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Lead team presentation

Afamelanotide for treating erythropoietic protoporphyria
Clinical effectiveness presentation

1st Evaluation Committee Meeting

Highly Specialised Technology, 23 November 2017

Lead: Glenda Sobey

Company: Clinuvel

Chair: Peter Jackson

Evidence review group: Southampton Health Technology Assessments Centre (SHTAC)

NICE team: Mary Hughes, Raisa Sidhu, Sheela Upadhyaya

Disease background
Erythropoietic protoporphyria (EPP)

- EPP is a genetic disorder of ferrochelatase enzyme deficiency which results in accumulation of protoporphyrin IX (PPIX) in skin and liver
- PPIX reacts to visible light (sunlight and some artificial light) and can this can cause anaphylactoid and phototoxic reactions in people with EPP
- Phototoxic reactions cause damage to subdermal capillary walls resulting in redness of skin, swelling and an intense burning sensation, which can last weeks until damage has healed. Symptoms are exacerbated or prolonged by further exposure to light, heat variation, pressure and air movement.
- Cumulative exposure to light has a ‘priming’ effect. An exposure to a few minutes of daily light will eventually trigger phototoxic reactions.
- Patients report severe anxiety during reactions and suicidal ideations have been reported
- 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.

Disease background

Erythropoietic protoporphyria (EPP)

- There are 394 known people with EPP in the UK. The company estimates an approximate prevalence of *** patients in England (company estimate, includes adults and children with EPP)
- 2 -5% of people with EPP experience liver failure, but for the majority of people with EPP life expectancy is normal
- The long term prognosis is uniform but the severity of the condition can vary from person to person

Current best supportive care for EPP

There is currently no effective treatment available on the NHS. No painkillers are beneficial . Patients need annual monitoring (including full blood count, iron stores, liver function, vitamin D and red cell protoporphyrin). Patient groups report that some 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

Afamelanotide

- Marketing authorisation granted by EMA (2014)
- Indicated for prevention of phototoxicity in adult patients with 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

- ***How and in which seasons will afamelanotide be used in clinical practice?***
- ***What are the anticipated stopping rules for afamelanotide?***

Decision problem

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

Source: final scope issued by NICE

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

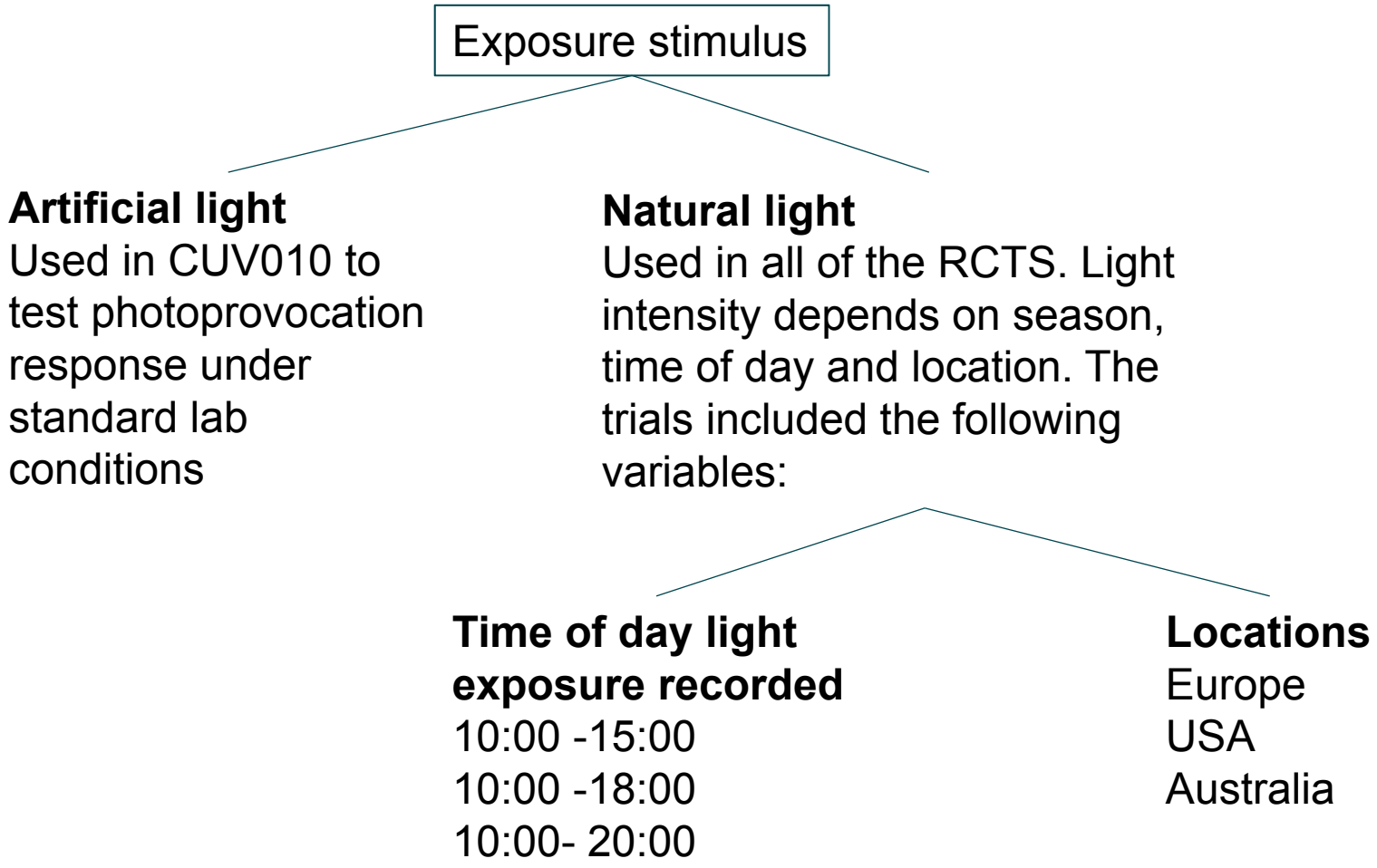
Source	Study name	description
Biolcati 2015a	N/A	Long term observational study of 146 patients with EPP treated with afamelanotide in Switzerland + Italy (Biolcati reports on 115). Incorporates data from single arm Phase II study (CUV010) and CUV017 as well as ongoing use of afamelanotide in compassionate use and expanded access programmes. Data reported from patients 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 to 31 May 2017
Harms 2009b	CUV010	Single arm study, n=5 of afamelanotide (20mg). Primary outcome was photoprovocation response time

