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NICE National Institute for Health and Care Excellence

# Afamelanotide for treating erythropoietic protoporphyria

## Chair's presentation

3rd evaluation committee meeting (post appeal)

Highly Specialised Technologies

Lead team: Glenda Sobey, Francis Pang and Jeremy Manuel

Chair: Peter Jackson

ERG: Southampton Health Technology Assessments Centre (SHTAC)

NICE technical team: Aminata Thiam, Ian Watson, Sheela Upadhyaya

Company: Clinuvel

14 March 2019

# Key issues for consideration

***Taking into account EPP as a disability and committee's duties under the Equality Act:***

- What, if any, further adjustments should be made to the processes, methods and committee's considerations?

- What is the committee's view of:
  - The evidence provided, including IPPN's
  - The nature of the condition
  - The health benefits provided by afamelanotide
    - Clinical trial data?
    - Qualitative evidence?
  - The economic evaluation
    - Effects of condition and treatment on QoL captured?
    - Suitability for decision-making?
  - The proposal for a Managed Access Arrangement

→ *Have the benefits of afamelanotide been captured?*

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# History of afamelanotide evaluation

## ECM1

Nov 2017

**Not recommended**

- True extent of clinical benefit unclear; dichotomy between expert testimony and trial outcomes
- Uncertainty about measures of quality of life in EPP
- Committee preferred ICER= £1.3m–1.8m per QALY gained

## ECM2

Feb 2018

**Not recommended**

- Trial shows relatively small benefits; expert believe effects would be greater than trial
- Uncertainty about measures of quality of life remains
- Same committee preferred ICERs as ECD

## Appeal hearing

July 2018

**Upheld points**:

- Appeals received from Clinuvel, IPPN, BPA and BAD
- Upheld: 6 points on 3 topics
- Evaluation remitted to committee

# Appeal outcome (1)

## *Upheld appeal points*

1. **Failure to include IPPN at the 2nd meeting** *(IPPN 1a.1)*
   - IPPN had an important role to play
   - Lack of UK experience of treatment makes international group particularly important

*IPPN has been invited to submit evidence and attend committee meeting*

2. **Failure to adequately consider duties under Equality Act** *(Clinuvel 1b.1, IPPN 1b.1)*
   - EPP meets the definition of disability under the Act
   - HST process is itself a reasonable adjustment, but no evidence of adequate consideration of equalities for EPP specifically

3. **Unreasonable to state that trial results showed small benefits** *(BAD 2.2 and 2.3, IPPN 2.2)*
   - Size of change in light exposure can only be interpreted in the context of the normal range
   - Benefits reported in FED would not necessarily seem small to a reader – lack face validity

# Appeal outcome (2)
## *Dismissed appeals*

1. **Failure to give opportunity to discuss and negotiate MAA with NHS England** *(Clinuvel 1a.1)*
   - No disadvantage by any lack of clarity; process followed was overall fair
2. **Unreasonable not to take into account full range of factors** *(BAD 2.1)*
   - Approach to weighing up importance of all factors was reasonable
3. **Unreasonable not to acknowledge overwhelming clinical benefit evidence in patient testimonies and expert physicians** *(IPPN 2.1)*
   - Careful consideration given to patient and clinician testimony
4. **Trial evidence shows treatment is "highly effective"** *(IPPN 2.3)*
   - Reasonable to not have described trial evidence as "highly effective"
5. **Unreasonable consideration of quality of life evidence** *(IPPN 2.4)*
   - Approach to considering controlled and uncontrolled trial data was reasonable; evidence from EPP-QOL and DLQI and associated limitations accounted for
6. **Patient and clinician testimonies not considered in economic model** *(BPA 2.1)*
   - Consideration of testimonies and incorporation into decision were reasonable
7. **Unreasonable to deny MAA** *(IPPN 2.5)*
   - Clear reasoning reported in FED
8. **Unreasonable to make decision based on flawed model** *(BPA 2.2)*
   - Careful consideration given to model limitations; limitations not so severe to be unreasonable

# Appeal point upheld - Equalities (1)

- Equalities Act 2010*: defines disability as “physical or mental impairment that has a ‘substantial’ and ‘long-term’ negative effect on your ability to do normal daily activities”

