NICE National Institute for Health and Care Excellence

Slides for public – contains no ACiC information

Afamelanotide for treating erythropoietic protoporphyria

Chair's presentation

4th evaluation committee meeting

Highly Specialised Technologies

Chair: Peter Jackson

ERG: Southampton Health Technology Assessments Centre (SHTAC)

NICE technical team: Alan Moore, Victoria Kelly and Richard Diaz

Company: Clinuvel

6th July 2022

Key issues for consideration

- Do the responses and new evidence presented at the consultation allow the committee to update its conclusions in relation to:
  - The preferred modelling approach (QALYs not DALYs)
  - Use of proxy conditions (may not fully capture the experiences of people with EPP)
  - Use of DLQI mapped to EQ-5D (preferred method but may underestimate the benefits of afamelanotide)
  - Assumptions in ERG's exploratory base case:
    - assuming effect of afamelanotide builds up over 2 months and slowly decreases over 6 months after last implant
    - maximum 4 implants per year
  - Not applying a QALY weighting criteria
  - Are there any additional impacts beyond the direct health benefits not currently captured?
- Have the upheld appeal points been sufficiently addressed by the committee?

NICE and Highly specialised technologies (HST)

- The HST Evaluation Committee is an independent advisory body. They make recommendations to the Institute regarding benefits and costs of highly specialised technologies for national commissioning by NHS England.
- Only technologies which meet the HST criteria will be considered by the HST programme
- HST decision-making is made in the context of a finite healthcare budget (budget for highly specialised technologies is ring-fenced) and considers opportunity costs
- In developing guidance HST committee considers nature of the condition, clinical effectiveness, value for money (includes ICERs any commercial arrangements and budget impact) and impact of the technology beyond direct health benefits
- HST positive recommendations are binding for NHS (England):
  - Recommending treatments with excessively high ICERs would result in displacement of more cost-effective technologies meaning health outcomes would be reduced overall for people with rare conditions.
- The role of the committee is to recommend against the use of a technology if benefits to patients are unproven or costs of technology are unreasonable

Abbreviations: ERG: Evidence review group, ICER: Incremental cost-effectiveness ratio, QALY: Quality adjusted life year

NICE and Highly specialised technologies (HST)

During the evaluation process the committee will consider the evidence submitted from a range of groups. The main evidence submission comes from the company

Role of companies, ERGs and stakeholders

Aspect	
Responsibility for submitting evidence	The core evidence submission is provided by the company developing the technology. The company provides a detailed evidence submission along with an economic model to estimate the value for money of a new technology. Evidence from other stakeholders are also considered
Role of the ERG	The ERG is an independent review group which provides an assessment of all the submitted evidence for committee consideration. The ERG remit is to critically evaluate the submission, identify its strengths and weaknesses, clarify where necessary and supplement it with further analysis as required. The ERG uses the company's model for carrying out its preferred economic analysis
Role of stakeholders	Stakeholders contribute at various stages of guidance production and provide important information, for example; on the condition, the impact of the technology on patients/caregivers and highlight important outcomes

Nature of condition

- Erythropoietic protoporphyria (EPP) is a genetic disorder of ferrochelatase enzyme deficiency, results in accumulation of protoporphyrin IX (PPIX) in the skin and liver
- PPIX reacts to visible light (sunlight and some artificial light). It causes anaphylactoid and phototoxic reactions lasting 2-3 days, up to >10 days
  - Often rapid, unbearable pain within <5 minutes in light
  - All encompassing tiredness as body heals from reaction which can take weeks
  - Anxiety and social isolation; study opportunities, job security and career development negatively affected by days lost to EPP symptoms
- Daily life driven by need to avoid light that triggers phototoxic reactions
- EPP not associated with shorter life expectancy for majority without liver complications

Description - Afamelanotide (Scenesse, Clinuvel)

Marketing authorisation*	Indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria
Administration & dose	Controlled release injectable implant, subcutaneous injection • 1 implant every 2 months before expected and during increased sunlight exposure e.g. spring to early autumn • Recommended 3 implants per year • Recommended maximum implants is 4 per year. The overall duration of treatment is at the specialist physician's discretion. • Average dose *** implants per year seen in treatment to date
Mechanism of action	Chemical analogue of alpha-melanocyte stimulating hormone. Increases melanin content of skin. Does not need exposure to light to stimulate melanin
Price	£12,020 per injectable implant; no PAS discount submitted (company say they do not give discounts on this technology)

