Chair's presentation
Afamelanotide for treating erythropoietic protoporphyria

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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 cause anaphylactoid and phototoxic reactions in people with EPP
  - Often rapid, unbearable pain within less than 5 minutes in light
  - All encompassing tiredness as the body heals from the reaction which can take up to weeks
  - Anxiety and social isolation; study opportunities, job security and career development negatively affected by days lost to EPP symptoms, with subsequent impact on earnings potential
- Daily life primarily driven by the need to avoid light that triggers phototoxic reactions
  - Impacts measurement of clinical effectiveness of afamelanotide in clinical trials
- EPP is not associated with a shorter life expectancy for the majority of people who do not have liver complications

Afamelanotide (Scenesse, Clinuvel)

Marketing authorisation	Granted by EMA in 2014 under 'exceptional circumstances' for 'the prevention of phototoxicity in adult patients with EPP'
Administration & dose	Controlled release injectable implant administered as a subcutaneous injection. • 1 implant administered every 2 months before expected and during increased sunlight exposure, for example, from spring to early autumn. • Recommended 3 implants per year • Up to 4 implants per year (life-long treatment) • Average dose of [redacted] implants per year seen in treatment to date.
Mechanism of action	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.
Price	£12,020 per injectable implants; no PAS discount submitted

EMA: European Medicines Agency; PAS: patient access scheme

ECD clinical 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	

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)

ECD clinical 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	

ECD clinical evidence: trial data vs real-life observations

- **Trial data** showed relatively small but statistically significant increase with afamelanotide in the amount of time a person could spend in daylight without pain, and a decrease in the number and severity of phototoxic reactions.
- **Clinical and patient experts testimony** reported better outcomes than in trial e.g. afamelanotide allowed a patient to increase time spent in light by hours rather than by minutes; life changing.
  - Experts explained that even small benefits such as being able to spend an extra few minutes in daylight or having fewer phototoxic reactions could have a large impact on people's lives.
  - A few minutes in full daylight would typically equate to many more minutes, and even hours, in dappled light. This would mean people with EPP would be in a much stronger position to manage their lives without being debilitated by the disease.
  - Additionally, clinical and patient experts believed the effects would be greater than that seen in the trials because of conditioned light avoidance behaviour

ECD: quality of life

- SF-36 and DLQI used in some of the clinical trials
  - No data reported with SF-36; DLQI showed a modest improvement in quality of life with afamelanotide
  - Company did not consider SF-36 and DLQI suitable to quantify the humanistic burden of EPP
- Company developed a condition-specific questionnaire EPP-QOL specifically to measure the impact on EPP.

- <u>ERG:</u>
  - EPP-QoL does not include questions on pain (one of the most debilitating aspects of the condition)
  - EPP-QOL has not been fully validated
  - EPP-QoL has been modified while the trials were ongoing

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

ECD clinical evidence: 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)

- The DLQI scoring range is 0-30 (0 no effect on QoL, >20 = extremely large effect on QoL)
- The EPP-QoL score 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)

[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.

ECD modelling approach

- The company did not present a cost-effectiveness model using QALYs because it did not consider the QALY framework to be appropriate, instead measuring treatment benefit in DALYs 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 maintained that this approach would not be suited to this condition.

- Because of absence of disability weights specific to EPP, the company used disability weights for a proxy condition it considered similar to EPP ([redacted] in base case)
  - EPP stratified by severity using EPP-QoL in 3 equal ranges (100 point scale: 'severe' 0 to 33.3; 'moderate' 33.4 to 66.6; 'mild' 66.7 to 100)
  - Pooled trial data on EPP-QoL collected at 4 months (120 days) and applied for the full year

DALYs: disability adjusted life years

Company's base case

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

ERG:

- 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 the proxy condition ([redacted]) is appropriate for EPP