  → ***EPP is a disability as defined in the Act***

- The committee must give due regard to the need to:
  - eliminate unlawful discrimination, harassment, victimisation and other prohibited conduct
  - advance equality of opportunity
  - foster good relations
- HST programme is itself a reasonable adjustment for rare diseases – but consideration must also be given to further reasonable adjustments
  - HST programme responds to situation where outcomes are difficult to measure and reliance solely on ICERs is unreasonable
  - Topic selection criteria: “Condition is chronic and severely disabling”
  - Adjustments include, for example,
    - “Discretion to take account of the full range of clinical studies…including RCTs, observational studies and any qualitative evidence”
    - Consideration of “extent of disease morbidity and patient clinical disability”
  - What, if any, further reasonable adjustments are required for this topic?

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*https://www.gov.uk/definition-of-disability-under-equality-act-2010

# Appeal point upheld - Equalities (2)

- Consideration must be given to *all* reasonable adjustments; i.e.:
  - Considering afamelanotide for EPP specifically
    - *E.g.: is there a characteristic of the disability in EPP that means people are disadvantaged by the HST methods?*
    - *E.g.: have people with EPP been given as much opportunity as people with a different disease to have a treatment for their disease ?*
    - *E,g.: Does EPP or the patient group have a unique feature compared to other patient groups or conditions ?*
  - What, if any, further reasonable adjustments – beyond those in HST methods – should be made
    - *E.g.: adjusting how different types of evidence contribute to the decision, or the weight put on particular evidence?*
  - Appeal panel concluded: "The appeal panel considers that this is likely to include express consideration of whether the methodology used in the evaluation discriminates against patients with EPP and if so what reasonable adjustments should be made"

- The committee is therefore asked to:
  - Give due regard to EPP as a disability within the Equality Act in considering the evidence
  - Acknowledge the reasonable adjustments made by the HST programme
  - Consider what (if any) further reasonable adjustments should be made



*https://www.gov.uk/definition-of-disability-under-equality-act-2010

# Appeal point upheld - Equalities (3)

## *Stakeholder comments*

**IPPN:**

- EPP is an inborn error of metabolism (not just dermatological) – severity and pain underestimated by committee and not fully taken into account :
  - Therefore EPP severity & pain underestimated by committee
  - UN Convention on disability rights states people with disability must have access to physical environment, and reasonable adjustments to prevent isolation and segregation
- "To meet these legal duties, our view is that NICE cannot do other than permit access to afamelanotide"
  - Drug enables normality, access to physical environment & less isolation

– EPP associated with behavioural adaptations – avoidance of outdoor activities, thick clothing, etc – and stigmatisation, bullying and social withdrawal

– Behavioural adaptations led to issues measuring treatment benefit in clinical trials

# Appeal point upheld - Equalities (4)

## *Stakeholder comments*

**BAD:**

- ICER has been used alone in a situation where the ICER was clearly inadequate
- Methods guide specifies that the qualitative evidence should be properly considered – should be formally analysed and incorporated into decision

**Clinuvel** (during appeal)

- ICERs are derived from quality of life measures, and there is no suitable measure to capture quality of life in EPP
- Therefore use of ICERs (based on such measures) to determine decision discriminated against all patients with EPP
  - Substantial disadvantage compared with others who do not have EPP
- Reasonable adjustment would have been to recommend afamelanotide subject to MAA; even if not, should have changed the methodology adopted

# Post-appeal considerations: Evidence

- Stakeholders invited to submit additional evidence following appeal:
  - Additional evidence not previously submitted, particularly regarding long-term effectiveness
  - Evidence that addresses concerns raised by committee and/or appeal panel
  - Benefits of afamelanotide not captured in modelling or committee deliberations

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

- Company also invited to consider:
  - New evidence that creates a more defined value proposition and/or revised model
  - Further evidence, for example:
    - Expert elicitation to extract treatment benefits or utilities
    - Post-authorisation data

- Committee will see a recap of previous evidence and additional evidence submitted in the following themes:

Nature of the condition | Benefits of treatment | Economic evaluation

# Nature of condition

## *Recap*

- Erythropoietic protoporphyria (EPP) is a genetic disorder of ferrochelatase enzyme deficiency, results in accumulation of protoporphyrin IX (PPIX) in skin and liver
- PPIX reacts to visible light (sunlight and some artificial light) cause 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