*SPC: This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

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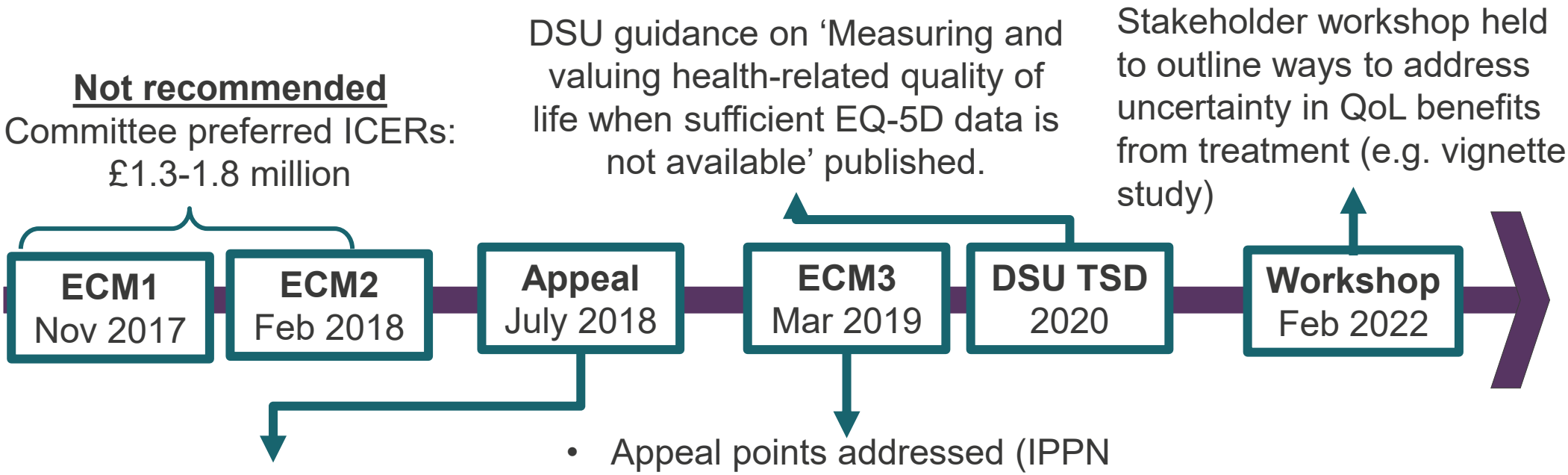
EMA: European Medicines Agency; PAS: patient access scheme

History of appraisal



3 appeal points upheld:

- IPPN were not included at ECM2
- Did not adequately consider duties under Equality Act
- Unreasonable to state that trial results showed small benefits

- Appeal points addressed (IPPN included, additional equalities considerations and benefits reconsidered)
- Committee preferred ICERs remained >£1 million
- **Outcome**: not recommended. Appraisal paused to give stakeholders an opportunity to explore further ways to obtain evidence

ECM: Evaluation Committee Meeting; ICER: incremental cost-effectiveness ratio; IPPN: International Porphyria Patient Network, QoL: quality of life

Recap of evidence & committee conclusions in the ECD

Nature of condition (1/2)

Recap: Patient impact (presented at ECM 3: March 2019)

- **Phototoxic reactions**
  - Immediate invisible burning pain, but eventually damage can be visible including up to 2nd degree burn wounds and scarring
  - Long lasting pain & like being “burnt alive”, analgesics ineffective
  - “Every ray of sunlight immediately induced massively painful burns”
- **Behavioural adaptations and mental health impacts**
  - Physical adaptations lead to stigmatisation of patients, suicidal ideation from young age
  - Non-recognition by doctors and society: supportive parents but concerns dismissed by clinicians/teachers, forced in sun as pain not visible, but swelling/redness next day
  - “Pain and impact on the mind and body is a key driver in the behaviour of EPP patients”; “All my life I have been bullied, isolated, misunderstood, shunned, picked on, alone, laughed at, alienated, mistreated and in constant unbearable pain”; “ridiculed … a hilarious excuse”
- **Impact on work and family**
  - Forced to give up career path as plant scientist as could not fulfil outdoor tasks; change studies at university
  - “My life has been completely dictated by EPP with respect to education, career and life style”; “I often felt anxious and I also had fears about my future. I felt as a burden to family and friends”

Nature of condition (2/2)

- **Family testimony**
  - Patient cannot join in family events or holidays (would be “paradise” if dad could join in); "I didn't understand why daddy couldn't come and play with me and I felt sad when he would not come"
  - Stressful, causes arguments, creates guilt
  - Unpredictable and unpreventable physical and psychological effects of patient
  - Family share the emotional devastation of his social isolation; “A cause of sadness and anxiety for all of the family"
- **Lack of alternative treatments**
  - Beta-carotene compounds, UVB and Dundee cream not effective
  - UVB can cause photosensitive reactions and concerns re skin cancer
  - No effective alternative treatment
- **BPA 2018 survey**
  - 93% want to try drug – suggests high patient need
  - EPP severely impacts patients’ lives in most categories – family life, engaging with friends, work/study, finance

Nature of condition – committee conclusions

EPP is a serious, debilitating and disabling condition with substantial effects on people with the condition and their families.

Committee conclusions (sections 4.1-4.8 of ECD)	• Recognised that phototoxic reactions cause serious and severe symptoms, including intense pain and extreme tiredness, that last for days • EPP has a substantial effect on day-day activities and acknowledged that the psychological and stigmatising effects of the condition are striking and significant • There is no effective treatment for preventing phototoxicity caused by EPP, so there is an unmet need for an effective treatment • Recognised that delay in the diagnosis of EPP is a problem • Acknowledged that there is some variation in how long people with EPP can be exposed to sunlight without a reaction • Concluded that it would take into account the nature of EPP as a disability throughout its decision making, and consider if and how it would be appropriate to adjust its approach in the context of this disability [upheld appeal point]

EPP: erythropoietic protoporphyria

Benefits of treatment

Recap – Trial evidence summary

- 4 randomised placebo controlled trials
  - CUV017: N=100; 12 month duration
  - CUV029: N=76; 9 month duration
  - CUV030: N=77; 6 month duration (unpublished)
  - CUV039: N=94; 6 month duration
    - Key outcomes: duration of tolerance of sunlight, phototoxic reactions, DLQI, EPP-QoL, SF-36
- 3 observational studies
  - Biolcati et al. 2015: long term clinical effectiveness study (N=115)
  - CUV-PASS-001: ongoing post authorisation disease registry safety study (***)
  - CUV010: single arm phase 2 study (N=5)
  - Holme et al. 2006: UK quality of life study (N=389)

