management plan agreed with the EMA, academic expert physicians will be trained and accredited by CLINUVEL to treat patients at the cost of the company. Only centres with existing, recognised expertise in EPP will be considered for training and accreditation (i.e., members of the European Porphyria Network (EPNET) and/or the British and Irish Porphyria Network (BIPNET)) (CS section 14.9, p 95). The company clarified that training should be conducted at least every two years and should apply to all staff involved in the care of adult patients with EPP (e.g. physicians, nurses, administrative staff, pharmacists) (clarification response question B7, 26/09/17). The duration of training (e.g. in terms of hours/days) and costs of training were not specified by the company.

[redacted]

7 Other submissions

Submissions were received from three consultee associations: the British Association of Dermatologists (BAD) (represented by four clinical experts); the British Porphyria Association (BPA) charity (represented by their vice-chairman who is also a helpline administrator) and the Royal College of Pathologists (RCP) (represented by a clinical expert from Salford Royal NHS Foundation trust). The ERG notes that the submissions from the BAD and the RCP both represent specialist porphyria services at Salford Royal NHS Trust which serves the greater Manchester area and other hospitals in north-west England. The BAD and RCP submissions represent the views of clinical EPP treatment specialists whilst the BPA submission represents the views of patients with EPP.

7.1 Number of patients with EPP

On referring to a 2006 academic paper (Holme et al. 2016[17]), the RCP quote the numbers of EPP patients in the UK to be 389 (which includes children under 18 years who are ineligible for treatment with afamelanotide). It should be noted that the BAD also quote this number but incorrectly state this number as those in England alone, where the reference quoted refers specifically to the number identified in the UK.

The BPA state that they currently have around 100 UK members who have EPP. They estimate that they have 25% of UK EPP patients on their database, which would agree with the number of around 400 in the UK previously quoted by Holme et al.[17] and Elder et al.[48]

7.2 Diagnosis and current treatment provision in the NHS

The BAD and RCP provide a general overview of the issues surrounding confirmation and average age of diagnosis as well as the lack of general practice and public knowledge of the condition.

The consultees acknowledge that there are no specific pharmacological treatments for EPP and the CS states that “The lack of available effective therapies for EPP means no formal treatment recommendations exist” (p 18). Current treatment options are limited to include effective sun protection, B carotene doses, correction of Vitamin D deficiency and narrow band UVB therapy.

In agreement with NICE and the CS, the use of currently available methods of managing the condition, high dose B carotene or Dundee cream were considered both ineffective and

impractical by the BAD, RCP and BPA consultees and ERG clinical experts. The BPA highlighted a systematic review of treatment options for dermal photosensitivity in EPP, stating that high dose beta-carotene is ineffective.[49] The use of narrow band UVB treatment by some patients (six treatments in quick succession every spring) was mentioned by the BAD and the RCP, as well as the ERG clinical experts. Although this was thought to be the best form of treatment, it was noted by these consultees that it can be problematic for patients who are working or live a long distance from a treatment centre given the frequency of administration necessary.

7.3 Impact on patients, families and carers

The BPA representative highlighted in detail, the patient's perspective of the effects of their condition on everyday life, stressing the distress experienced during a phototoxic reaction. Using quotes from EPP patients the BPA submission highlighted the effects of intense pain and extreme tiredness on not only the patients but families and carers. They discussed the impact on earning capacity for both the patients and families. The report quoted a study on the effect of EPP on work attendance, carried out by an EPP patient organisation in the Netherlands (as described earlier in Section 6.1 of this report), stating the negative impact on job retention and career choice. The BPA representative discussed the potential effects on mental health (anxiety) on patients. The CS in agreement with the BPA also stated that EPP severely impacts upon quality of life and ability to function normally, inhibiting social participation, education and employment (p16).

7.4 Advantages of the technology

It was noted by the BPA that despite the sub-optimal timing of trials for UK patients afamelanotide has a positive effect on symptoms (NB. They do not elaborate on the timing). As acknowledged by both the BPA representative and ERG clinical experts, afamelanotide may have a significant effect on the lifestyle of EPP patients. People who benefit most from the treatment are those who are willing and able to gradually recondition themselves to exposure to light. The BPA submission includes a number of emotive quotes to support the positive effect of afamelanotide on patients, stating their positive effect on family life, the parenting of young children and general lifestyle. This consultee stated that their information was obtained from consulting patient members who had participated in trials in the UK and comments correlated with consensus themes that emerged from presentations and discussions at a recent medical conference International Conference on Porphyrins and Porphyrias (ICPP2017) – Bordeaux

(June 2017; no data or reference provided). In addition, it is the BPA's opinion that, for those patients who are able to tolerate some degree of exposure to visible light (having less severe reactions), afamelanotide is a "complete life changer, effectively eliminating the impact of light exposure on working day life and opening up all but the most exposed of activities to EPP patients".