Generalisability of trials to clinical practice in England

- Limited information about study populations and patient characteristics were available
- ERG: 2 of the RCTs included patients from the UK
- British Porphyria Association stated: 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.
- British Association of Dermatologists: 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

⊙ ***Are the trials generalisable to clinical practice in England?***

Light stimuli used in the clinical trials



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

Conditioned light avoidance behaviour

- In the trials, patients were asked to voluntarily expose themselves to natural light for a period of time they felt comfortable with and did not have pain
- The company identified that conditioned light avoidance behaviour as a variable affecting the measurement of clinical effectiveness of afamelanotide in clinical trials.
- Patients have learnt to cope with, manage, and accept their disorder since birth and are conditioned to avoid light sources
- Uniquely, people with EPP patients experience a prodromal phase, signifying that the seconds/minutes of insulting emitted light causes afferent nerve stimulation, which compels patients to withdraw from light sources and avoid further exposure.

- ***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 is reversible?***

Duration of tolerance to sunlight and other sources of visible light

Outcome	Description	Trial in which measured	Data reported (source)
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			

Pain was classified using the Likert scale (0, no pain; 10 worst pain). Cut-off for mild pain 1-4 in CUV030 and 1-3 in all other trials.
Compliance in keeping the diary was reported to be high. In CUV039 there were 185 (1.2) out of 15608 diary days with missing Likert scores and 296 days (1.9%) with missing information about time outdoors

Hours in direct sunlight with no pain

Outcome	Study CUV029 9 months (Europe)		Study CUV030 6 months (USA)		Study CUV039 6 months (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	p=0.007*		p=0.06*		p=0.044	

AFA, afamelanotide; PLA, placebo; SD, standard deviation

Source: * 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

- 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

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

Outcome	Description	Trial in which measured	Data reported (source)
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		

Phototoxic reactions: number

Outcome	Study CUV029 (Europe)		Study CUV039 (USA)	
	Afamelanotide N=38	Placebo N=36	Afamelanotide N=46	Placebo N=43
Number of phototoxic episodes per person, 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 per trial arm population	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 (extracted from Langendonk et al 2015). [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 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 increased during the first 30 days after administration at all tested sites with one exception in one patient.
  - Change in melanin density 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 skin, with a natural appearance
- ERG: Biolcati et al (long term observational study) reported an increase in melanin density that was maintained over the six year treatment assessment period. The increase was around 1 unit (1 unit roughly the difference in skin colour between 2 skin types on the 6-point Fitzpatrick scale of skin types).
- ERG: Melanin density is cited in the afamelanotide EPAR as an indicator of pharmacodynamics rather than an effectiveness outcome

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.

ERG commented: 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. For the long-term observational study the publication by Biolcati et al. states that one patient died of heart failure, but does not specify whether this was treatment-related.

ERG comments on clinical effectiveness

- **Systematic review.** All relevant clinical effectiveness studies have been included in company submission
- **Applicability to clinical practice in England**: Two of the RCTs included a small number of patients from UK expert porphyria treatment centres (amongst patients from other countries)
- **There is a lack of detail about the trials in the company submission.** A full independent assessment of the methodological characteristics and results of the studies was not possible.
- **Full baseline data for trials were not available to ERG**. Some baseline characteristics presented in Langendonk et al. 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%)
- **Risk of unblinding because of tanning effect of afamelanotide**. Noted this was acknowledged by the company, but company did not consider it would result in a change of behaviour because beta carotene (received as part of best supportive care) causes skin discolouration

ERG comments on clinical effectiveness

- **Unclear if true Intention-To-Treat analysis was used in all trials** (which would require all randomised patients to be analysed)
- **Clinical effectiveness studies measured a range of outcomes of relevance to patients.**
- **No clinically important outcomes were omitted from the trial programme.**
- **There were no unexpected differences in people dropping out of each arm of the trials**
- **Criticisms by EMA of studies CUV029/CUV030 in its Good Clinical Practice inspection need to be taken into account.** Key criticisms were:
  - Design of the patient diary for capturing data not suitable for capturing endpoints related to duration of sun exposure
  - Statistical analysis plan of CUV030 was changed after data had been analysed
  - Improper statistical planning and data handling for both trials
  - Verification of the databases and of relevant events such as database lock/unlock was not possible

Adverse events

- No serious treatment related adverse events reported in 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.
- No treatment related deaths.