Benefits of treatment

Recap trial evidence - 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)	[redacted]	[redacted]	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	

→ ***Results showed statistically significant increases in time spent in light without pain***

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)

Benefits of treatment

Recap trial evidence - Phototoxicity

Outcome	Study CUV029 (Europe)		Study CUV039 (USA)	
	AFA (N=38)	PLA (N=36)	AFA (N=46)	PLA (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	
Sum of Likert score for phototoxic reactions during study; mean ± SD; median (range)	[redacted]	[redacted]	16.3 ± 33.2 4.0 (0-196)	34.1 ± 86.7 6.0 (0-507)
	Difference p=0.025		Difference p=0.44	
Overall maximum Likert score per patient; mean ± SD; median (range)	[redacted]	[redacted]	3.5 ± 3.1 4.0 (0-8)	3.9 ± 3.3 5.0 (0-9)
	Difference p=0.010		Difference p=0.544	

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→ ***CUV029 results showed a statistically significant decrease in the number and severity of phototoxic reactions***

Benefits of treatment

Recap quality of life

- EPP-QoL: condition-specific questionnaire, developed by company; improvement with afamelanotide
  - ERG highlighted limitations: no question on pain, not fully validated, modified while trials ongoing

- SF-36 and Dermatology Life Quality Index (DLQI) used in some clinical trials
  - SF-36: No data reported by company
  - DLQI: dermatology questionnaire, validated for various dermatological conditions but not for EPP; some improvement with afamelanotide
  - Company: SF-36 and DLQI not suitable to quantify humanistic burden of EPP

SF-36, Short Form 36; DLQI, Dermatology Life Quality Index

Benefits of treatment

Recap quality of life - CUV039 results

		DLQI[1]		EPP-QoL[1]	
Visit (day)		AFA	PLA	AFA	PLA
1 (0)	N	47	43	47	43
	Mean (SD)	**10.7 (6.3)**	**10.4 (5.7)**	**26.6 (19.9)**	**26.2 (19.4)**
2 (60)	N	47	43	47	43
	Mean (SD)	**4.7 (5.7)**	**6.4 (6.0)**	**70.6 (24.2)**	**49.6 (29.8)**
3 (120)	N	46	42	46	42
	Mean (SD)	**2.8 (4.2)**	**4.1 (4.8)**	**76.9 (22.0)**	**55.8 (30.2)**
4 (180)	N	46	43	46	43
	Mean (SD)	**2.4 (4.2)**	**3.1 (4.1)**	**78.1 (24.9)**	**63.0 (26.2)**

- DLQI scoring range is 0-30 (0 no negative effect on QoL, >20 = extremely large effect on QoL)
- EPP-QoL scoring range 0-100; improvements observed over time indicate a change from moderate to mild EPP according to the company's EPP-QoL score thresholds (stratified as 'mild' – 66.7 to 100; 'moderate' – 33.4 to 66.6, and 'severe' – 0 to 33.3)

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[1]Because no results were presented by the company, the ERG extracted DLQI data from the EPAR for study CUV039 (table 11 ERG report). The EPP-QoL scores were extracted from Langendonk by the ERG.

Recap qualitative evidence: patient perspectives

- **Patient and expert views**: Clinical and patient experts testimony reported better outcomes than in trial e.g. afamelanotide increased time spent in light by *hours* rather than minutes; life changing.
  - Experts: even few extra minutes in daylight, fewer phototoxic reactions could have large impact for patients
  - Few minutes in full daylight equates to much longer (even hours) in dappled light; people in much stronger position to manage lives without being debilitated by disease
- Clinical and patient experts believed effects would be greater than that seen in trials, because of conditioned light avoidance behaviour
- **Cumulative/multiplier effect** of benefit of afamelanotide; not just allows patients to spend more time in light but:
  - Patients can carry out additional work with less EPP events
  - Able to withstand considerably longer periods in cloudy daylight or even, for some patients, in artificial light with benefits for education and work
  - True impact of the gain cannot be assessed by simplified ‘time in sunlight’ data

Impact of the new technology

Afamelanotide is an effective medicine that provides benefits that would be highly valued by patients - there are important uncertainties in the evidence and the size of the clinical benefits.

Committee conclusions (sections 4.9 – 4.26 of ECD)

- Results showed a statistically significant increase in the median amount of time a person could spend in daylight without pain compared with placebo → committee noted issues with incomplete trial data & was aware EMA highlighted concerns with CUV029 and CUV030, including unsatisfactory collection and analyses of data.
- Considered evidence from observational studies, patients' and experts' testimonies, and additional evidence described by the clinical experts
- Significant problems in measuring quality of life:
  - factors such as fatigue, particularly impact on the lives of patients and their families, and that the effects of stigma may not be fully reflected in any of the quality-of-life measures
- Uncertainty about how the EPP-QoL could be interpreted (including the arbitrary severity banding used by the company)
- Disappointed that available SF-36 data had not been presented by the company because this measure includes questions on fatigue and anxiety that are not captured by the DLQI

Economic evaluation

Recap: Modelling approach (1)

- Company's model: cost per DALY averted
  - Company considered QALY framework inappropriate
  - Therefore cost-effectiveness model & results presented in ICERs per DALY averted
    - Outside of NICE reference case – company were encouraged (but declined) to present QALY-based analyses as base case

- ERG
  - Considered that it would be possible to model value for money in cost per QALY gained in line with reference case
  - Presented exploratory analyses:
    - Direct conversion of company model to QALYs
    - Alternative modelling approach