# Nature of condition

## *Patient impact – post-appeal submissions (1)*

- 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

## *Patient impact – post-appeal submissions (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

## *Patient impact – challenges of measurements*

- Lack of adequate scientific tools
  - Quality of life tools and other scientific instruments are not applicable and appropriate to assess clinical or economic benefit
  - DLQI neither adequately reflects EPP characteristics nor captures treatment effects
- Effect of conditioned behaviour on measurement of treatment effects:
  - Benefits of treatment in permitting greater light exposure are not properly captured in trial measurements
  - Patients learned to cope/ manage/ accept EPP since birth and are conditioned to avoid light
  - Experience of prodromal phase (= seconds/minutes of insulting emitted light cause afferent nerve stimulation), which compels patients to withdraw from light and avoid further exposure

# Benefits of treatment

## *Description - Afamelanotide (Scenesse, Clinuvel)*

| | |
|---|---|
| **Marketing authorisation** | Granted by EMA in 2014 under 'exceptional circumstances' for 'the prevention of phototoxicity in adult patients with EPP'<br>• inability to provide comprehensive data on efficacy and safety under normal conditions of use |
| **Administration & dose** | Controlled release injectable implant, subcutaneous injection<br>• 1 implant every 2 months before expected and during increased sunlight exposure e.g. spring to early autumn<br>• Recommended 3 implants per year<br>• Up to 4 implants per year (life-long treatment)<br>• Average dose [redacted] 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 do not give discounts on this technology) |

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EMA: European Medicines Agency; PAS: patient access scheme

# Benefits of treatment

## *Recap – Trial evidence summary*

- 4 randomised placebo controlled trials
  - CUV017: N=100; 12 month duration (unpublished)
  - 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 (N=[redacted])
  - CUV010: single arm phase 2 study (N=5)

# 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 equivalent to minutes per day***

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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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→ ***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 DLQI used in some clinical trials
  - SF-36: No data reported
  - DLQI: dermatology questionnaire, validated for various dermatological conditions but not for EPP; modest 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 was 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 (1)

- Sources of evidence pre-appeal:
  - Patient submission from British Porphyria Association, International Porphyria Patient Network
  - Consultation comments from Company (Clinuvel), British Association of Dermatologists and Royal College of Pathologists
  - Web comments from 35 patients/ families

- Submissions described substantial and life-changing benefits

- **Trial vs. Qualitative evidence**: 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

# Recap qualitative evidence: patient perspectives (2)

- 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
- BPA considered that quantifying patient and clinical experts testimonies would have resulted in acceptable ICERs; should take the testimonies into account perhaps using a managed access agreement

# Benefits of treatment

## *FED consideration and appeal outcome*

| Issue | Committee's conclusion |
|---|---|
| Clinical effectiveness | • Even numerically small clinical benefits are important to patients<br>• Patient/clinical expert testimony vs. trial<br>  • Trial shown relatively small benefits, may have been influenced by conditioned light avoidance<br>  • Patient/clinical experts believe effects would be greater than those seen in trial |
| Quality of life | • Likely to be improved but true size of any improvement is uncertain<br>• Substantial uncertainty on EPP-QoL; DLQI may not be fully applicable, but could capture some key aspects of EPP<br>• EPP-QoL and DLQI both taken into account into decision-making |

**Appeal outcome:**

- The appeal panel concluded it was unreasonable for committee to state that the trial results show small benefits with afamelanotide. This is because
  - Size of change in light exposure can only be interpreted in the context of the normal range
  - Benefits reported in FED would not necessarily seem small to a reader – lack face validity

# Appeal point upheld – Benefits shown in trial

## *Stakeholder comments*

- Additional light exposure time brings people into range for health indoor workers
  - Trial results: afamelanotide 25 min/day, placebo 15 min/day
  - Healthy indoor worker on weekdays: 22 min/day
- Extra 10 mins/day 'can be life changing'
  - Change can be made because of diminution of phototoxic reaction and associated extreme pain → lengthy, painful consequences of light exposure are so reduced that exposure can be tolerated
  - Permits more 'normal' behaviour
- Trial issues
  - 10 min/day gain is the average – some people gain more
  - Weather, seasonal variation and occupations – longer exposure may have been possible but limited by daily activities, rainy weather, etc
  - Conditioned light avoidance behaviour