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: 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 outcomes in trials

Outcome	Description	Trial in which measured	Data reported (source)
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

Quality of life assessed for people with EPP (not carers)
SF-36, Short Form 36; DLQI, Dermatology Life Quality Index

Quality of life- 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
  - There were no marked trends over time between the two groups associated with the dose administered per period

  Company gave the following suggested explanations

  - 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 and may also reflect the reluctance of some EPP patients to admit that they have a disease which can alter their lifestyle
- EPAR states that in study CUV017 results “showed no improvement in QoL during and after treatment with Scenesse”

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.

Dermatology Life Quality Index (DLQI)

The ERG extracted the following data from the EPAR for CUV039. The DLQI scoring range is 0-30. (0=no effect on quality of life, >20 = extremely large effect on quality of life)

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

Table 11 ERG report

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 – data from CUV029 and CUV039 (extracted from Langendonk et al.)

The ERG plotted the mean EPP-QoL scores reported in Langendonk et al. 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)

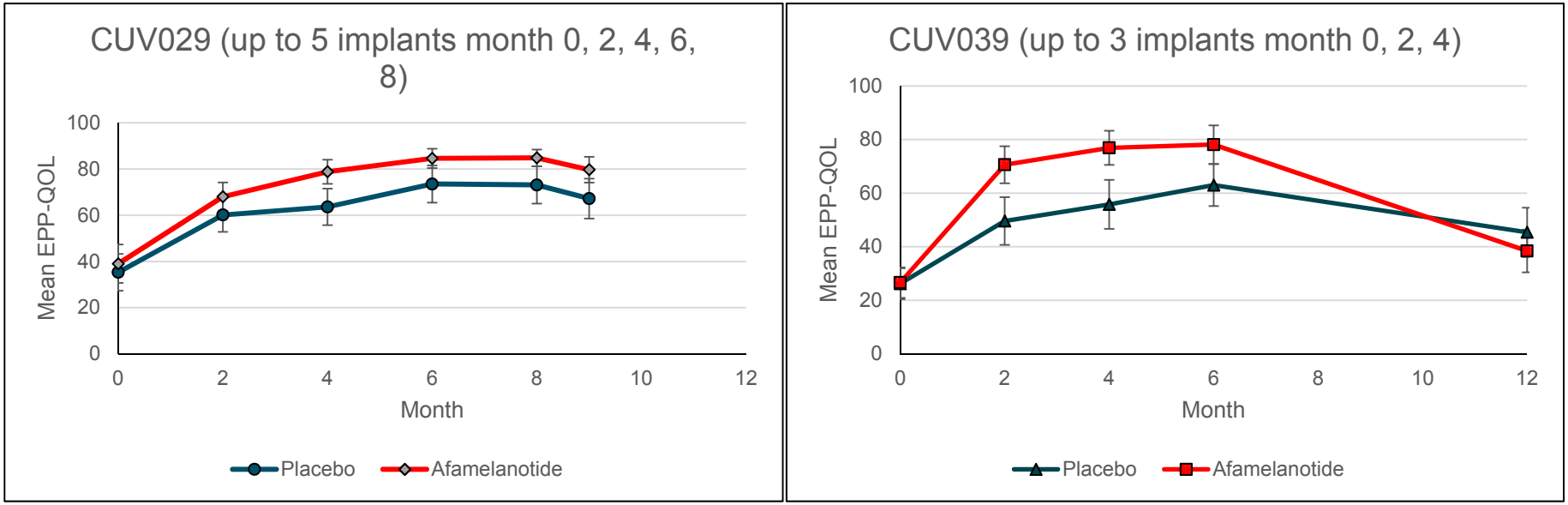


Figure 1 ERG report page 80 (data plotted from Langendonk et al 2015)

Quality of life: 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 DQLI 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 in It demonstrated that DLQI scores in EPP patients are higher [worse] 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.

Quality of Life: ERG comments

EPP-QoL

- 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 quality of life 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.

Equality

Royal College of Pathologists noted that the marketing authorisation covers an adult population, but EPP is present from birth and so children wouldn't have access to treatment.

N.B. This is not a potential equality issue that can be addressed by the Committee because NICE does not normally make recommendations outside the terms of the marketing authorisation of the technology being appraised, as published in the summary of product characteristics, unless instructed to do so by the Secretary of State.