8 DISCUSSION

8.1 Summary of clinical effectiveness issues

The RCTs evaluating afamelanotide show statistically significant differences across outcomes in favour of the treatment. Compared to placebo patients were able to spend longer in sunlight without experiencing pain, or experiencing only mild pain. Statistically significant differences were observed in two of the RCTs (CUV029 and CUV039) demonstrating consistency in effects. The median increase in pain free sunlight exposure varied between approximately five hours to 24 hours depending on the study (taking into account its geographical location and overall study length, and the time period during each day in which outcomes were measured). The clinical significance of these results is unclear as these outcomes appear to have been devised specifically to evaluate this treatment and minimal important clinical differences have not yet been established. The effects could be interpreted as being modest. For example, in study CUV029 the median five hour increase in pain free direct sunlight exposure, measured between 10:00 to 15:00 hours per day, is only a small proportion of the total available daylight time over the nine study month period. However, there are a number of factors which influence an EPP patient's exposure to sunlight, including their long-standing fear of going outside, weather conditions, their daily activities (work, leisure, family commitments), and their physical mobility. Indeed, it has been commentated that the effects seen in the studies could be underestimated given patients' lifelong reluctance to expose themselves to light.[14]

The clinical significance of treatment effects is reinforced by patient testimonials, as reported in the consultee submissions to NICE (see section 7). Patients describe the positive impact that treatment has made on their lives, and say that even a relatively small increase in the time that light exposure can be tolerated can make a significant difference. The BPA in their submission states that they have not encountered a patient who has not received a significant benefit from afamelanotide. The BPA also suggest that people who would benefit most from treatment are those who are able to gradually recondition themselves to light exposure. Given that behaviour

takes time to change and maintain, the relatively short durations of the RCTs may be inadequate to demonstrate the optimum effectiveness of afamelanotide. Furthermore, it may be necessary for behavioural therapy to be provided to some patients receiving afamelanotide to enable them to overcome their fear of light exposure.

Another factor which may have influenced the results of the RCTs is a potential placebo effect. The journal publication for studies CUV029 and CUV039 mentions that a few patients who received placebo were convinced that they received afamelanotide and reportedly increased their sun exposure.[7] The ERG notes that placebo group EPP-QoL and DLQI scores improved during the study, indicating a potential unexplained placebo effect. However, it is also known that the tanning effect of afamelanotide unblinded some treated patients in the RCTs. This could have potentially encouraged treated patients to increase their sun exposure, thus mitigating the possible placebo effect in the studies. However, as stated above, the long-standing behavioural avoidance of sun exposure may have inhibited patients who had guessed that they were receiving afamelanotide from exposing themselves to light.

The generalisability of the size of the treatment effects from the studies to England and the UK is not straightforward. The CUV039 study was conducted in the USA and the trial journal publication suggests that the difference in the magnitude of sunlight exposure time gained between this trial and the European trial (CUV029) can be explained, in part, by differences in latitude. The European centres were at higher latitudes and it could be suggested that the amount of daylight available to patients in the European centres would, on average, be less than patients in the US centres. They would therefore have less opportunity to spend time outdoors and be exposed to light. Conversely it could be assumed that the strength of sunlight at lower latitudes would be greater and that this would limit the amount of time patients could spend in sunlight without experiencing pain. Furthermore, the results seen in the RCTs reflect a single period of months in time which may or may not have been typical in terms of weather patterns (and hence potential for sunlight exposure) in both continents. Thus, a number of factors need to be taken into consideration when generalising the results of the RCTs - particularly CUV039 - to the UK.