DALYs: disability adjusted life years

Company's scenario analyses
inclusion of societal costs

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

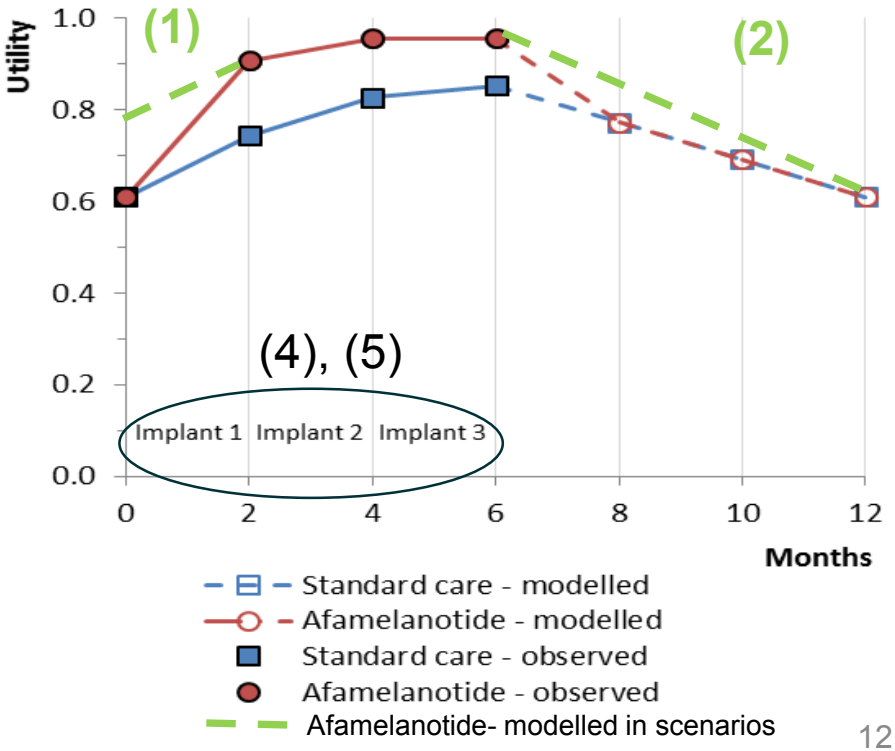
Scenario	Analysis	Incremental costs	Incremental DALYs	ICER
Inclusion of societal impact	AFA: increase from 50% to 100% of mean wage over 3 years	[redacted]	[redacted]	£172,302
	AFA: 50%, SoC: 0%	[redacted]	[redacted]	£165,442
	AFA: 50%, SoC: 20%	[redacted]	[redacted]	£210,654
	AFA: 50%, SoC: 10%	[redacted]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

AFA: afamelanotide; SoC: standard of care

ERG's exploratory analyses (1)

- **ERG simple QALY adaptation** of the company's base case model produced similar results as the company DALY model (ICER=278,386 £/QALY)
  - ERG: not plausible because
    - same limitations as the company's base case apply
    - company assumed benefits would be immediate and would remain constant for the whole year, including after the last implant therefore the ERG developed an alternative base case

- **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
  - Several scenarios: (1) fast onset of treatment effect, (2) slow attenuation of treatment effect, (3) fast onset and slow attenuation of effect, (4) max of 2 implants per year and (5) max of 4 implants



DALYs: disability adjusted life years

ERG's exploratory analyses (2)

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

AFA: afamelanotide; SoC: standard of care

ERG's exploratory analyses (3)

ERG base case

Treatment	Incr. costs (£)	Incr. QALYs (discounted	Incr. QALYs (undiscounted)	ICER (£/QALY)
scenario 2.0: ERG exploratory base case*				
SoC	-	-		-
AFA	[redacted]	[redacted]	[redacted]	£1,605,478
scenario 2.1: fast onset of effect, attenuation effect 2 months				
SoC	-	-		-
AFA	[redacted]	[redacted]	[redacted]	£1,290,678
scenario 2.2: gradual onset, slow attenuation of effect over 6 months				
SoC	-	-		-
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	-	-		-
AFA	[redacted]	[redacted]	[redacted]	£1,785,957

