NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY EVALUATION

APPEAL HEARING

Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927]

Decision of the panel

Introduction

1. An appeal panel was convened on 30 July 2018 to consider an appeal against NICE's final evaluation determination, to the NHS, on afamelanotide for treating erythropoietic protoporphyria (EPP) [ID927].

2. The appeal panel consisted of:

• Prof Jonathan Cohen	Chair
• Mr Tom Wright	Non-executive director
• Dr Biba Stanton	NHS representative
• Mr Uday Bose	Industry representative
• Mr Colin Standfield	Lay representative

3. None of the members of the appeal panel had any competing interests to declare.

4. The panel considered appeals submitted by the British Association of Dermatologists, the International Porphyria Patient Network, the British Porphyria Association and CLINUVEL (UK) Ltd.

5. The British Association of Dermatologists (BAD) was represented by:

• Dr Robert Sarkany	Consultant Dermatologist
• Prof Lesley E Rhodes	Professor of Experimental Dermatology, Honorary Consultant Dermatologist, Director of the Photobiology Unit

6. The International Porphyria Patient Network (IPPN) was represented by:

• James Rawnsley	EPP patient representative
• Emily MacKenzie	Brick Court Chambers
• Dr Jasmin Barman-Aksözen	Co-founder and Vice-Chair of the International Porphyria Patient Network

7. The British Porphyria Association (BPA) was represented by:

• John Chamberlayne	BPA Chair
• Dr Geoff Sloan	EPP patient representative

8. CLINUVEL (UK) Ltd was represented by:

• Lachlan Hay	General Manager, CLINUVEL (UK) Ltd
• Marie Manley	Sidley Austin LLP
• Sarah Love	Brick Court Chambers

9. In addition, the following individuals involved in the evaluation were present and available to answer questions from the appeal panel:

• Dr Peter Jackson	Highly Specialised Technologies (HST) Evaluation Committee Chair
• Mrs Sheela Upadhyaya	Associate Director – HST, NICE
• Mr Meindert Boysen	Centre for Health Technology Evaluation Director, NICE
• Miss Aminata Thiam	Technical Lead, NICE
• Mr Francis Pang	HST Evaluation Committee Member
• Mr Jeremy Manuel	HST Evaluation Committee Member

10. The appeal panel's legal adviser Alistair Robertson was also present.

11. Two members of the NICE appeals panel (Mr Christopher Rao and Prof Ruairidh Milne) were present as observers but did not participate in any of the discussions of the appeal panel, or in the decision-making.

12. Under NICE's appeal procedures, members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

13. There are two grounds under which an appeal can be lodged:

1) **<u>Ground One</u>: In making the assessment that preceded the recommendation, NICE has:**
   (a) Failed to act fairly; and/or
   (b) Exceeded its powers.

2) **<u>Ground Two</u>: The recommendation is unreasonable in light of the evidence submitted to NICE.**

14. The Vice Chair of NICE (Dr Rosie Benneyworth) in preliminary correspondence had confirmed that:

- The British Association of Dermatologists (BAD) had potentially valid grounds of appeal as follows: Ground 2.

- The International Porphyria Patient Network (IPPN) had potentially valid grounds of appeal as follows: Grounds 1(a), 1(b) and 2.

- The British Porphyria Association had potentially valid grounds of appeal as follows: Ground 2.

- CLINUVEL (UK) Ltd had potentially valid grounds of appeal as follows: Grounds 1(a) and 1(b).

15. The evaluation that is the subject of the current appeal provided advice to the NHS on the use of afamelanotide for the treatment of EPP.

16. EPP is a genetic disorder. It is caused by impaired activity of the enzyme, ferrochelatase. The condition results in excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma and red blood cells. EPP is a cutaneous porphyria, and the major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and some types of artificial light. The skin may become painful, swollen, itchy and red, and skin erosions can also occur. A phototoxic reaction typically lasts between 2 days and 3 days. However, it can last 10 or more days, with severe pain and loss of sleep. These symptoms, along with anxiety and social isolation because of sunlight avoidance, can have a profound impact on quality of life.

17. During the appeal hearing, Dr Sloan, Dr Barman-Aksözen and Mr Rawnsley gave personal testimony about their experience of EPP as patients. They emphasised the profound suffering caused by EPP and the pervasive impact of the disease on their lives. They also discussed their own experiences of treatment with afamelanotide. The panel found their testimony powerful and moving, and would like to thank them all for their particular efforts to attend the hearing. The panel also wishes to acknowledge the arrangements made by NICE to ensure that patients were not exposed to direct sunlight during the hearing.

18. Before the appeal panel inquired into the detailed complaints, the following preliminary statements were made: Emily MacKenzie on behalf of the International Porphyria Patient Network (IPPN), John Chamberlayne on behalf of the British Porphyria Association (BPA), Dr Robert Sarkany on behalf of the British Association of Dermatologists (BAD), Sarah Love on behalf of CLINUVEL (UK) Ltd and Dr Peter Jackson on behalf of the evaluation committee.

Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

Appeal by International Porphyria Patient Network (IPPN)

Appeal Ground 1a.1: The committee failed to act fairly by demonstrating consistent discrimination against IPPN as a stakeholder group
(This appeal point was named IPPN 1a6 in initial correspondence and during the hearing).

19. Dr Barman-Aksözen, for IPPN, stated that the specific circumstances of this evaluation made the involvement of her organisation as a consultee vital. Specifically, it was important for the committee to hear evidence on the long term experience of treatment with afamelanotide in a real world setting, and this is available only from international patients.

20. Ms MacKenzie, for IPPN, explained that the IPPN had participated as a stakeholder at the scoping stage but had then been told by NICE that they could not be a consultee for the remainder of the process. It was only after protracted correspondence that they were once again recognised as a consultee. Despite this, they did not have the opportunity to participate in the second meeting of the committee held on 20 February 2018.

21. Mrs Upadhyaya, for NICE, agreed that the IPPN had been consulted during scoping before being excluded and later readmitted as consultees. She explained that the rationale for this initial exclusion had been that they might not have access to UK patients. In response to questions from the panel, she agreed that the process guide does not specifically exclude international organisations as consultees but said that patients with experience of the UK system are generally preferred as patient representatives.

22. It was pointed out during the hearing that the IPPN was represented by patients from the UK at the scoping meeting.

23. Dr Jackson, for NICE, said that the Chair of the evaluation committee is responsible for selecting which of the patient and clinical experts nominated by consultees should attend the second committee meeting. Given that the size of meetings is limited, he would usually prefer patients from England as they know the English health service well and, of particular importance for this appeal, experience the weather in this country. He said that IPPN had been able to comment at all stages of the process and that their input had been very helpful.

24. In response to a question from the panel, Dr Barman-Aksözen, for IPPN, said she hoped the final decision of the committee would have been different if an IPPN patient representative had been able to participate in the second committee meeting because they would have highlighted additional information about patients' experience from long term treatment. She also confirmed that the BPA and IPPN are the only patient groups for EPP that she is aware of.

25. The appeal panel concluded that the IPPN had an important role to play in this evaluation. Whilst recognising that UK patient representatives are often the most appropriate to include, in this particular case, the panel judged that the lack of UK patients with experience of long term treatment with afamelanotide made it important to include international patients. In addition, for this rare disease where there are only two patient groups who represent UK patients with EPP (BPA and IPPN), it would seem logical to include both of these patient groups as consultees throughout the process. The panel did not accept that the IPPN suffered discrimination, and noted that the IPPN did have opportunities to contribute to the evaluation process. However, the appeal panel judged that excluding the IPPN from the second committee meeting was an unfair approach, as they had an important contribution to make.

26. The appeal panel therefore upheld the appeal on this point.

Appeal by CLINUVEL (UK) Ltd

Appeal Ground 1a.1: NICE acted unfairly by failing to give the Company an opportunity to discuss and negotiate its proposed MAA to NHS England before presenting it

(This appeal point was named CLINUVEL 4 in initial correspondence and during the hearing).

This part of the appeal was held in private at the request of the appellant.

27. Sarah Love, for CLINUVEL, stated that the use of Managed Access Agreements (MAAs) as part of the highly specialised technology (HST) evaluation process is relatively new and pointed out the HST process guide does not set out in detail the procedural details regarding MAAs. She argued that the company was therefore reliant on advice given by NICE about the procedure to follow. She went on to say that because an MAA is a multi-party agreement, it seems unlikely that a company could arrive at an acceptable MAA alone, in the absence of an iterative process. Ms Love stated that the process that occurred did not allow CLINUVEL a fair opportunity to propose an acceptable MAA. In particular, she stated that NICE told the appellant that they would facilitate a meeting with NHS England and then did not follow through on that assurance.

28. Sarah Love, for CLINUVEL, went on to state that in CLINUVEL's opinion, the MAA the company submitted did address both of the concerns expressed by the committee in paragraph 4.22 of the FED concerning data collection and the sharing of financial risk.

29. Ms Love went on to state that NICE invited CLINUVEL to submit an MAA on 13 April 2018. She argued that if the high Incremental Cost-effectiveness Ratios (ICERs) in the FED were an insurmountable barrier to an acceptable MAA, this invitation should not have been made so that CLINUVEL did not waste time and resources pursuing it.

30. Lachlan Hay, for CLINUVEL, provided a detailed timeline of the interactions between NICE and CLINUVEL regarding an MAA, as set out in an appendix to their original appeal letter. He stated that the company was keen to engage with the process of negotiating an MAA and emphasised that the company were expecting NICE to facilitate a discussion with NHS England before submission of the proposed MAA and the publication of the FED.

31. Maria Manley, for CLINUVEL, said that the only meeting between NICE, NHS England and CLINUVEL took place on 30 May 2018 (after publication of the FED). She stated that this meeting consisted of feedback on a decision that had already been made by NICE and NHS England rather than an opportunity for CLINUVEL to engage with a collaborative process.