Economic evaluation

Recap: Modelling approach (2)

Company

[redacted]

Mild: EPP-QoL 67-100
Moderate: EPP-QoL 33-67
Severe: EPP-QoL 0-33

Disability weight

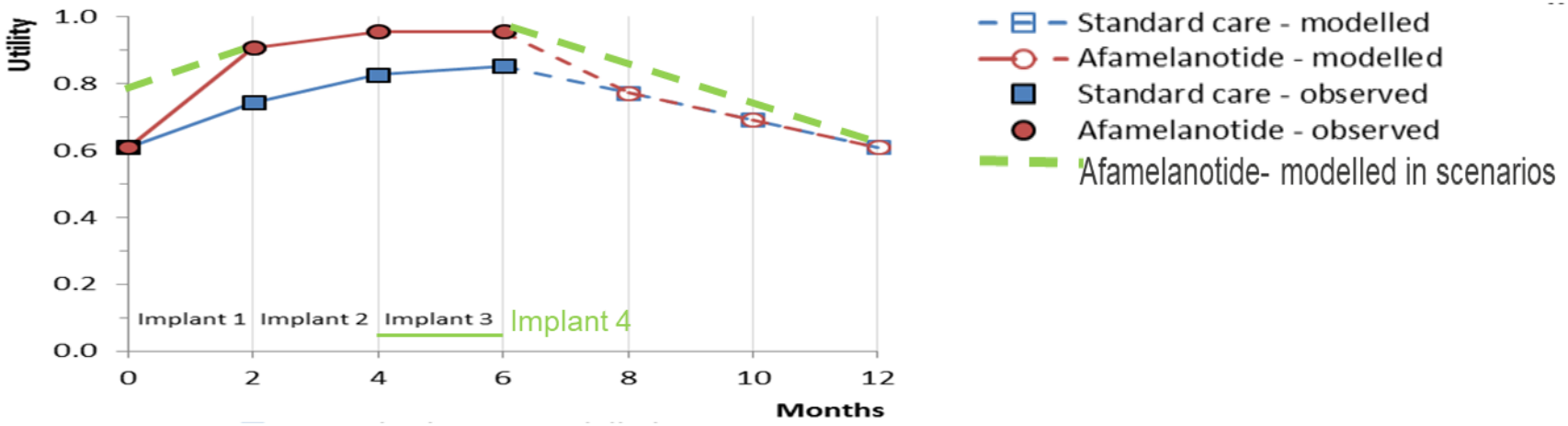
[redacted]

Clinical effectiveness
% of mild, moderate, severe based on trial data (CUV029/30/39) for afamelanotide vs placebo at days 0 to 120

Impact on QoL
Based on proxy
[redacted]

ERG exploratory

[redacted]



Clinical effectiveness
DLQI at months 0–6 from trial data (CUV039) for afamelanotide vs placebo

Impact on QoL
Mapped from DLQI to EQ-5D

Economic evaluation

Recap: Key features of company and ERG base case (1/2)

	Company base case	ERG 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
Mean implant use	*** 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

Economic evaluation

Recap: Key features of company and ERG base case (2/2)

	Company base case	ERG simple QALY version	ERG base case
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. Afamelanotide assumed: linear onset of benefit over 2 months after the 1st 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]	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

GBD; global burden of disease

Economic evaluation

Recap: Results

Company base case

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

- Uses DALYs and EPP-QoL severity levels based on trial results
- Lowest ICERs per DALY averted were £97,624 (societal impact assuming AFA 90% & SoC 10% of earnings retained) and £165,442 (AFA: 50%, SoC: 0%)
- Highest ICER per DALY £727,143 (changing DALY proxy condition to [redacted])

ERG base case

Scenario	Incr costs (£)	Incr QALYs (discounted)	Incr QALYs (undiscounted)	ICER (£/QALY)
ERG exploratory base case	[redacted]	[redacted]	[redacted]	£1,605,478

- ERG base case mapped from DLQI to EQ-5D using trial results
- ERG explored several other scenarios, with different combinations of implants per year, onset of effect, and attenuation
  - All >£1 million per QALY gained

ERG's exploratory analyses (1)

simple QALY adaptation of company's base case

Treatment	Incr costs (£)	Incr QALYs (discounted)	Incr QALYs (undiscounted)	ICER (£/QALY)
SCENARIO 1.0: company base case				
SoC	-	-	-	-
AFA	[redacted]	[redacted]	[redacted]	£278,386
SCENARIO 1.1: adjustment for distribution of severity for baseline differences				
SoC	-	-	-	-
AFA	[redacted]	[redacted]	[redacted]	£454,800
SCENARIO 1.2: adjustment for baseline and attenuation of effect*				
SoC	-	-	-	-
AFA	[redacted]	[redacted]	[redacted]	£779,657
SCENARIO 1.3: utilities for proxy condition from literature				
SoC	-	-	-	-
AFA	[redacted]	[redacted]	[redacted]	£1,726,802

*assuming a linear loss of the treatment benefit between 180 days and the end of the year

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AFA: afamelanotide; SoC: standard of care

ERG's exploratory analyses (2)