# Benefits of treatment

## *Post-appeal submissions (1)*

- Some treatment benefits would take long period to arise
  - Although Biolcati et al. showed QoL improvement in first 6 months then nothing substantial thereafter, conditioned light avoidance may take even longer to overcome
  - Light exposure determined by life style – e.g. chosen job, leisure activities
  - Patients report that even after years of treatment, psychological barriers remain
  - Requires years until patients to move to higher light exposure work-places
- Treatment benefits not captured:
  - Fatigue not fully reflected in QoL measures
  - Impact on patients' life (education, finances, etc.) & family
  - NICE Social Value Judgments is aware that
    - stigma may affect people's behaviour in a way that changes effectiveness of an intervention
    - relief of stigma may not always be captured by routine quality of life assessments
- Emphasised key uncertainty in rigorously establishing the magnitude of clinical effectiveness – patient and expert testimony suggest trial result have under-estimated overall impact and benefit of the treatment

# Benefits of treatment

## *Post-appeal submissions (2)*

- High level of adherence and continuation supports effectiveness
  - New evidence from Post Authorisation Safety Study (PASS): >98% long-term compliance; only a few patients reported lack of effectiveness
  - Continuation rate: 2018 – 98.5%; [redacted]
  - *NB: FED stated "committee appreciated the compliance rate was high but noted that it was not a quantifiable marker of effectiveness"*
- Treatment with afamelanotide
  - Slow release implant formulation which provides almost complete protection against phototoxic reactions for about 8 weeks; applied with thick needle to fat tissue just above hip
  - Disadvantages include fixed dose and few mild side effects which are outweighed by considerable benefits (slight nausea after injection, 1-2 days of little bit fatigue)
  - With afamelanotide "life changed": less pain, hours of direct sun without pain for the first time in life; don't worry about the few mins needed outside for commuting; full member of society now
  - Patient expert reports 5 patients in Switzerland, German, Austria who did not experience sufficient treatment effect and stopped (reasons unclear) – significantly outnumbered by the ~180 people they are in contact with who experience a massive benefit
  - "Treatment would be life changing...giving us as a family simple day to day choices that are currently non-existent with EPP"

# Benefits of treatment

## *Post-appeal submissions (3)*

- Importance of qualitative evidence
  - Qualitative evidence not fully utilised
  - Considered by EMA – should be accepted by NICE and accounted for in a structured and measurable way
    - Precedent for impact of patient testimony, e.g. in appraisals of insulin-glargine, elosulfase alfa for MPS IVa, eculizumab for atypical haemolytic uraemic syndrome
    - Should consider recognised formal methodology, e.g. framework analysis
    - Expert testimony should be outcome measure; they illustrate “what level of improvement is clinically meaningful”
  - International patient testimonies should be considered – British patients lack drug experience
  - Patient/physician testimony showed “striking and dramatically effective therapeutic effect”, >35 expert testimonies describing treatment effects “truly life changing”

# 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

- *No new economic evaluation was submitted post-appeal*

# Economic evaluation

## *Recap: Modelling approach (2)*

**Company**

[redacted]