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

ECD: committee's considerations

Issue	Committee's conclusion
Nature of the condition	Phototoxic reactions are associated with intense pain and extreme tiredness that lasts for days. Very debilitating with far reaching consequences on living a normal life.
Unmet need	No current effective treatment for preventing phototoxicity
Symptoms severity	Some variation in how long people can be exposed to sunlight without a reaction but it is unclear because of lack of data
Clinical effectiveness	• Even small clinical benefits are important to patients • Trial results may have been influenced by ingrained light avoidance • Dichotomy between patient and clinical expert testimony and trial outcomes • True extent of benefit unclear
Quality of life	• Substantial uncertainty about EPP-QoL • DLQI may not be fully applicable, but could capture some of the key aspects of EPP
Company's model	Uncertainties around disease severity stratification using the EPP-QoL
Proxy condition	May not fully capture the experience of people with EPP

ECD: committee's considerations

Issue	Committee's conclusion
DALY averted vs QALY gained model	Committee's preferred approach is aligned with NICE reference case although it would take a DALY-based model into account in its decision-making
Modelling approach	Committee preferred ERG's exploratory modelling although may have underestimated real-life benefits of afamelanotide
Treatment duration	Effect likely to build up over the first 2 months and slowly decrease over 6 months after the 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. All results highly uncertain but in both the company's base case and the ERG's exploratory analyses, the ICERs were >100,000£/QALY and afamelanotide did not meet the criteria for QALY weighting to be applied.
Impact of the technology beyond direct health benefits	Afamelanotide would have an impact beyond direct health benefits but extent of this impact is unclear (i.e., financial implication of career choices, impact of phototoxicity reduction on people's ability to work or study). Even taking such factors into account, it was unlikely that afamelanotide would be considered a cost-effective use of NHS resources.

ECD preliminary recommendation

Afamelanotide **is not recommended**, within its marketing authorisation, for preventing phototoxicity in adults with erythropoietic protoporphyria.

ECD consultation responses

Consultee comments from:

- Company (Clinuvel)
- British Porphyria Association
- International Porphyria Patient Network
- British Association of Dermatologists (endorsed by Royal College of Pathologists)
- Royal College of Pathologists

Other comment from:

- Department of Health ‘no comments’.

Web comments

- 35 statements received
  - Including comments from the German EPP Association

ECD consultation comments: Clinuvel (1)

- ECD states *'extent of the clinical effectiveness of afamelanotide is unclear'*
  - incomprehensible since clinical and patient evidence have shown the effectiveness of drug and impact on QoL; recognised in EPAR
- Failure to take into account relevant qualitative evidence on impact beyond direct health benefits
- NICE should not reopen the EMA's conclusion on (1) the clinical effectiveness and (2) Good Clinical Practice compliance in clinical trials
- There is a lack of scientific instruments and tools to measure the disease, rather than lack of data
  - Failure to account for the significance of the marketing authorisation having been granted 'under exceptional circumstances' and recognition for the company not to be able to provide data due to ethical and scientific limitations around the conduct of clinical studies
  - In order to assess the cost effectiveness of afamelanotide, NICE should rely on the real-life evidence provided by the patients and clinical experts regarding efficacy, as there is no other way to appropriately interpret the evidence
- Lack of guidance as to when non-reference models should be accepted resulting in non-transparent and arbitrary decisions

ECD consultation comments: Clinuvel (2)

- Maintain that the EPP-QoL is more suitable than DLQI:
  - partially validated tool developed with extensive expert advice
  - critiqued on grounds of not including ‘pain’ but relatively rare that adult patients will experience pain’ because of adapting their lives to avoid it. Measuring “pain” will yield no results of any significance.
  - anxiety included via question on “how often did you feel you were at risk of developing EPP symptoms?”
  - fatigue not included as tool developed before awareness of it symptom