32. Meindert Boysen, for NICE, stated that NICE is aware that NHS England will not consider an MAA unless there is plausible potential for that MAA to resolve uncertainty in a way that leads to NICE being able to make a decision to recommend a technology as cost-effective. He said that the committee were

aware of the company's policy of only offering a single price for their product and that they do not offer discounts. In this case, NICE had to consider how far away the key ICERs in the FED were from the usual threshold for cost-effectiveness in the HST process. He said that the committee concluded that this distance was so great that it was implausible that any data collected in an MAA could lead to a decision to recommend the technology. Whilst it is not for NICE to seek a change in the price of a product, this was an option that was open to the company throughout the process.

33. In response to questions from the panel, Mr Boysen said that NICE is not a "gate-keeper" to NHS England, and that a company can approach NHS England directly to discuss an MAA.

34. In response to further questions, Mr Boysen said that an MAA was indeed mentioned at the committee meeting of 20 February 2018 by the British Association of Dermatologists and that NICE offered to help the company to understand what NHS England's expectations might be. However, soon after that it became apparent that an MAA did not have plausible potential to result in a decision to recommend the technology.

35. Sheela Upadhyaya, for NICE, said that during the teleconference between NICE, CLINUVEL and NHS England on 30 May 2018, CLINUVEL were advised that they needed to respond to the concern in the FED about the lack of plausible potential for afamelanotide to be considered cost-effective. Meindert Boysen, for NICE, said that if CLINUVEL had offered a proposal that led to plausible potential for afamelanotide to be cost-effective this would have "opened a door" to an MAA that could then attempt to address uncertainties in the evidence base.

36. In response to questions from the panel, Lachlan Hay said that CLINUVEL have always been consistent and transparent about their policy of only offering a single price for their product and that they do not offer discounts. He said that CLINUVEL understood the ICERs to be the material driver of the decision not to recommend the product. However, the company believed the issue of sharing financial risk during the MAA had been addressed by their proposal.

37. The appeal panel concluded as follows:

38. Although the appeal panel had some sympathy with the company's view that there had been a lack of clarity regarding the procedure surrounding the development of MAAs, they did not feel that this was sufficient to make out the ground of appeal.

39. The question is whether the final decision was arrived at fairly. A company must know, during an evaluation, what all of the material drivers of a decision are. The key moment to consider is the moment at which the committee takes its final decision: at that point, has the company been made aware of all of the material drivers, has it had a chance to address them, and has whatever submission it has made informed the committee? Furthermore, the panel were clear that the

company would have had the opportunity to approach NHS England directly at any time. The panel was satisfied that the FED contained adequate reasoning for why an MAA was not judged appropriate, in particular the fact that it was highly unlikely that afamelanotide had plausible potential to be considered cost-effective. CLINUVEL were aware that cost-effectiveness was a material driver for the decision that an MAA was not appropriate, which was clear some time before the finalisation of the FED, and CLINUVEL had opportunities to address this. The appeal panel therefore concluded that CLINUVEL were not disadvantaged by any lack of clarity concerning the MAA procedure and that overall the process followed was fair.

40. Therefore the panel dismissed this appeal point.

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.

Appeal by International Porphyria Patient Network (IPPN)

Appeal Ground 1b.1: The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward
(This appeal point was named IPPN 1b2 in initial correspondence and during the hearing).

41. In their appeal, the IPPN state that they raised a concern about the equalities impact of the decision during the consultation process. They state that the committee responded by simply stating that “no potential equalities issues have been identified” without providing further justification of this.

42. During initial scrutiny, there was some discussion on whether this was a valid point of appeal. It was accepted on the grounds that another appellant (CLINUVEL) argued that the committee’s decision does not take proper account of equality issues and was put to the appeal panel on this basis. The appeal panel therefore considered this appeal point together with CLINUVEL 1b.1 and this decision letter will deal with these two points together in the section below.

Appeal by CLINUVEL (UK) Ltd

Appeal Ground 1b.1: NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities
(This appeal point was named CLINUVEL 5 in initial correspondence and during the hearing).

43. Sarah Love, for CLINUVEL, argued that:

(a) NICE is a public authority within the meaning of the Equality Act 2010;
(b) EPP constitutes a disability under the meaning of the Act;
(c) The method used by the evaluation committee to determine cost effectiveness is a 'provision, criterion or practice' within the meaning of the Act;

(d) In this case, the practice adopted was to treat the incremental cost effectiveness ratios (ICERs) as effectively determinative of the committee's decision;
(e) ICERs are derived from quality of life measures, and there is no suitable measure to capture quality of life in EPP;
(f) Therefore use of ICERs (based on such measures) to determine the decision discriminated against all patients with EPP (not just a subset of that group). It put them at a substantial disadvantage to others who do not have EPP, as there is no metric that can produce an accurate ICER. People without EPP could expect to have a treatment for their (different) condition evaluated using metrics that adequately assess that treatment's impact on patients' quality of life, whereas people with EPP could not;
(g) Accordingly reasonable adjustment(s) are required;
(h) The reasonable adjustment to be made in the circumstances would have been to recommend afamelanotide subject to a Managed Access Agreement. Even if NICE was not prepared to go that far, NICE should have changed the methodology adopted.