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

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

Disability weight

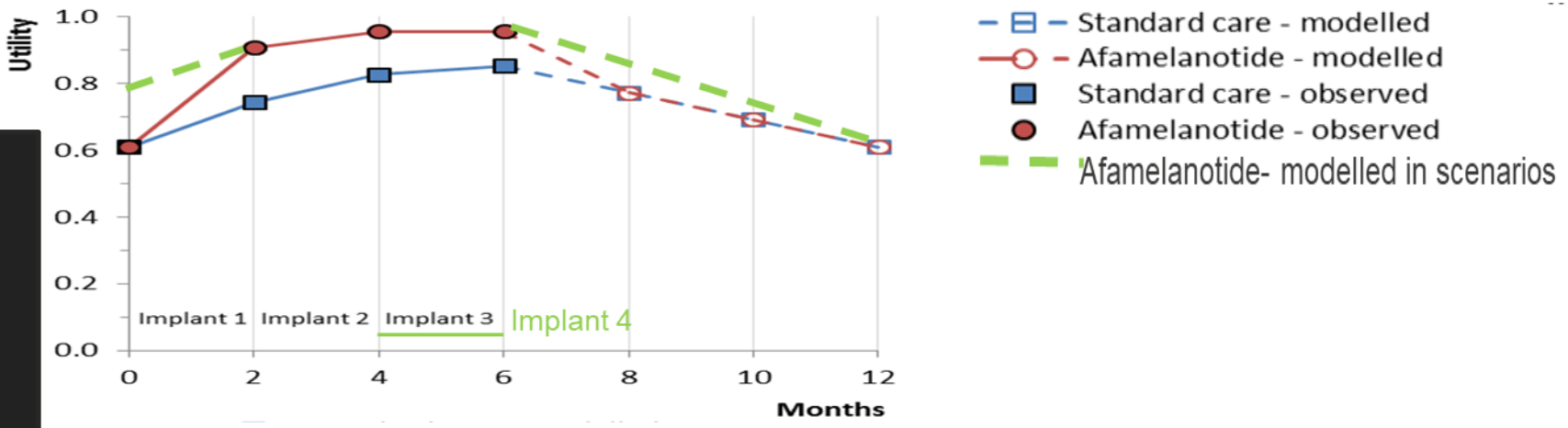
[redacted]

***Impact on QoL***
*Based on proxy*

[redacted]

**ERG exploratory**

[redacted]




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

***Impact on QoL***
*Mapped from DLQI to EQ-5D*

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# Economic evaluation

## *Recap: ERG comments and exploratory analyses*

Comments on company base case

- EPP-QoL might not be appropriate to define level of severity
- Duration of 120 days may not be representative of quality of life over the whole year; 180 days would have been better
- Unclear if proxy condition ([redacted]) is appropriate for EPP
- Assumes benefits immediate and constant for whole year, including after last implant

Exploratory analyses: direct conversion to QALYs

- Simplest conversion: utilities based on 1 – disability weight
- Alternative: utilities for proxy condition taken from published source
- ERG: not plausible because same limitations as the company's base case apply

Exploratory analyses: alternative modelling approach

- Assumed max 3 implants per year, gradual onset of effect, slow attenuation effect over 2 months
- Explored scenarios around onset and attenuation of treatment effect and number of implants

# Economic evaluation

## *Recap: Results*

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

- 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])

| Scenario | Incr costs (£) | Incr QALYs (discounted) | Incr QALYs (undiscounted) | ICER (£/QALY) |
|---|---|---|---|---|
| **1.0: company base case** | [redacted] | [redacted] | [redacted] | £278,386 |
| **1.3: utilities for proxy condition from literature** | [redacted] | [redacted] | [redacted] | £1,726,802 |

| Scenario | Incr costs (£) | Incr QALYs (discounted) | Incr QALYs (undiscounted) | ICER (£/QALY) |
|---|---|---|---|---|
| **2.0 ERG exploratory base case** | [redacted] | [redacted] | [redacted] | £1,605,478 |

- ERG explored several other scenarios, with different combinations of implants per year, onset of effect, and attenuation
  - All >£1 million per QALY gained

# Economic evaluation

## *FED consideration*

| Issue | Committee's conclusion |
|---|---|
| DALY averted vs QALY gained model | Committee's preferred approach aligned with NICE reference case although would take DALY-based model into account in decision-making |
| Modelling approach | Uncertainties on disease severity stratification using EPP-QoL<br>Proxy condition may not fully capture the experience of people with EPP<br>Committee preferred ERG's exploratory modelling although may have underestimated real-life benefits of afamelanotide |
| Treatment effect | Effect likely to build up over first 2 months and slowly decrease over 6 months after last implant |
| Dosage | People may have up to 4 implants |
| Committee's most plausible ICERs | Between £1,343,359 and £1,785,957 per QALY gained<br>All results highly uncertain, although may have underestimated real-life benefits of afamelanotide<br>In all plausible scenarios, ICERs were >100,000 £/QALY and afamelanotide did not meet criteria for QALY weighting to be applied |
| Impact of the technology beyond direct health benefits | Afamelanotide would have an impact beyond direct health benefits (i.e., financial implication of career choices, impact of phototoxicity reduction on people's ability to work or study) but extent of impact is unclear<br>Even taking such factors into account, unlikely that afamelanotide would be considered a cost-effective use of NHS resources |