ERG base case

Treatment	Incr. costs (£)	Incr. QALYs (discounted	Incr. QALYs (undiscounted)	ICER (£/QALY)
scenario 2.0: ERG exploratory base case*				
SoC	[redacted]	[redacted]		-
AFA	[redacted]	[redacted]	[redacted]	£1,605,478
scenario 2.1: fast onset of effect, attenuation effect 2 months				
SoC	[redacted]	[redacted]		-
AFA	[redacted]	[redacted]	[redacted]	£1,290,678
scenario 2.2: gradual onset, slow attenuation of effect over 6 months				
SoC	[redacted]	[redacted]		-
AFA	[redacted]	[redacted]	[redacted]	£1,343,359
scenario 2.3: fast onset and slow attenuation of effect over 6 months				
SoC	-	-		-
AFA	[redacted]	[redacted]	[redacted]	£1,115,671
scenario 2.4: maximum 2 implants per year + ERG base case				
SoC	-	-		-
AFA	[redacted]	[redacted]	[redacted]	£1,337,494
scenario 2.5: maximum 4 implants per year + ERG base case				
SoC	[redacted]	[redacted]		-
AFA	[redacted]	[redacted]	[redacted]	£1,785,957

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*ERG base case: maximum of 3 implants per year, gradual onset of effect, slow attenuation effect over 2 months

Cost to the NHS and Value for Money

The economic modelling had significant uncertainties, influenced by the important challenges in measuring the effects of the condition and the benefits of treatment

Committee conclusions (sections 4.27 – 4.41 of ECD)

- Although the committee took the DALY-based model into account in its decision making, its preferred approach was the use of QALYs
- Use of proxy conditions may not fully capture the experience of people with EPP (proxy conditions considered confidential by the company)
- ERG's approach (mapping from DQLI to EQ-5D) may have underestimated the benefits of afamelanotide – not possible to know by how much
- Recognising limitations of all available approaches, the committee preferred the ERG's exploratory modelling approach for decision making
- ERG's analyses, assuming effect of afamelanotide builds up over 2 months (base case), and slowly decreases over 6 months after last implant, plausible
- Should take into account that people may have up to 4 implants per year
- QALY weighting criteria not met (ERG base case: 0.56 undiscounted QALYs)
- Preferred ICERs were between £1,343,359 and £1,785,957 per QALY gained
- Reasonable to consider alternative methods to capture benefits: suggested utility scores estimated through an indirect method such as a 'vignette'

Impact of the technology beyond direct health

Afamelanotide would have an impact beyond direct health benefits but quantifying this was difficult

Committee conclusions (section 4.42 of ECD)	• People with EPP often alter career plans to accommodate effects of their disease, and might be unable to take up enhanced career opportunities • Clinical experts explained that, after treatment with afamelanotide, patients may feel confident enough in careers with a higher level of light exposure and this may lead to a higher income • No data provided on how afamelanotide impacted on ability to work/study • Company exploratory analysis estimated loss of earnings due to EPP – but the committee were unsure of what data these analyses were based on • Treatment with afamelanotide has substantial social, educational, financial and psychological benefits for families – quantifying this was difficult

Responses to the ECD consultation

Responses to ECD2 – Summary

- **The company did not provide any comments, evidence, or analysis/model in response to ECD2**

Comments received from

International Porphyria Patient Network (IPPN)

- New evidence published since last ECM
- Comments on HST methods/past decision-making
- Suggestions for calculating QALYs in EPP
- Comments on upheld appeal points and potential for a managed access agreement

The British Porphyria Association (BPA) and Global Porphyria Advocacy Coalition (GPAC) – joint response

- New evidence published since last ECM
- Further comments on nature of the condition, quality of life and disease classification

The British Association of Dermatologists (BAD)

- New evidence published since last ECM
- Comments on upheld appeal points and potential for a managed access agreement

IPPN response – New clinical data (1/4)

Committee conclusions in the ECD:

- Afamelanotide is effective and provides important benefits for patients, but there are important uncertainties in the evidence and the size of the clinical benefits.

- New clinical evidence presented:
  - Results of the European SCENESSE PASS-001 (Wensink et al. 2020, n=117) 3-year observational study (effectiveness, safety and QoL)
  - Maximum burn time (new outcome; Barman-Aksözen et al. 2020)
  - Time to prodromal symptoms (new outcome; Wensink et al 2021)
  - Normalisation of circadian rhythm and sleeping pattern (Wensink et al. 2022)
  - Liver protection (Minder et al. 2021)

IPPN response – New clinical data (2/4)

European SCENESSE PASS-001 study (Wensink et al. 2020)

- Single-centre, ongoing (indefinite) prospective post-authorisation safety and efficacy cohort study of afamelanotide.
- N=117 receiving afamelanotide, of whom 115 (98.3%) continued treatment, with a median follow-up time of 2.0 years and a mean of 8.0 (IQR 5.5 to 10.0) implants per patient.

- **Results**:
  - Time spent outside in week 1 **increased** 1.85 hours per week with afamelanotide (95% CI, −0.07 to 3.78 hours; p=0.06
  - Time spent outdoors **increased** during the observational period 2016 to 2018: increasing 1.41 hours per week per year on treatment (95% CI, 0.04 to 2.77 hours; p=0.04).
  - Time spent outside in week 5 showed a significant **increase** of 6.14 hours per week (95% CI, 3.62 to 8.67 hours; p<0.001). Time spent outside varied by 6.40 hours (95% CI, 0.60 to 12.19) between the month with the lowest (November) and highest (August) number of hours
  - EPP QoL **increased** significantly by 14.01% (95% CI, 4.53% to 23.50%; p<0.001)
  - Score for pain associated with phototoxic reactions significantly **decreased** by 0.85 points (95% CI, −1.43 to −0.26; p<0.001).