44. Ms Love emphasised that equalities concerns had been raised by both BPA and IPPN during the consultation, but that the response to these concerns in the documents did not address them adequately. She stated that there was no evidence of the committee considering the need to make a reasonable adjustment to their usual methodology in order to meet their duties as a public authority under the Act. She argued that there was no evidence of consideration of the committee's obligations under the public sector equality duty.

45. Ms Love referred to the High Court judgment in the case of *R(Eisai) v NICE* [2007] EWHC 1941 (Admin), and in particular to the need for proper consideration to be given to NICE's duties as a public authority to promote equal opportunities and to have due regard to the need to eliminate discrimination. Although that case was subsequently considered by the Court of Appeal, Ms Love explained that this part of the High Court judgment was undisturbed by that subsequent consideration.

46. The appeal panel's legal adviser drew the appeal panel's attention to paragraph 92 of the *Eisai* judgment and the "series of simple questions that the appeal panel could have asked both the appraisal committee and themselves" set out in that paragraph. The appeal panel found these instructive and put them to the committee, in particular asking in terms: "has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?"

47. Dr Peter Jackson, for NICE, stated that the HST process was specifically set up to address the particular challenges faced by rare diseases. He commented that measuring outcomes is generally challenging in all rare diseases that the HST evaluation committee considers. He stated that the ICERs were an important factor, but not the only factor in the committee's decision. He explained that they are "an element that gives structure to our thinking. They are one of the things that we think about, and an important thing, but not the only thing we think about".

48. Meindert Boysen, for NICE, said that NICE had completed an Equality Impact Assessment for the evaluation that was signed off on 12 March 2018 but that this was not published on the NICE website or otherwise provided to any other party in error. He apologised for this.

49. Meindert Boysen, for NICE, said that NICE has consistently implemented their positive duty to make reasonable adjustments to protected groups in the way recommendations are implemented, but has not typically considered this relevant to making a recommendation in the first place. He explained this by saying "If we are saying no to everyone, then there is no particular issue within the group and no need to make adjustments".

50. Jeremy Manuel, for NICE explained that the HST process itself was established in response to potential discrimination faced by sufferers of rare diseases. He felt that the same arguments used with regard to afamelanotide in this appeal point (concerning the complexities of capturing the full benefits of treatment) could potentially be applied to any rare disease. He argued that if a different method had been used in this particular case, it could be unfair to those with other rare conditions.

51. In response to the question "has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?" Dr Jackson replied that the committee did not consider EPP as a disability in the meaning of the Act. In response to a request for clarification from the panel, Dr Jackson elaborated by saying that they had interpreted "disability" as referring to a patently visible disability, and that it would be problematic if every disease before them were regarded as a disability.

52. The appeal panel concluded as follows.

53. The panel took the view that EPP very clearly meets the definition of a disability under the Equality Act 2010. It is also clear that NICE is a public authority as defined in the Act. The panel accepted that the Interim Process and Methods of the HST Programme[1] is NICE's institutional response to the problem of highly specialised technologies in respect of which outcomes are difficult to measure and where reliance solely on ICERs would be unreasonable. It is itself a reasonable adjustment made for the benefit of people with rare diseases. In particular, the appeal panel noted paragraph 41 of that document, which states that:

> *41. The Evaluation Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Evaluation Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers*

[1] https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf

and clinical experts who have used the technology being evaluated or are familiar with the relevant condition. In evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions.

54. However, in this case, the panel were not able to consider the Equalities Impact Assessment said to have been completed by NICE as this had not been published and was not available to either the appellants or the panel. The panel could not see evidence of consideration of NICE's duties under the Act with respect to the use of afamelanotide in EPP specifically, elsewhere in the documents provided. Furthermore, the evaluation committee confirmed during the hearing that they had *not* taken into account any anti-discrimination legislation in reaching their decision. Irrespective of whether ICERs were indeed determinative of the committee's decision, or whether the use of ICERs in this way would constitute a discriminatory "provision, criterion or practice", the panel therefore concluded that NICE had not demonstrated adequate consideration of the legal obligations placed on it as a public authority.

55. The appeal panel therefore upheld the appeal on this point and on the linked IPPN Ground 1b.1 (see paragraph 42). The appeal panel suggests that the Committee may wish to seek further guidance from the Institute, if the Committee considers that it is required, on the relationship between the HST Process Guide and any specific need for reasonable adjustment(s) in relation to a particular cohort of people sharing a protected characteristic.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal by British Association of Dermatologists

Appeal point Ground 2.1: The NICE committee have not taken into account the full range of factors.
(This appeal point was named BAD 2.4 in initial correspondence and during the hearing).