- ECD suggests that DLQI ‘addresses some factors’ and’ could capture some of the key aspects of EPP’
  - far from a finding that DLQI can accurately capture impact of disease on patients
  - dismissing EPP-QoL for omitting two issues relevant to EPP (pain and work or study) but accepting DLQI despite its broad focus is contradictory

ECD consultation comments: Clinuvel (3)

- Misquotation of Biolcati study in the ECD on quality of life. ECD says “there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials”. The company stated that Biolcati paper reports that ‘*we therefore conclude that afamelanotide treatment strongly improved QoL in these patients, likely due to mitigated light intolerance’*

  n.b. Biolcati states ‘During the sunshine-rich and -intense summer season the QoL scores of treated patients only slightly decreased compared with winter time; thereby, the mean QoL scores were clearly higher in treated patients than in untreated ones. We therefore conclude that afamelanotide treatment strongly improved QoL in these patients, likely due to mitigated light intolerance.’

  n.b. Biolcati reports “The mean QoL remained stable at between 73% and 80% of a maximum with a slight increase in year 5”
  - *QoL scores increase from 30 to 75 with first dose and then little change over next 4 years*[1]
- Assumption of average [redacted] implants per patient per annum based on average seen in expanded access and commercial distribution of the drug to date
- Reasonable to keep the model confidential because it is part of Clinuvel’s intellectual property and does not impact the interpretation of the data

[1] As seen in figure 3 from Biolcati et al. 2015

ECD consultation comments: British Porphyria Association (1)

- Pleased that EPP recognised as a severe and little understood condition but extreme extent and burden of the impact has still to be fully comprehended
- Differences between trial results and efficacy observed in patient testimonies should not be underestimated simply because it does not fit the standard criteria on clinical effectiveness
  - patient reports backed up by significant differences observed in these patients by recognised clinical experts in EPP
  - qualitative evidence must be taken more seriously
- Cumulative/multiplier effect of the 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

ECD consultation comments: British Porphyria Association (2)

- Afamelanotide can considerably change the future prospect of patients and their families and without full and proper consideration of the contentious issues that remain, patients will continue to suffer from lack of economic opportunity and social isolation
- Costs associated with living with EPP are generally misunderstood; if these were taken into account, it would lower the ICER
- Trial outcomes fail to measure for some aspects of the disease e.g. light avoidance behaviour, seasonal impact
- ERG analysis is uncertain due to DLQI
- Patients still continue to take afamelanotide despite the significant travel cost to themselves; this explains the difference this treatment makes to their quality of life
- NICE should review the guidance sooner than in 3 years if significant evidence becomes available

ECD consultation comments: International Porphyria Patient Network (1)

- EPP is unique: absence of accessible and measurable biochemical or other clinical features to objectively assess magnitude and duration of phototoxic reactions, and consequently the lack of efficacy biomarkers Benefits of afamelanotide are life-altering and dramatic
- Collective evidence from Biolcati paper, co-author Prof Dr Elisabeth Minder and EPAR confirms afamelanotide is clearly and significantly effective
  - 97.4% patients reported benefit from afamelanotide; only effective therapy in 30 years
  - Experience in Switzerland - very few patients who did not benefit stopped treatment after first dose - no additional ineffective use of resources
- Contrary to the EMA, NICE did not take into account the uniqueness of EPP by
  - minimising and overriding patients and clinical experts testimonies
  - insisting on using generic assessment methods
- Holme paper reported time for onset of symptoms following exposure to sunlight (median=20 min) although ECD stated a lack of data
- Spontaneous sunlight exposure (measured by trials) vs. light tolerance (not diluted by days of no sun etc..)
- Improvement in QoL occurs 2-3 years before change in life style e.g. decrease in their fear of light (study led by Prof Dr Elisabeth Minder)