ERG comments: Significant uncertainty remains; results have wide confidence intervals and there are limitations in reporting. High likelihood of recall bias. PASS-001 study does not provide convincing new evidence

IPPN response – New clinical data (3/4)

Maximum burn time (New outcome):

- Single-centre retrospective chart review (Barman-Aksözen et al. 2020) analysed maximum burn time (the maximum time spent in sunlight without phototoxic reaction assessed on a Likert scale) for patients in the Swiss EPP cohort between 2016 and 2018 (N=39).
- **Results**: Median phototoxic burn time was 180 minutes, (range 15 to 420 minutes) on afamelanotide vs 10 minutes on standard treatment (range 2 to 120 minutes); p<0.0001

ERG comments: Lacks clarity around important aspects of participant recall and the results may potentially be at high risk of differential recall bias. Population characteristics are not reported. Reliability of the study findings is therefore uncertain

Time to prodromal symptoms (New outcome):

- Wensink et al 2021 reported 2 retrospective studies - EPP patients interviewed using questionnaire on characteristics of prodromal symptoms (reversible “warning” symptoms that precede phototoxic reactions which occur with sunlight exposure in patients with EPP). Pilot study in the US n= 31 interviewed by phone between January and April 2018. N=58 in Netherlands face-to-face in clinics between June and August 2018 using same questions
- **Results**: In both cohorts, patients’ time to first prodromal symptom significantly improved during afamelanotide treatment (p<0.0001 and p<0.0001 in US and Dutch cohorts, respectively)

ERG comments: Lacks clarity on important aspects of participant recall. Instrument used lacks validation and was administered by only one or an unknown number of investigators, making the study methodologically weak

IPPN response – New clinical data (4/4)

Normalisation of circadian rhythm and sleeping pattern:

- Open-label single-centre longitudinal case-control study by Wensink et al. 2022 quantified the white light exposure and activity levels of patients with EPP (N=26) before and during afamelanotide therapy, compared to healthy controls (N=23) using a light and activity sensing wristwatch (actigraph)
- **Results**: Patients on afamelanotide had 71.6% more light exposure during spring compared to patients off treatment ($p<0.01$). Patients on afamelanotide treatment experienced fewer painful moments in the morning (6.5% decrease; $p=0.005$) and the afternoon/evening (8.1% decrease; $p =0.004$).

ERG comments: A strength of this study is that the actigraph provides an objective measure of light exposure not subject to recall bias. The study is subject to several limitations, for example differences between groups and missing data excluded – means findings uncertain

Liver protection

- A single-centre retrospective chart review study by Minder et al. 2021 analysed the safety laboratory data of 38 Swiss patients who had received at least one dose of afamelanotide from 2016 to 2019
- **Results**: aspartate transaminase (AST) levels decreased statistically significantly. However, whilst 24/38 patients (63%) experienced a decrease (i.e. improvement) in AST on treatment with afamelanotide, 14/38 patients (37%) experienced a slight increase.

ERG comments: suggests afamelanotide may improve liver function and/or reduce risk of liver dysfunction in some but not all EPP patients. It is unclear if findings would be replicated by a more substantive set of liver function and/or imaging tests

IPPN Response – EPP-QoL validated (1/2)

Committee conclusions:

- Committee preferred quality of life measure was Dermatology Life Quality Index [DLQI] scores mapped to the EQ-5D to derive utility values using a published, validated algorithm.
- Company presented EPP-QoL → a condition specific quality of life questionnaire developed by the company & clinicians. Committee noted the measurement was not validated and did not capture aspects of EPP that patients and clinicians consider important.

IPPN Response:

- The EPP-QoL instrument now validated (Biolcati et al. 2021) → IPPN consider validation of EPP-QoL should lead to a reconsideration of QoL outcomes. Highlight that the ECD stated:
    - *"The committee concluded that the EPP-QoL provided relevant evidence that it would take into account in its consideration of the clinical effectiveness of afamelanotide. However, without full and appropriate validation, it concluded that there remained uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide".*

IPPN Response – EPP-QoL validated (2/2)

ERG comments on EPP QoL validation:

- Biolcati et al. 2021 provided evidence for reliability and validity of the 10-item EPP Symptoms score as a summary measure of EPP symptoms and impact on daily activities and behaviours
- The study did not support validity of EPP Wellbeing scale, (two questions related to wellbeing and quality of life). Agree with authors' recommendation that EPP Wellbeing scale and related questions should not be used
- Some limitations of study include limited reporting of methods used, small sample size and post-hoc nature of validation
- EPP Symptoms scale not suitable for use in QALY calculations, because it has not been valued using a choice-based method and it is not measured on a ratio scale with 0 representing a utility equivalent to death and 1 the utility of 'perfect health'

IPPN Response – New EQ-5D evidence (1/2)

Committee conclusions:

- There remained a critical uncertainty in how effects of condition and treatment benefits were quantified and translated into QALYs. Suggested use of other methods (e.g vignette study)

New evidence on quality of life measurement:

- Use of EQ-5D administered directly to patients – NICE preference
- A small feasibility study undertaken in Switzerland (n=5) to assess use of EQ-5D – unpublished – HST committee has previously accepted small utility studies (e.g HST8 and HST11)
- Included 5 individuals under long-term treatment (≥ 2 years) with afamelanotide
- Study collected EQ-5D-5L (mapped to EQ-5D-3L) and EPP-QoL data for current situation ("today"), and retrospectively for a phototoxic reaction and without treatment, i.e., a treatment interruption period due to reimbursement issues
- **Results**: 5 patients under long-term treatment had utility values comparable to age-matched population. A phototoxic reaction and treatment interruption is comparable to utility values assocatied with acute burn injuries and chronic neuropathic pain