In summary, the ERG's interpretation of the evidence is that afamelanotide is associated with benefit to patients in the trials in terms of increased ability to be exposed to sunlight with little or no pain. In turn their HRQoL improved with an increased ability to take part in daily activities

outside of the home. However, there are a number of potential confounding factors which limit interpretation of the magnitude of the treatment effect and its generalisability to the UK. The ERG's interpretation is similar to that of the EMA assessment of the evidence as part of the marketing authorisation application.[2]

8.2 Summary of issues for costs and health effects

The ERG identified an abstract published in 2016 by Thompson et al.,[3] reporting an economic evaluation that estimated the cost-effectiveness of afamelanotide for EPP, using DALYs as the measure of effect. This abstract report a base case and sensitivity analysis range for DALYs averted that [redacted] Thompson et al. reported a base case ICER of £373,000 per DALY averted, which was higher than the company base case estimate of £278,471 per DALY averted. Thompson et al. also presented results for a sensitivity analysis using QALYs, reporting an ICER of £401,000 *per QALY gained* using the condition hereditary angioedema (swelling under the skin) as a proxy for EPP, and a range from £208,000 to £1.1 million per QALY with alternative sources for utility weights.

8.2.1 ERG critique of company model

The ERG critically appraised the company's submitted cost-effectiveness model. This estimates the value of health outcomes in the form of DALYs avoided, because the company did not consider QALYs to be an appropriate measure for EPP. We consider the basic structure of the company model – [redacted] - to be reasonable, although we note that it entails some strong assumptions: [redacted] These may be unlikely in practice, but we have not identified evidence to support alternative modelling assumptions. However, we do have serious concerns about the way in which the magnitude of treatment effect was estimated and valued in the company model.

The company's estimate of mean DALYs averted per year of treatment was based on EPP-QOL data from three randomised studies, CUV029, CUV030 and CUV039. The ERG is concerned that we have not had sufficient access to information about the methods and results of studies CUV029 and CUV30 to be able to assess their quality or check the results. We have also had insufficient information about how the results of the three trials were analysed and pooled. There is a lack of basic information about whether ITT datasets were used, the number of

patients included from each trial and whether the method of pooling accounted for clustering or randomisation. Furthermore, we are concerned about the lack of evidence over how the EPP-QOL scale was developed and validated. In particular, post hoc changes to the scoring system which were introduced after initial analysis of trial results, introduces a risk of bias.

With regard to the valuation of health effects, we do not have confidence that the disability weights for mild, moderate and severe disease in the company model are appropriate for EPP, or that they are consistent with the company's definitions of severity based on EPP-QOL scores. We do not know if [redacted] is an appropriate proxy condition for EPP – the clinical experts who we have consulted have suggested that it might not be. There may be some similarities in psychological and functional impacts, but it is not at all clear if the magnitude and severity of these conditions are comparable. The same applies to the alternative proxy condition of [redacted] The definition of mild, moderate and severe disease by division of the EPP-QoL scale into thirds is also arbitrary and we cannot assess if it is consistent with the definitions used to elicit the proxy disability weights.

Another set of problems with the company's approach, relate to how they have extrapolated treatment effects from a single time point to estimate mean DALY loss under standard treatment and with afamelanotide. The company's model only makes use of the 120 day results and assumes that these values apply for the whole year, including around half the year when patients would not have afamelanotide implants. We believe that this is simplistic and likely to have biased DALY estimates in favour of afamelanotide. The company stated that they chose 120 days as this was the longest time point available from all three trials, but the CS indicated that EPP-QoL data was also collected at 180 days in the three trials. The approach also fails to correct for baseline imbalance in EPP-QoL severity, which would have favoured afamelanotide. And we also question the assumption

We also have some questions about the cost estimates used. These were very largely driven by an assumption about the mean number of implants per person per year. This figure was estimated from 'real world' data, and it is not clear whether this was consistent with use in the clinical trials. If not, this would be a source of bias. We do also consider that the estimated administration and monitoring costs for afamelanotide, and usual care appear to be high for a UK context. However, these costs are small in relation to the drug acquisition costs, and so have little influence on the ICER.

Finally, we note that the analysis of uncertainty presented in the CS was inadequate. In particular, there was no attempt to estimate the extent or consequences of uncertainty over the effectiveness parameters and assumptions. Given the discussion above, we think this could be considerable. There was also no probabilistic analysis of uncertainty.

We conducted additional analysis based on the company's model. First, we developed a very simple QALY model as a platform to investigate alternative scenarios and sensitivity around the company's base case. This demonstrated that the company's incremental cost per DALY averted of £278,471 (£278,386 per QALY gained after a small correction by the ERG) is likely to be an underestimate. With correction for baseline differences in EPP-QoL, this rose to £454,800 per QALY gained. The ICER rose further, to £779,657 per QALY gained, when we assumed that treatment benefits would gradually decline over a 2 month period from month 6. Use of utility estimates from the literature for the same proxy condition as in the company base case, further increased the estimated ICER to over £1.7 million per QALY gained.