56. Professor Lesley Rhodes, for the British Association of Dermatologists (BAD), stated that real world evidence, clinical expertise and photobiological science were ignored by the committee. She argued that the following factors were not taken seriously by the committee: clinicians' views on the dramatic benefits of afamelanotide, the testimony of non-UK patients, and the evidence of efficacy provided by the high rate of long term compliance with treatment in the observational study Biolcati et al 2015: Br J Dermatol 72:1601.

57. Professor Rhodes stated that conditioned light avoidance probably resulted in the clinical trials under-estimating the benefit of treatment compared with that seen in the longer term.

58. Professor Rhodes also stated that the photo-provocation test used in the clinical trials showed a highly significant increase in light tolerance with treatment.

59. Jeremy Manuel, for NICE, said that all patient and clinician testimony was taken seriously by the committee, who spent time discussing the potential wider benefits of treatment for patients' lives and activities.

60. Dr Jackson, for NICE, said the committee had considered whether conditioned light avoidance was likely to have resulted in the clinical trials substantially under-estimating the benefit of treatment. They concluded that this was unlikely, because in the observational study by Biolcati et al (2015) there was a substantial improvement in quality of life over the first 6 months of treatment with no additional substantial change thereafter.

61. The appeal panel concluded that both the FED and the responses of the evaluation committee during the hearing indicated that the committee had considered the full range of factors put forward by the BAD in this appeal point. Whilst opinions might differ on whether all these factors were given sufficient weight by the committee, the panel judged that the committee's approach to weighing up the importance of all these factors was reasonable.

62. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.2: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide
(This appeal point was named BAD 2.1 in initial correspondence and during the hearing).

And

Appeal point Ground 2.3: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide
(This appeal point was named BAD 2.5 in initial correspondence and during the hearing).

63. These two grounds of appeal from BAD, together with IPPN 2.2, (see paragraphs 84-85) overlapped to the extent that it was difficult to disentangle separate points, and they have been considered together in this decision letter.

64. Professor Rhodes disputed the committee's view that the clinical trial results suggest "small" benefits with afamelanotide. She stated that the average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). She argued that this increase puts patients with EPP who are on treatment into the normal range for this measure. (She quoted data that showed that healthy indoor workers spend an average of 22 minutes in the sun between 10am and 3pm). She also pointed out that the figure of approximately 10 minutes extra per day of sun exposure represents an <u>average</u> daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest.

65. James Rawnsley, for IPPN, explained that for a patient with EPP, a small absolute change in the number of minutes in the sun could be life-changing. He commented that when he took part in the trial he was able to spend a whole day outside in the sun without any reaction, but that sometimes the feedback in his trial diary about how much time he had actually spent in the sun appeared less positive because of poor weather or his own work commitments.

66. Dr Jasmin Barman-Aksözen, for IPPN, referred to data from an observational study by Biolcati et al (2015) which found improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first six months of treatment.

67. Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.

68. Dr Jackson stated his view that the differences in minutes per day of time in the sun found in the randomised controlled trials were indeed numerically small. He mentioned that the European Medicines Agency (EMA) had also referred to the magnitude effect of afamelanotide seen in the clinical trials in this way. In response to a question from the panel he stated that there is no established minimally important difference for the outcome measures used in the trials, including minutes per day of time in the sun. However, he emphasised that the committee did not intend to imply that the overall benefit experienced by patients was small[2].

69. The appeal panel concluded as follows:

70. Whilst the panel noted Dr Jackson's comment that the term "small benefits" was intended to refer to the randomised trial results rather than the overall benefit of treatment, it also noted that this term was used repeatedly both in the FED and during the hearing. The panel was persuaded by Professor Rhodes' argument that whether an increase of 10 minutes represents a small or a large change can only be interpreted with regard to the normal range for this measure. The panel noted that FED paragraph 4.7 cites differences in the amount of time spent in daylight and decreases in phototoxic reactions that would not necessarily sound small to someone reading the document. The panel judged that describing these differences as small lacks face validity. Whether or not this choice of words was relevant to the final recommendation made, it is important that the FED describes the results of the trial data in a way that appears to "add up". Overall, the panel concluded that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide.

71. The appeal panel therefore upheld the appeal on these two points (and IPPN point 2.2, see below paragraph 85).

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[2] The panel noted a minor typographical error in the FED, page 5 paragraph 4.2 where "47% (n=66/127") should read 47% (n=60/127)" as written in the original Holme paper.

Appeal by International Porphyria Patient Network (IPPN)

Appeal point Ground 2.1: The committee failed to act fairly by not acknowledging the evidence provided in patient testimonies and by expert physicians on the overwhelming clinical benefit
(This appeal point was named IPPN 1a1 in initial correspondence and during the hearing).

72. Dr Jasmin Barman-Aksözen, for IPPN, emphasised the importance of patient testimonies for understanding the real world impact of rare and poorly understood conditions like EPP. She illustrated this with her own powerful personal testimony. She said that every patient treated with afamelanotide reports life-changing benefits.

73. James Rawnsley, for IPPN, also described very eloquently the devastating impact that EPP has had on his own life, and the dramatic benefits he experienced with treatment.