Time point	EQ-5D
Phototoxic reaction (retrospective data, n=5)	0.215 ± 0.10
Treatment interruption (retrospective data, n=5)	0.331 ± 0.46
Today: Afamelanotide treatment (n=5)	0.965 ± 0.08

IPPN Response – New EQ-5D evidence (2/2)

New evidence on quality of life measurement (patient survey):

- IPPN conducted informal survey (involving patients in 4 European countries)
- 13 EQ-5D-5L (mapped to EQ-5D-3L) questionnaires from patients having at least two years of treatment
  - On average, the patients were on treatment for 8.6 years (mean, median: 8, range: 3-14 years)
- Data from 4 patients having less than 2 years of treatment and from one patient without treatment was also collected

Results from patient survey

Time point	EQ-5D
Today: Afamelanotide treatment ≥ 2 years (n=13)	0.975 ± 0.038
Today: Afamelanotide treatment < 2 years (n=4)	0.619 ± 0.23
Today: No afamelanotide treatment (n=1)	0.397

ERG comments – New EQ-5D evidence

- Limited information provided on methods of data collection/analysis. Very small sample sizes
- It is unclear what criteria were used to select participants and whether they are representative of the UK population who could potentially be treated with afamelanotide
- Retrospective assessment of quality of life is vulnerable to recall bias, and no information is provided about the timing and duration of the phototoxic reaction or period without treatment
- EPP symptoms and their impact on activities and behaviours are affected by sunlight levels. Hence the timing of assessment within the year may be important but is not reported
- EQ-5D index scores were obtained using the German value set

Conclusion on feasibility study: highly uncertain (small sample size, retrospective assessment and lack of information on inclusion criteria and methods of data collection and analysis). Study may indicate potential for use of EQ-5D to detect treatment effects. Do not consider results from Swiss EQ-5D feasibility study are suitable for use in QALY calculations

Conclusion on IPPN patient survey: patient survey does not provide substantive new evidence on utility with afamelanotide treatment, due to small sample size and high risk of selection bias.

IPPN response – suggested method for calculating QALYs in EPP

IPPN suggest an alternative approach to calculate QALYs

- Use of Holmes et al mapping from DLQI to EQ-5D for baseline utility values for intervention and placebo group from the clinical trials (mean = ~0.6)
- Use of Switzerland EQ-5D feasibility study (unpublished) to estimate treatment effect (Afamelanotide treatment = 0.965). Use of a lifetime time horizon

ERG comments:

- ERG do not believe additional evidence provided could reduce uncertainty over QALY gain
- Not desirable/necessary to use unadjusted indirect comparison or data from very small unpublished studies when a mapping approach can be used to estimate utilities from randomised trial data.
- Feasibility study and patient survey subject to measurement error due to small sample sizes. There is also a risk of selection bias. Mean EQ-5D values in Swiss feasibility study (0.965) and IPPN survey (0.975) are higher than UK population norms
- Different sources for utilities in treatment and standard care arms introduces a high risk of bias. Without information to compare/adjust for differences in study populations, cannot attribute utility differences to treatment. Methods of utility assessment differ between studies
- Extending time horizon does not substantively change undiscounted QALYs

Further ERG comments on uncertainty in valuing health benefits in EPP

- Additional scenarios could be produced if other suitable proxies with published utilities could be identified (some proxy condition utility values have already been used in the analysis)
- Further research to build on the EQ-5D feasibility study or to conduct an indirect valuation in a vignette study may be worthwhile
- Other major uncertainties over how to model cost-effectiveness for afamelanotide for treating EPP remain, and include:
  - seasonal trends in utility related to EPP
  - the timing of onset of the protective effect of afamelanotide from the first implant of the year and the waning of effect after the last implant
  - the magnitude and speed of long-term change in utility as learned responses to EPP are unlearnt
  - the mean number of implants per year

IPPN response – Managed access

Committee conclusions:

- Committee considered company's managed access arrangement (MAA) proposals. A study (such as a vignette) would be needed before it could confirm whether a MAA could be possible. An MAA could be an option, but plausible potential for value for money with afamelanotide would first need to be shown

Comments on managed access agreements and committee's request for a vignette study:

- HST committee stated one of reasons that prevented an MAA was that it was unlikely that data collected in the MAA would resolve existing uncertainties
- IPPN note that 2 European HTA bodies (Germany and Scotland [under ultra-orphan pathway]) have recommended use of afamelanotide based on either post MA data collection (Germany) or to collect further data (Scotland)

IPPN response – inconsistency between HSTs

Inconsistency between this evaluation compared to previous HST topics:

- IPPN reviewed past HST documents and highlight:
  - HST5 (Gaucher disease) included a QALY benefit for oral therapy
    - Utility increment accepted for oral treatment was 0.05. The economic model preferred by HST committee for EPP, treatment with afamelanotide is only associated with a utility increment of [redacted] (annual), and does not exceed [redacted]
    - Lacks face validity that effective treatment for EPP is associated with only [redacted] QALYs (over the model time period) while switching from an infusion to an oral therapy (having the same efficacy) is already associated with 1.05 QALYs (HST5)
- IPPN question the use of a 35 year time horizon for afamelanotide
- HST16 (acute hepatic porphyria) – non statistically different EQ-5D trial results. Committee accepted proxy condition utility values and EQ-5D data from a natural history study instead (chronic symptoms and psychological factors may not reduce as quickly as frequency of attacks and 6 months might have been too short to capture quality of life benefits)
  - Similar situation for afamelanotide, but committee preferred to use results based on the DLQI outcomes despite acknowledging these results underestimate benefit of treatment