⊙ ***Are there any equality issues?***

Key issues

Clinical effectiveness

- Are the clinical trials generalisable to clinical practice in England?
- How and in which seasons will afamelanotide be used in clinical practice?
- Is there variability in the severity of EPP?
- Does the evidence from the 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 is reversible?
- Do the trial outcomes reflect the anticipated real life benefits of afamelanotide?
- What are the anticipated stopping rules for afamelanotide?
- Are there any equality issues?

Projector and Public slides redacted

Lead team presentation

Afamelanotide for treating erythropoietic protoporphyria
Cost effectiveness presentation

1st Evaluation Committee Meeting

Highly Specialised Technology, 23 November 2017

Lead: Francis Pang

Company: Clinuvel

Chair: Peter Jackson

Evidence review group: Southampton Health Technology Assessments Centre (SHTAC)

NICE team: Mary Hughes, Raisa Sidhu, Sheela Upadhyaya

Decision problem

- 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 ERG considers that measuring QALYs is feasible and have presented these results.
- NICE methods allow consideration of non-reference case methods alongside reference case methods

Overview of modelling approach

- The company model uses a proxy condition to estimate the disability associated with EPP. The company have stated that the proxy condition it selected is confidential
- 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
- The company consider many of its modelling assumptions to be confidential including:
  - the proxy condition it used in its base case,
  - the health states it has used in its model and other assumptions such as age of the modelled cohort, survival assumptions and discounting rate.
  - total and incremental costs and DALYs

  There will be opportunity to ask questions and discuss these aspects in the non-public part of the meeting

Company's economic model: structure and assumptions

Model structure	• ********** • **********
Survival	**********
Parameters	**********
Starting age and time horizon	********** ********** **********
Benefits	Modelled disability adjusted life years (DALYs) averted using a proxy condition ********** to derive disability weights
Discounting	**********

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 a sum of years of life lost and years lived with a disability. For each year in the model, one year of healthy life is lost (1 DALY) for each member of the cohort who is dead, and a proportion of a year of health 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.

⊙ What is the most appropriate measure of benefits for the purpose of evaluating whether afamelanotide is a value for money use of NHS resources? *DALYs or QALYs?*

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 [the proxy condition] due to a fear of certain environmental factors.
- ********** 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 [the alternative proxy condition]. 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 stratified EPP using the EPP-QoL (transformed to a 100 point scale):
  - '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 = 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 strata)
- 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	Personal Social Services Research Unit (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 company's total modelled annual admin cost of afamelanotide as a higher value ***)		

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)

- Scenarios 1 and 2: applied alternative multiplying factors to the disability weights for its proxy condition.
- Scenario 3: used an alternative proxy condition **********

	Mild	Moderate	Severe	AFA	SoC
Base case	****	****	****	****	****
Scenario 1	****	****	****	****	****
Scenario 2	****	****	****	****	****
Scenario 3	****	****	****	****	****

Scenario	Analysis	Incremental costs	Incremental DALYs	ICER
	Base case	*********	*****	£278,471
DALY proxy change	Scenario 1	*********	*****	£208,854
	Scenario 2	*********	*****	£417,707
	Scenario 3	*********	*****	£727,143

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

Company scenario analyses (2)

- Age of cohort: assumed 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.
- Number of implants people received:
  - the number of implants recommended per year in the marketing authorisation for afamelanotide (3 implants)
  - 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
- 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 (1)

- Structure of model appropriate but uses strong simplifying assumptions
- Assumptions on life expectancy, and adverse effects 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 and compliance and continuation of treatment
  - Costs of monitoring and other treatment for EPP
- There were 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 (2)

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 disease strata 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 strata in the DALY calculations.
- There were more people in the mildest strata 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 (3)

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. Noted 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

- Unclear if the proxy condition is appropriate 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. Similarly for the alternative proxy condition explored.

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 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
- The model results were 1.87 more DALYs averted with afamelanotide and the ICER was £373,000 per DALY averted compared with standard care
- Abstract also presented a sensitivity analysis using QALYs from 'preliminary SF-36 data from early clinical trials' and from other 'similar' conditions to EPP
- 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 question about this abstract "**********
**********"

ERG's exploratory analyses

The ERG produced a:

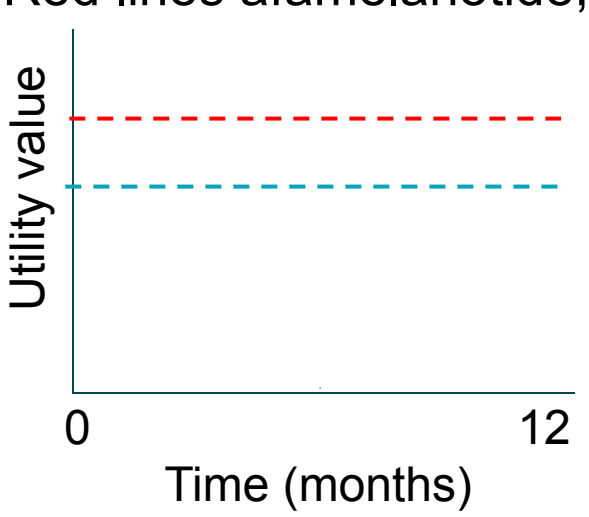
- Simple QALY version of the company model: applied utility estimates for disease strata for the company's proxy
  - i) Assumed utility value = 1 – disability weight (using the disability weights identified by the company)
  - ii) Identified published EQ-5D data for the disease strata for the company's 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

⊙ *Which of the ERG's approaches to estimate cost per QALY estimates is more suitable for decision-making*?