74. Emily MacKenzie, for IPPN, said that the committee themselves acknowledge that the existing measures of quality of life used in EPP (the DLQI and EPP-QOL) are unsatisfactory. Ms MacKenzie said that the committee also acknowledge in the FED that the trials are likely to have under-estimated the true clinical benefit of treatment. She argued that this means patient and physician testimony should have been given greater weight but this was not done. She expressed concern that the committee were "paying lip service" to acknowledging the importance of patient and expert testimony, whilst at the same time demonstrably preferring the trial data.

75. Ms MacKenzie referred to paragraph 41 of the HST process guide which requires the committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical experts. She argued that the committee had rejected evidence from patient and clinician testimony simply because these factors could not be quantified. She stated that it was inappropriate to use patient testimony only at the stage of judging whether the usual threshold for an ICER could be applied flexibly. Rather, patient testimony should have been given greater weight throughout the process as an alternative approach to one based on economic modelling.

76. Ms MacKenzie referred to paragraph 46 of the HST process guide regarding QALY weighting. She rejected the committee's conclusion that even accounting for the patients' and clinicians' testimony would be unlikely to result in an incremental QALY gain of at least 10, as being based on "woefully inadequate data".

77. Ms MacKenzie referred to paragraph 55 of the HST process guide, which concerns the circumstances in which the usual ICER threshold can be "flexed". She stated that in this case there is a strong reason to indicate that there are substantial uncaptured benefits. She argued that the committee have not shown evidence that they took this into account in making their final decision not to recommend treatment.

78. Dr Peter Jackson, for NICE, explained that the HST evaluation committee have substantial experience in evaluating treatments for rare diseases where because of small sample sizes it is indeed often more challenging to capture all the benefits of treatment with quantitative tools. He said that the HST evaluation committee must apply a rigorous approach to evaluating information from patient and clinician testimonies. This would include consideration of the range of responses, how respondents were elicited and any potential biases. In response to a question from the panel about whether the patient and clinician testimony was unusually compelling and uniform in this case, Dr Jackson replied that the HST evaluation committee very commonly sees a similar picture of very positive responses with technologies that come before them. When the committee looked at descriptions of EPP in the literature, they felt that while the testimony of the nominated patients and clinicians was very powerful, this might not be a complete picture. Dr Jackson said the committee have considerable experience of using a process of deliberative discussion to gauge patient testimony against that from other diseases, but acknowledged that the nature of this discussion can be hard to capture in a simple description.

79. Dr Jackson stated that whilst the committee recognised the limitations of the outcome measure used to assess quality of life for the economic model (the DLQI) they certainly did not accept it was so flawed that it could not be useful. The DLQI has been widely validated in other conditions. Scores on the DLQI correlate with both biochemical and clinical measures of the severity of EPP, and are sensitive to the impact of EPP on quality of life.

80. Asked by the panel what the committee thought were the most likely reasons for the apparent discrepancy between the trial results and the patient testimony, Dr Jackson gave a detailed response but concluded that they had not reached a satisfactory explanation. He said that the committee had therefore put these two pieces of information together as best they could in reaching a decision.

81. The panel asked about how the committee had incorporated patient and clinician testimony into their decision making. Dr Jackson said that they discussed each factor that had been raised (such as impact on occupational functioning) in detail. They had then considered to what extent this would allow them to "flex" the standard ICER threshold for HSTs (as set out in paragraph 55 of the HST process guide). In response to a question from the panel, Dr Jackson said that the ICERs were an order of magnitude away from the usual threshold. The committee had therefore concluded that, whilst the quantitative data was likely to have underestimated the benefit of treatment, it was not plausible that it had been underestimated to the extent that the treatment could plausibly be cost-effective.

82. The appeal panel concluded that there was evidence both from the FED and the committee's responses during the hearing that they had carefully considered the patient and clinician testimony. The panel judged that the committee had shown detailed consideration of the strengths and limitations of different sources of information as well as possible reasons for apparent discrepancies. The committee clearly stated the process they had used to incorporate patient and clinician testimonies into their final decision, and this process was judged by the panel to be reasonable.

83. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.2: The evidence provided shows that the benefit is significant and not small, as assessed by the committee
(This appeal point was named IPPN 2.1 in initial correspondence and during the hearing).

84. This appeal point overlapped with BAD Appeal points 2.2 and 2.3 to the extent that it was difficult to disentangle separate issues. They were discussed together at the hearing and considered together by the panel (paragraphs 63-71).

85. The appeal panel therefore upheld the appeal on this point.

Appeal point Ground 2.3: The evidence provided of the measured trial outcome shows that the treatment is highly effective
(This appeal point was named IPPN 2.2 in initial correspondence and during the hearing).

86. Dr Jasmin Barman-Aksözen, for IPPN did not accept the perception that there was a discrepancy between the randomised trial results and patient testimony. Rather, she argued that the trial results concur with patient testimony in showing that afamelanotide is highly effective. She highlighted the points made by Dr Rhodes (paragraph 64) about how the absolute change in minutes of sunlight per day should be interpreted.