ECD consultation comments: International Porphyria Patient Network (2)

- Discrimination not to use a condition-specific tool to capture QoL:
  - EPP-QoL is adequate to capture symptoms of EPP; SF-36 and DLQI are not
  - EPP-QoL was developed in collaboration with experts; only questionnaire that patients ever considered adequate to capture the symptoms and limitations of their disease
  - removal of the questions from the first version of the EPP-QoL questionnaire did not affect the results
  - EMA notes: 'If quality of life is measured, it should always be assessed using scales validated for the particular indication being treated. It is recognised that sometimes there are too few patients for validation exercises as well as separate treatment evaluation.'
- Emphasis should also be given to the decrease of severity of phototoxic reactions and duration of recovery after a phototoxic reaction
- NICE's committee is discriminating against British patients compared to other patients in Europe suffering from EPP who have access to afamelanotide
- Contradiction between negative recommendation and stating that even small increases in time spent under light could significantly improve people's lives
- Quantitative assumptions leading to the recommendations inadequate since the methods applied are not appropriate in measuring treatment effects in EPP

ECD consultation comments: British Association of Dermatologists

- Quantification of patient and clinical experts testimonies would have resulted in acceptable ICERs; NICE should think of way in taking into account the testimonies perhaps using a managed access agreement[1]
- Seasonal variation in severity is likely to undermine the full assessment of efficacy
  - Holme paper missed reporting that DLQI was collected during spring and summer, which justifies the difference with DLQI results from EPP clinical trial (data collected patients developed seasonal worsening)
- EPP is a rare condition, so the total cost of treating all the EPP patients in the UK with afamelanotide would be relatively low

Royal College of Pathologists

- Recommendations appear to be sound and fair[2]

[1]Clinuvel did not propose a managed access agreement
[2]Although they have endorsed British Association of Dermatologists

ECD consultation comments: Web comments

- In trials, *"sun exposure times were limited not only by the onset of pain, but also because of working hours and other factors like rainy weather, during which trial participants were not exposed to sunlight"* therefore the mean daily values per patient which include rainy days "*cannot capture the full extent of the therapy's benefit"*
- *"Imagine burning yourself on the iron or pouring boiling water on your skin, now imagine that level of pain on every part of your body that is exposed to the sun."*
- *"If EPP stops me working then the cost will be far greater than the cost of drug."*
- *"My thoughts at that time were if I cut my hand off, will the pain stop?" "considered suicide"*
- *"All my life I have been bullied, isolated, misunderstood, shunned, picked on, alone, laughed at, alienated, mistreated and in constant unbearable pain."*
- EPP has *'has destroyed my childhood'* '*As I type this with one extended finger I am thinking about the pain of the light from my tablet screen and how my finger will burn later'*
- After afamelanotide *'I am able to go outside for hours - into the direct light without covering up and without being in pain. Sometimes I still experience pain after being outside. But those times are very rare and the most important thing is that the pain is not nearly as intense and not as long as before. It is just like a normal mild sunburn.'*

Key issues for consideration (1)

- Has the committee's conclusion changed regarding:
  - The clinical effectiveness of afamelanotide?
    - Including apparent discrepancy between clinical trial results and expert testimony
  - Preference for an approach based on QALY weighting?
    - Has the committee been persuaded of the merits of a DALY based approach and if so could they consider a simple DALY adaptation?
  - Preference for an approach based on clinical trial QoL measures?
    - Including preference of DLQI above EPP-QOL
  - The most plausible ICERs?

- Has the impact beyond direct health benefits been appropriately captured/ incorporated? (e.g. education, employment)

Key issues for consideration (2)

- Some stakeholders call for an MAA. If there is agreement from other stakeholders to explore this possibility what are the committee's views on:
  - Measures to share financial risk?
  - The need for specific starting and/or stopping rules?
  - Information to be collected to assist review of decision beyond the MAA?