IPPN response – upheld appeal points

IPPN provide additional comments on the upheld appeal points

EPP as a disability

- The committee in ECD2 states that EPP is now recognised as a disability in the meaning of the Equality Act following the appeal
  - However, acknowledging disability status without subsequent effect on methods used/interpretation of the evidence does not resolve the upheld appeal points nor the discriminatory behaviour towards patients with EPP
  - Methods used in this evaluation need particular consideration to ensure NICE avoids further unlawful discrimination against patients with EPP on grounds of their disability

Treatment benefit with afamelanotide

- Appeal panel concluded that it was unreasonable for the committee to state that trial results show small benefits with afamelanotide, but ECD2 states “the size of the benefits it provides has not been quantified.”
  - Trial results and new evidence published since last committee meeting shows benefits have been quantified

- IPPN consider that appeal points have been insufficiently addressed in ECD2

The British Porphyria Association (BPA) and Global Porphyria Advocacy Coalition (GPAC) – joint response

- Also highlight new published evidence since last committee meeting
  - Studies show high levels of adherence and highly significant health benefits patients with a painful and life limiting condition
- Afamelanotide is a first in class treatment, and there is no alternative treatment available

- Reiterate points made in previous submission on wellbeing and quality of life:
  - Difficulty in physically maintaining a healthy body due to the inability to exercise outdoors
  - There is an psychological aspect that is very difficult to capture: unsure how this can be factored into the economic model
    - Specifically, the psychological impact that the visual imagery of the sun has on someone with EPP
  - Challenges of an invisible disability
    - Adaptations may be harder to achieve for people with EPP compared to visible disabilities
    - Previous inappropriate comments from committee highlight the lack of understanding of this invisible condition

The British Porphyria Association (BPA) and Global Porphyria Advocacy Coalition (GPAC) – joint response (2)

Committee conclusions – severity of condition :

- The company considered that arbitrary division of EPP QoL into thirds to be the fairest approach in the absence of validated cut-offs for EPP severity using the EPP QoL. The committee recalled the challenges associated with measuring quality of life in EPP using EPP QoL. It concluded that the company's approach to stratifying disease severity according to arbitrary quantiles contributed to uncertainties in the economic modelling.

- The BPA notes prior research that correlates levels of erythrocyte protoporphyrin to time to first symptom. BPA hope this information may be utilised to enhance the economic model and reduce uncertainties through a different form of disease stratification
  - Source: Balwani M, Naik H, Anderson KE, et al. **Clinical, Biochemical, and Genetic Characterization of North American Patients With Erythropoietic Protoporphyria and X-linked Protoporphyria.**
- Study finds that levels of erythrocyte protoporphyrin are related to disease severity

British Association of Dermatologists (BAD)

- Also highlight that new evidence has been published since the last appraisal meeting;
  - Real-world evidence shows larger benefits than trial data
  - This evidence shows that with time patients unlearn light avoidance behaviour
- Consideration should be given to the IPPN EQ-5D feasibility study. This is the NICE preferred QoL measure.
- Physical and mental health benefits of being outdoors have not been considered
- EPP-QoL is now validated and should be considered
- Upheld appeal points have been insufficiently addressed:
  - The appeal panel found it was unreasonable to conclude that clinical trial results suggest “small benefits” with afamelanotide
  - This upheld appeal point has not lead to a revaluation of the data
- Managed access agreement (MAA): financial risk is low (only up to ~200/250 patients likely to start treatment in a 5 year period). Cost of afamelanotide compares favourably to many NICE approved treatments. Unreasonable to insist on a vignette study as part of an MAA
  - Urge NICE to look again at potential for a managed access agreement – taking into account the new data
- The committee needs to ensure that EPP patients are not disadvantaged due to their disability

Factors affecting the guidance

Nature of the condition

- Extent of disease morbidity and patient clinical disability with current standard of care
- Impact of disease on carer quality of life
- Extent and nature of current treatment options

Value for money

- Incremental cost effectiveness using cost per QALY adjusted life year
- Patient access schemes and other commercial agreements
- Nature and extent of resources needed to enable new technology to be used (incl. budget impact in NHS and PSS, including patient access schemes)

Clinical Effectiveness

- 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

Impact beyond direct health benefits

- Whether there are significant non-health benefits
- Whether a substantial proportion of costs (savings) or benefits are incurred outside of NHS and personal and social services
- Potential for long-term benefits to NHS of research and innovation
- Impact of technology on overall delivery of specialised service
- Additional staffing and infrastructure requirements, including training and planning for expertise

Key issues for consideration

- Do the responses and new evidence presented at the consultation allow the committee to update its conclusions in relation to:
  - The preferred modelling approach (QALYs not DALYs)
  - Use of proxy conditions (may not fully capture the experiences of people with EPP)
  - Use of DLQI mapped to EQ-5D (preferred method but may underestimate the benefits of afamelanotide)
  - Assumptions in ERG's exploratory base case:
    - assuming effect of afamelanotide builds up over 2 months and slowly decreases over 6 months after last implant
    - maximum 4 implants per year
  - Not applying a QALY weighting criteria
  - Are there any additional impacts beyond the direct health benefits not currently captured?
- Have the upheld appeal points been sufficiently addressed by the committee?