We conducted a 'best case' analysis, which combined the most favourable scenario that we had tested (our simple QALY conversion of the company's base case model), with the most favourable sensitivity analysis limits for treatment effects, disability weights and mean number of implants used for costing. This brought the ICER down to £151,212 per QALY gained. The ERG does not believe that this or any of the other ICER estimates based on our simple adaptation of the company model are plausible.

Our preferred set of analyses were based on mean DLQI data from the pivotal study (CUV039) mapped to EQ-5D utility values using a published algorithm. Results from this model were less favourable, and did not fall below £1.1 million per QALY gained in any of the scenarios that we tested. The ERG believes that this set of estimates is more plausible than the company's approach.

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06 November 2017

Re: Afamelanotide for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)

Dear Sir Andrew, Dr Boysen,

Background
SCENESSE® (afamelanotide 16mg) was approved by the European Medicines Agency (EMA) in October 2014, a decision ratified by the European Commission on 22 December 2014. The product is approved for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP). EPP is a rare metabolic disorder affecting some 513 individuals in England and currently under review by NICE as a Highly Specialised Technology (HST).

NICE review process
Following extensive submissions by CLINUVEL to NICE, it is clear that NICE has been unwilling or unable to appropriately review SCENESSE® for use in England. We are concerned that NICE has not appeared to have conducted its assessment in a rational or reasonable manner and has not given due regard to all relevant considerations. This has included misinterpreting or failing to take into account information that the Company has provided to NICE (sometimes on more than one occasion).

CLINUVEL has reviewed the recently supplied ERG report, the foundations of which are flawed. There is no rationale for the analyses proposed by the Southampton Health Technology Assessments Centre, who have shown a lack of understanding of erythropoietic protoporphyria, of the rationale to undertake more than a decade of research into the unmet medical need, and of the significance of a 2.5-year scientific review by the European Medicines Agency.

NICE's requests for information throughout the review process should have been tailored and adequate to enable a fair assessment of a medicine which is essential to patients suffering from EPP (and which is the only available medicine for these patients). Requesting information that is impossible to deliver due to the specificities of the medical condition under review is contrary to the task that NICE has been entrusted with.

We would take this opportunity to remind NICE that, as explained in our letter of 12 September 2017, NICE has a discretion to assess HSTs using a methodology other than QALYs, where appropriate. It would be unreasonable and/or irrational for NICE to apply the QALY criteria to an Orphan designated medicinal product which has been approved under exceptional circumstances under Article 14(8) of Regulation (EC) No

726/2004, given the impossibility to provide the required data, and the nature of the underlying condition. By rejecting the DALY model developed by CLINUVEL, on the basis of the data accepted by the EMA and other regulatory body similar to NICE, and provided by CLINUVEL in support of the assessment to be conducted by NICE, NICE would be acting irrationally and unreasonably.

In addition, we would note that on several occasions NICE takes a position which appears to diverge from the conclusions of the European Medicines Agency (EMA), and we would take this opportunity to remind NICE that according to the Court of Appeal in the case of Servier v NICE[1] if a regulatory authority has assessed the data and on that basis granted a marketing authorisation, NICE must justify any departure from it. It will not be acceptable for NICE's assessment to be 'similar' to that of the EMA, rather the EMA's conclusions on the data must be accepted by NICE unless NICE can justify taking a contrary interpretation or departing from them.

To conclude it is clear that NICE has significant discretion in determining the procedure and the criteria for assessing medicinal products under the HST appraisal process. Therefore, CLINUVEL respectfully requests that, as other Agencies have done previously and for all the reasons explained in this letter, NICE accepts to assess SCENESSE® based on a DALY economic model rather than unreasonably insisting on a QALY model.

Summary overview document
CLINUVEL has taken additional steps to provide a clear overview of the background, rationale, use and impact of SCENESSE® in its use in EPP in England, summarised in a document appended.

We would note that none of the concerns raised in this letter or the attached summary document amount to the provision of new data. All of the data within this letter and its appendix has been provided to NICE already either within the Company Submission, and/or in the letters of 12 September 2017 and 2 October 2017.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

Appended:
SCENESSE® (afamelanotide 16mg) Budget Impact Assessment England

[1] [2010] EWCA Civ 346, Court of Appeal, on appeal from QBD Administrative Court.