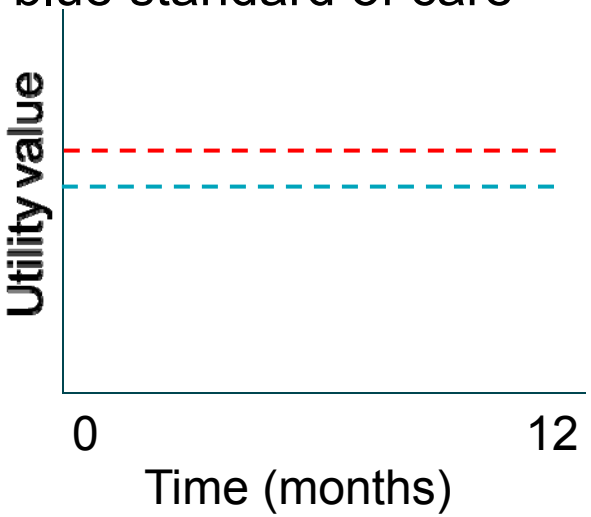
Scenarios tested around simple QALY adaption

These figures are not to scale because the disability weights from which the utility values are estimated are confidential (to-scale figures showing actual values are on pages 103 and 104 of the ERG report).

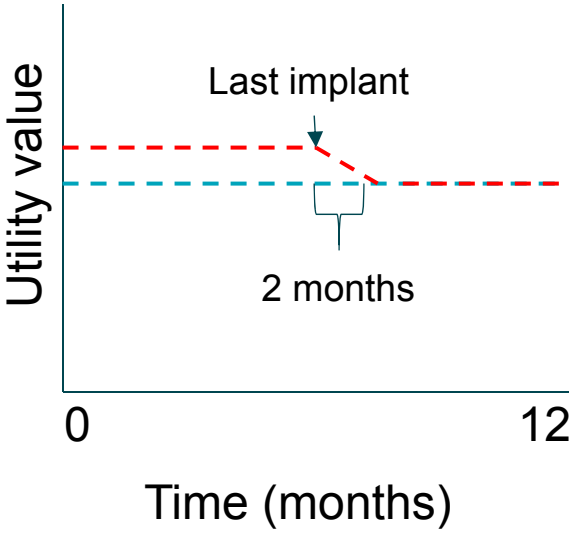
Red lines afamelanotide; blue standard of care



Simple QALY adaption
Difference in quality of life (QoL) at day 120 constant for whole year



Scenario 1.1. Afamelanotide utility value adjusted for QoL difference between afamelanotide and placebo at baseline



Scenario 1.2 Afamelanotide utility value adjusted and treatment effect attenuated within 2 months of last implant

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))	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	months 0-6 ***** months 8-12 *****
	Standard of care	months 0-12 *****

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

ERG simple QALY adaption: using published EQ-5D values for proxy condition

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)

- The source of the utility for disease strata for the proxy condition is confidential because the proxy condition is confidential. For committee:
  ****
  ****
- 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 EPP with each disease strata based on pooled data from CUV029/030/039 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 (Holmes et al)
- 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.

Comparison of EPP-QoL and DLQI

The ERG provided a top-level comparison of the concepts in the EPP-QoL and DLQI questionnaires (copyright prevents presentation in full; EPP-QoL questions removed in later version shown with strikethrough)

Concepts	DLQI Over the last week, how much has skin affected...	EPP-QoL Over the last two months, how much has EPP affected...
Symptoms	Itchy, sore, painful or stinging	Frequency: being at risk of developing EPP symptoms; of typical EPP skin complaints; ~~need to seek out shade~~
Feelings	Embarrassed or self conscious	
Daily activities	Going shopping, looking after home or garden; clothes you wear	Going shopping, looking after home or garden on sunny day; choice of clothes on sunny day; ~~frequency not wearing protective clothing on sunny day;~~ transportation method or seating preference
Social and leisure activities	Social or leisure activities; sport	Social or leisure activities on sunny day; outdoor social activities with family and friends; amount of outdoor activities; need to plan before leaving house; ability to undertake activities in spontaneous manner
Work and study	Prevented or problem with work or study	~~Capacity to go to work or school~~
Personal relationships	Problem with partner, close friends or relatives; sexual difficulties	
Treatment	Treatment problems, e.g. making home messy or taking time	
Overall		Well-being; quality of life