87. The appeal panel concluded as follows;

88. As described in paragraph 70 of this decision letter, the panel was persuaded by the specific arguments made by Professor Rhodes and Dr Barman-Aksözen (paragraphs 64 and 86). It is for this reason that the panel concluded that it was not reasonable for the committee to describe the magnitude of benefits seen in the trial as "small" and thus upheld appeal points BAD 2.2, BAD 2.3 and IPPN 2.2.

89. However, insofar as it differs at all from IPPN 2.2, this appeal point seems to go further in stating that the trial outcomes showed the treatment to be "highly effective".

90. It should be noted that it is not for the appeal panel to draw its own conclusions on the evidence presented, but only to comment on the reasonableness of the conclusions reached by the committee. From the totality of the evidence presented, the panel were confident that it was reasonable for the committee not to have described the trial evidence as showing that afamelanotide was "highly effective".

91. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.4: The evidence provided shows that quality of life before treatment is low and under treatment with afamelanotide increases dramatically and sustainably
(This appeal point was named IPPN 2.3 in initial correspondence and during the hearing).

92. Dr Jasmin Barman-Aksözen, for IPPN, emphasised the data from the observational study by Biolcati et al (2015) which found improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first six months of treatment. Dr Barman-Aksözen expressed concern that these findings had not been given sufficient weight by the committee (or perhaps had been misinterpreted by the committee) because no further improvements were seen after six months (even though the improvements were sustained).

93. Dr Barman-Aksözen argued that the EPP-QOL was a more appropriate tool to measure quality of life in EPP than the DLQI because it is disease-specific and designed with input from patients and clinical experts. She said that the EPP-QOL is sensitive to treatment effects and can even detect differences in quality of life between summer and winter. She expressed concern that the DLQI fails to capture non-skin components of EPP such as fatigue and that it has not shown to be sensitive to treatment effects.

94. Dr Peter Jackson, for NICE, pointed out that the Biolcati study was uncontrolled. Whilst there was indeed a large improvement on the EPP-QOL in this study, he noted that there were also improvements on this measure amongst patients treated with placebo in the controlled trials.

95. Dr Jackson explained that the committee had considered in detail the strengths and weaknesses of the two scales used to measure quality of life in the trials. Whilst they recognised the limitations of the DLQI in not capturing all the symptoms of EPP, they noted that DLQI has been widely validated in other conditions. Scores on the DLQI correlate with both biochemical and clinical measures of the severity of EPP, and are sensitive to the impact of EPP on quality of life. In addition, DLQI scores can be mapped onto the EQ5D to generate utility values. They recognised the strengths of EPP-QOL (it being disease-specific and having been developed with patient input) but felt that it was insufficiently validated as a measure of quality of life, and that the fact that pain was not included lacked face validity. Overall, the committee preferred DLQI for their economic model. However, they took account of the fact that the DLQI may not capture all the benefits of treatment in their decision making (see

paragraph 78 of the FED) and also considered exploratory models based on the EPP-QOL.

96. The appeal panel concluded as follows:

97. It was reasonable for the committee to put less weight on data from uncontrolled studies than randomised controlled trials. The lack of further improvement after 6 months in the Biolcati study was highlighted in the FED as evidence that most benefits can be seen within the time frame of the controlled trials rather than to imply that these data were not important. The conclusion drawn by the committee was that these data did not support the assertion that one reason for the apparently modest effect seen in the clinical trials may have been because it takes a considerable period of time for the learned behaviour of light avoidance to change. The concern expressed by IPPN in this regard (paragraph 92) may have been a simple misunderstanding of the wording of the FED by the IPPN.

98. The panel judged that the committee demonstrated (both in the FED and during the hearing) that they had considered in detail the relative strengths and weaknesses of the DLQI and EPP-QOL and that their decision to prefer the DLQI was not unreasonable. The panel noted that the committee had explicitly considered both results from the EPP-QOL and the limitations of the DLQI in their overall decision-making process. This process was therefore reasonable.

99. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.5: The committee failed to act fairly by denying a Managed Access Agreement (MAA) based on the same arguments put forward on why it already rejected a recommendation for reimbursement, thereby using circular reasoning which leaves no possibility for access whatsoever (This appeal point was named IPPN 2.4 in initial correspondence and during the hearing).

100. Dr Jasmin Barman-Aksözen, for IPPN referred to the reasons given in the FED for an MAA not being pursued. She said she was not able to comment on cost, but that she disagreed with the conclusion in the FED that an MAA would be likely to suffer from the same problems as the trials and therefore fail to resolve uncertainty in the data. In particular, she argued that a longer duration of follow-up during an MAA compared to the randomised trials would allow patients to change their light-avoidance behaviour, helping to capture quality of life benefits. She referred to the PASS (post authorisation safety study) being conducted in Europe and pointed out that this is collecting efficacy data, the first year of which has just been accepted by the EMA for the purpose of extending approval of the product.