# Economic evaluation – stakeholder comments

## *Post-appeal submissions*

- Suitability of model for decision-making:
  - Economic decision made using a flawed model is unreasonable
  - ICERs derived from QoL measures, but no suitable measure to capture QoL in EPP – puts patients at substantial disadvantage vs other conditions
    - Requires reasonable adjustment

- IPPN – EPP-QOL vs DLQI:
  - EPP-QoL: disease specific tool, rated by Swiss patients as mainly “appropriate” or “very appropriate”
  - DLQI neither adequately reflects EPP nor captures treatment benefit – not accepted by patients and not validated for EPP
  - Committee concerned about placebo increase in EPP-QoL – but same issue with DLQI
  - Model should not use tool which underestimates benefit: DLQI is inappropriate, not interchangeable with EPP-QoL, so should not be used for model

# Impact beyond direct health benefits - stakeholder comments

## *Post-appeal submissions*

- Impact on patients' wider life and families remain largely unconsidered
  - "Treatment with afamelanotide gives highly beneficial impacts on a family household, not only socially, but educationally, financially and psychologically too, thus increasing their quality of life"
- The "direct social environment" (parents, partners, children and friends) are affected by EPP

# Company budget impact

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]

| Annual budget impact | Year 1 to 5 |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

# Economic evaluation

## *Post-appeal company Managed Access Agreement – final proposal*

Committee previously considered possibility of a managed access agreement to address uncertainties; FED states:

- Data collection in an MAA unlikely to resolve uncertainties – similar challenges to those in trials
- Unlikely that afamelanotide had a plausible potential to be cost effective

Appeal panel dismissed appeals relating to consideration of an MAA: process was fair (Clinuvel 1a.1) and reasoning for not recommending MAA was clear (IPPN 2.5)

Company reiterated it would be willing to consider MAA :

- [redacted]
  - [redacted]
- [redacted]
  - [redacted] eligible EPP patients – [redacted]
  - [redacted]
    - [redacted]



Commercial proposals have not yet been considered by NHSE
Text in *italic* is new (post-appeal)

# Economic evaluation

## *Post-appeal company MAA – final proposal*

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

- *Monitor usage with European EPP Disease Registry*
- Agree start/stop criteria
- [redacted]
- [redacted]
  - [redacted]



Commercial proposals have not yet been considered by NHSE
Text in *italic* is new (post-appeal)

# Economic evaluation

## *Post-appeal company MAA – final proposal*

- Company:
  - Based on the above, financial risk with MAA is “zero”
  - Technology is “an exception to other therapies and is therefore a unique case in its health economic assessment”
  - Company noted it does not engage in marketing and is proactive in stopping off-label use
    - Ensures clinical need for EPP indication drives prescribing
    - Continuation rate accurately indicates effectiveness
  - Guaranteed limited prescription and distribution
- Stakeholder submissions:
  - Stakeholders generally supportive of an MAA
  - Given that key uncertainty is magnitude of clinical uncertainty, MAA seems appropriate – specifically intended for this type of situation
  - Would be irrational to deny access only because quantification of benefit is coupled with uncertainties caused by necessary behavioural adaptations
  - EMA collects efficacy data
  - NICE Social Value Judgments is aware that
    - stigma may affect people’s behaviour in a way that changes effectiveness of an intervention
    - relief of stigma may not always be captured by routine quality of life assessments

# 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 carers' 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

***Taking into account EPP as a disability and committee's duties under the Equality Act:***

- What, if any, further adjustments should be made to the processes, methods and committee's considerations?

- What is the committee's view of:
  - The evidence provided, including IPPN's
  - The nature of the condition
  - The health benefits provided by afamelanotide
    - Clinical trial data?
    - Qualitative evidence?
  - The economic evaluation
    - Effects of condition and treatment on QoL captured?
    - Suitability for decision-making?
  - The proposal for a Managed Access Arrangement

→ *Have the benefits of afamelanotide been captured?*

→ *Have the benefits of afamelanotide been captured?*