Abridged from ERG report table 27

ERG exploratory base case methods

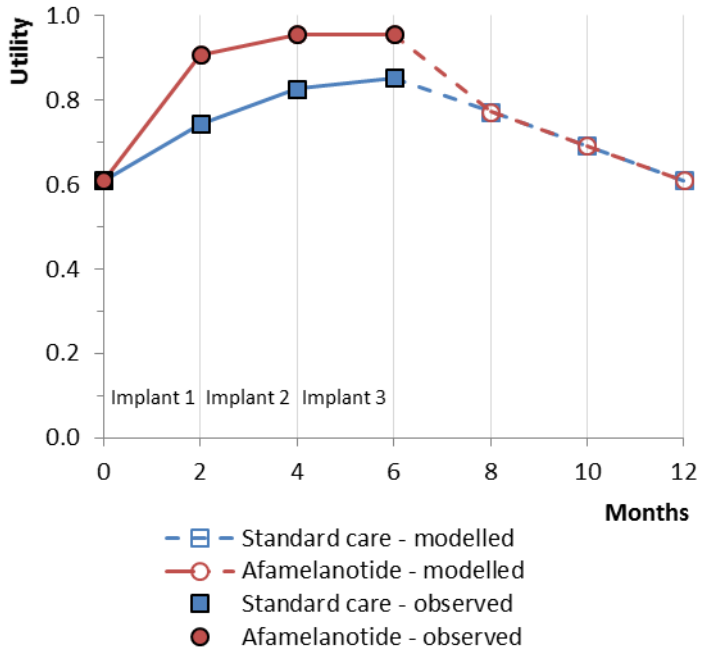
- Baseline values were from CUV039 and both modelled arms were assumed to start with same utility
- Used mean DLQI results from CUV039 (at 0, 60,120 and 180 days) to model treatment effect on quality of life
- Estimated utility values were mapped from the estimated mean DLQI at each time point using 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

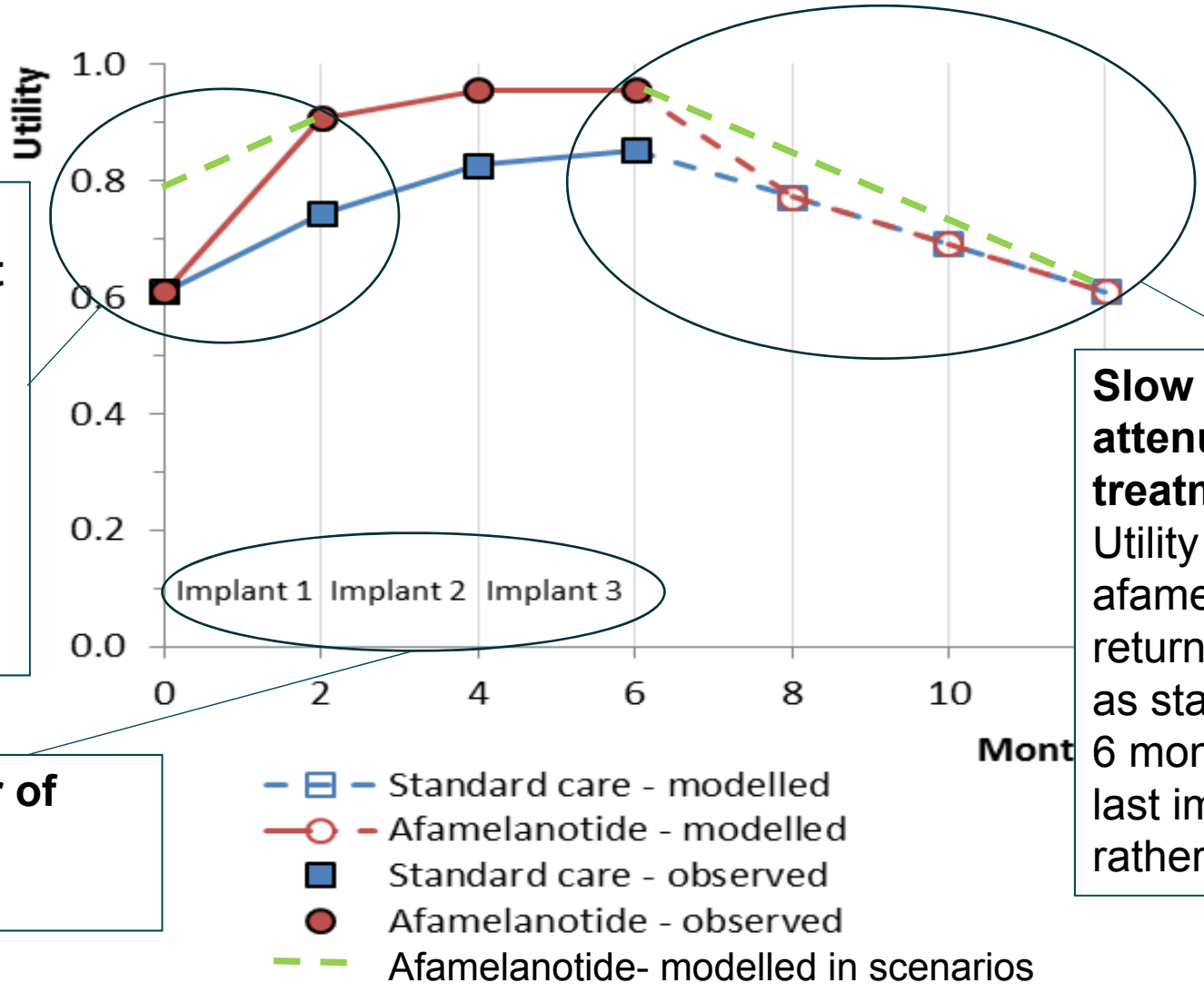


The simple QALY adaption figure contains confidential information (QALY values are shown which are calculated from confidential disability weights). Key points about the simple adaption:

- the modelled QALYs are based on 4 month EPP-QoL data from the trial at which point people receiving afamelanotide had better quality of life than placebo
- the modelled QALYs in each arm are constant for the whole year meaning the benefit is modelled to be immediate after starting treatment and is sustained after last implant

Figures 2 and 6 pages 103 and 108 of ERG report

Scenario analyses around ERG exploratory base case



Fast onset of treatment effect
treatment effect is immediate not gradual over 2 months

Max number of implants
2 or 4 tested

Slow attenuation of treatment effect
Utility with afamelanotide returns to same as standard care 6 months after last implant rather than 2

Simple QALY adaption 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: published utility values for proxy condition					
Standard care	****	****	-	-	-
Afamelanotide	****	****	****	****	£1,726,802

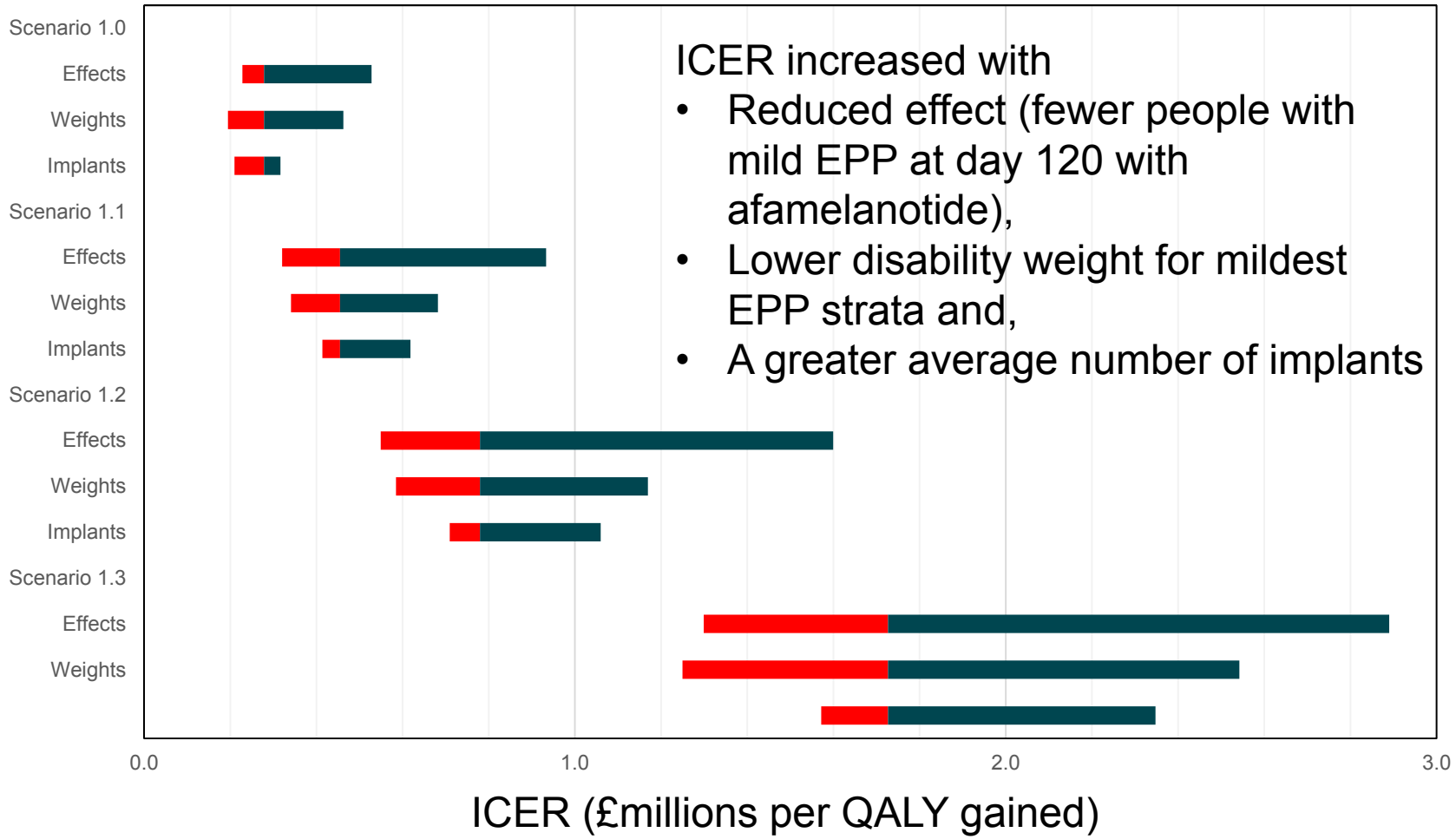
The ERG does not believe that any of these scenarios are plausible because they rely on an analysis of trial data that was post hoc and not transparent, the definitions of disease strata were arbitrary and not related to the levels of severity in the disability weights/ utilities, which were also derived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