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

Afamelanotide for treating erythropoietic protoporphyria ADDENDUM

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed 17 November 2017

Correction to ERG deterministic sensitivity analysis tables

The ICERs for the upper and lower limits of effectiveness and utility parameters in Tables 34 and 35 (page 114 ERG Report) were incorrectly labelled. Corrected tables are shown below.

Table 34 Simple QALY model: ICERs for lower and upper parameter ranges

Scenario	Effects[a]		GBD disability weight (mild)		Mean implants per year	
	Lower	Upper	Lower	Upper	Lower	Upper
	60.0%	90.0%	0.02	0.04	2	3
1.0	£405,664	£221,520	£417,579	£208,790	£253,371	£378,444
1.1	£933,075	£320,421	£682,200	£341,100	£413,934	£618,266
1.2	£1,599,556	£549,293	£1,169,486	£584,743	£709,600	£1,059,884
	Effects[a]		Disutilities (moderate; severe)[b]		Mean implants per year	
	60.0%	90.0%	(0.021;0.047)	(0.045;0.093)	2	3
1.3	£2,889,993	£1,299,022	£2,542,183	£1,249,637	£1,571,639	£2,347,455

[a] Proportion mild (120 days with treatment)
[b] Disutility vs. mild (moderate; severe)

Table 35 ERG preferred model: ICERs for lower and upper parameter ranges

Scenario	Effects[a]		Utility loss[b]		Mean implants per year	
	lower	Upper	lower	Upper	lower	Upper
	(-4.9;-4.8;-4.5)	(-0.4;-0.0;-0.0)	0.018	0.033	2	3
2.0	£552,284	£17,543,596	£2,263,826	£1,198,119	£1,461,217	£2,182,524
2.1	£457,817	£11,963,277	£1,819,939	£963,194	£1,174,704	£1,754,578
2.2	£438,286	£17,539,848	£1,894,222	£1,002,508	£1,222,651	£1,826,193
2.3	£376,615	£11,961,534	£1,573,167	£832,591	£1,015,422	£1,516,669
	Effects[a]		Utility loss[b]		Mean implants per year	
	(-0.4;-0.0;-0.0)	(-4.9;-4.8;-4.5)	0.018	0.033	1.3	2
2.4	£500,501	£11,766,004	£1,885,952	£998,131	£1,218,005	£1,815,451
	Effects[a]		Utility loss[b]		Mean implants per year	
	(-0.4;-0.0;-0.0)	(-4.9;-4.8;-4.5)	0.018	0.033	2.7	4
2.5	£534,044	£23,318,720	£2,518,313	£1,332,805	£1,625,012	£2,429,736

[a] Mean difference DLQI change (day 60;120;180)
[b] Utility loss per unit increase in DLQI

Undiscounted QALY gains

Without discounting, the company base case model gives an estimate of [redacted] DALYs avoided for a 38 year old starting age over a 35 year time horizon ([redacted] DALYs with standard care and [redacted] with afamelanotide). The ERG 'simple QALY' adaptation of the company base case also gives an estimate of [redacted] undiscounted QALYs gained ([redacted] with standard care and [redacted] with afamelanotide). Other ERG scenarios yield lower estimates of the undiscounted QALY gain with afamelanotide (see Table 38 below).

The ERG 'best case' model (simple QALY version of company base case with upper limits of treatment effectiveness and utility gain and lower limit of mean implants used per year), gives a mean undiscounted QALY gain of 5.4 (25.44 under standard care and 30.84 with afamelanotide). The same 'best case' model with a starting age of 18 and 60 year time horizon yields a total undiscounted QALY gain of 9.21.

Table 38. Undiscounted QALY results (starting age [redacted] year time horizon)

Scenario	Standard care	Afamelanotide	QALY gain
1.0	[redacted]	[redacted]	[redacted]
1.1	27.33	29.30	1.97
1.2	27.33	28.48	1.15
1.3	20.39	20.91	0.52
2.0	26.44	27.00	0.56
2.1	26.44	27.14	0.70
2.2	26.44	27.11	0.67
2.3	26.44	27.25	0.80
2.4	26.44	26.89	0.45
2.5	26.44	27.11	0.67

Thus, none of the scenarios tested by the ERG yielded an undiscounted QALY gain of more than 10 QALYs.