ERG report table 32 page 113

ERG exploratory base case (mapped from DLQI)

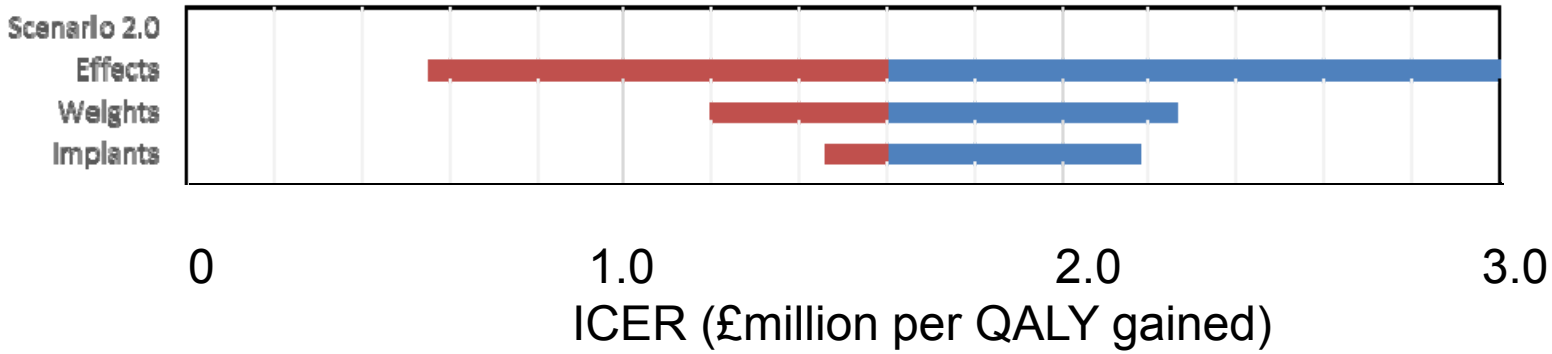
Treatment	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SCENARIO 2.0: ERG exploratory base case					
Standard care	****	****	-	-	-
Afamelanotide	****	****	****	****	£1,605,478
SCENARIO 2.1: fast onset of effect					
Standard care	****	****	-	-	-
Afamelanotide	****	****	****	****	£1,290,678
SCENARIO 2.2: slow attenuation of effect					
Standard care	****	****	-	-	-
Afamelanotide	****	****	****	****	£1,343,359
SCENARIO 2.3: fast onset and slow attenuation of effect					
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: simple QALY adaption



ERG report figure 12

Deterministic sensitivity analyses: ERG exploratory base case



ICER increased with

- Reducing effect size (smaller mean difference in DLQI change at day 60, 120, 180 between afamelanotide and standard care)
- Assuming a smaller utility loss per unit increase in DLQI
- Greater average number of implants

Results around base case taken from figure 12 ERG report

ERG's 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 a greater proportion of people with mild disease at day 120 with afamelanotide, higher 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: 0.56 (maximum 0.8 in scenario assuming fast onset of effect and slow attenuation)
- ERG exploratory most optimistic scenario (simple QALY adaption with lowest ICER in deterministic sensitivity analysis) 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

Innovation

- Company stated: two UK sites were involved in the clinical development programme for [afamelanotide] (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 [afamelanotide]. Access to [afamelanotide] 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.
- Clinical expert: 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 afamelanotide innovative?***
⊙ ***Does innovation add demonstrable and distinctive benefits of a substantial nature that may not have been adequately captured in the reference case QALY measure?***

Key issues 1

- 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?
- 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?

Key issues 2

- 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?
- Which of the ERG's approaches to estimate cost per QALY estimates is more suitable for decision-making?
- 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?
  - What is the expected average number of implants per year?
- Are there any groups of people for whom afamelanotide would be expected to be more or less cost effective?
- Is afamelanotide innovative?
- Does innovation add demonstrable and distinctive benefits of a substantial nature that may not have been adequately captures in the reference case QALY measure?

Contains no confidential information. For committee, public and projector

Lead team presentation

Afamelanotide for treating erythropoietic protoporphyria
Patient perspectives presentation

1st Evaluation Committee Meeting

Highly Specialised Technology, 23 November 2017

Lead: Jeremy Manuel

Company: Clinuvel

Chair: Peter Jackson

Evidence review group: Southampton Health Technology Assessments Centre (SHTAC)

NICE team: Mary Hughes, Raisa Sidhu, Sheela Upadhyaya

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: 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: 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"

Key issues

- How much extra time in light without pain would make an important difference to patients' lives?
- Would a reduction in phototoxic reactions make an important difference to patients' lives?
- Conditioned light avoidance:
  - What support may be required to reverse conditioned light avoidance?
- Does afamelanotide improve quality of life?
- Are patient experiences of EPP and afamelanotide in England similar to those reported in other European porphyria centres?