101. Dr Robert Sarkany, for BAD, said that they had the impression that the decision not to pursue an MAA had been made with undue haste, without adequate consideration and without BAD having a full opportunity to suggest how uncertainty in the existing evidence could be resolved.

102. Dr Peter Jackson, for NICE, said that because MAAs are burdensome to patients and costly to NHS England they are only recommended where they are likely to be helpful. He argued that there seemed to be agreement on the difficulty of capturing treatment response in EPP and there was no suggestion that an alternative tool was being developed that would allow this to be done better in an MAA than it had been in the trials. In response to a question from the panel, he said that he did not believe that any of the data being collected in the PASS study was likely to resolve the substantial uncertainty which the committee had identified.

103. Dr Jackson said that an even more important consideration was where the ICER was in relation to the threshold. The committee had to ask themselves whether it was possible that data from an MAA could reduce uncertainty sufficiently to bring the ICER to within an acceptable range. They considered the range of ICERs from all models as well as the degree of uncertainty around this and they concluded that this was not plausible.

104. Dr Jackson was asked by the panel whether the appellants were made aware of the nature of the uncertainty in the evidence base. He replied that the FED was clear that the fundamental uncertainty related to whether existing outcome measures are able to capture the full benefit of treatment.

105. Asked by the panel whether the committee engaged with appellants in any discussion about alternative ways of measuring outcome, Dr Jackson said that they had enquired of the company what future steps they were proposing to reduce uncertainty.

106. Sarah Love, for CLINUVEL, said that they had suggested that CLINUVEL and NICE could collaborate to develop a better outcome measure.

107. The appeal panel concluded that although an MAA was ultimately not felt by the committee to be a useful way forward, it was clear that this had been considered and discussed. The panel judged that the FED gave clear reasoning for the decision not to recommend an MAA. The panel thought that both the difficulty in resolving uncertainty and the very large distance between current ICERs and the threshold were reasonable considerations in reaching this decision.

108. The appeal panel therefore dismissed the appeal on this point.

Appeal by British Porphyria Association

Appeal point Ground 2.1: There is a huge gulf between the results of clinical trials that are communicated by NICE as "small" and the benefits that patients in receipt of Afamelanotide repeatedly report as life changing … Despite this recognition, the FED recommendation has been made primarily on the grounds of the ERG economic analysis that was published before this information came to light, which we consider to be unreasonable.

109. There was some overlap between this appeal point and IPPN appeal point 2.1. The additional comments made at the hearing specifically in relation to BPA 2.1 are set out here, but this should be read in conjunction with the discussion of IPPN 2.1 above.

110. Dr Geoff Sloan, for BPA, emphasised the discrepancy between the notion that the trial showed small benefits and his own experience of the drug as life-changing.

111. Asked by the panel to clarify which information they felt had come too late in the process, John Chamberlayne said that this referred to the patient and clinician testimonies being heard after the ERG economic model was produced.

112. Dr Peter Jackson, for NICE, said that the committee had listened with great care to input from patients and were indeed impressed by their testimony. Dr Jackson explained in detail the committee's view on the strengths and limitations of both the economic modelling and patient/clinician testimony, and how both of these factors were incorporated into this decision making process. This is described in full in paragraphs 78-81 of this letter.

113. The appeal panel concluded that there was evidence both from the FED and the committee's responses during the hearing that they had carefully considered the patient and clinician testimony. The panel judged that the committee had shown detailed consideration of the strengths and limitations of the trial data and information from patients as well as possible reasons for the apparent discrepancy between these. The committee clearly stated the process they had used to incorporate patient and clinician testimonies into their final decision, and this process was judged by the panel to be reasonable.

114. The appeal panel therefore dismissed the appeal on this point.

Appeal point Ground 2.2: The economic decision has been made using a flawed model that means the decision is unreasonable in light of the evidence submitted to NICE.

115. There was some overlap between this appeal point and IPPN appeal points 2.1 and 2.4. The additional points made at the hearing specifically in relation to BPA 2.2 are set out here, but this should be read in conjunction with the discussion of IPPN 2.1 and 2.4 above.

116. John Chamberlayne, for BPA, stated that the economic model had been developed without any input from stakeholders. He argued that the flaws in the model were such that its conclusions could not be considered reliable.

117. Dr Peter Jackson, for NICE, acknowledged that the sensitivity of the DLQI to capturing benefit was a limitation of the model used. However, the alternative model using the EPP-QOL used an indirect method to determine cost effectiveness. The committee had carefully considered different approaches before choosing their preferred model.

118. Mr Francis Pang, for NICE, further described the limitations of the company's proposed model (which used DALYs in place of QALYs and relied on proxies for developing disability weight) but explained that nevertheless this was given due consideration.

119. The appeal panel concluded that the committee had shown careful consideration of the limitations of the economic modelling performed. The appeal panel judged that the limitations of the preferred model were not so severe as to make it unreasonable to use it in decision making. The panel noted that the committee had made efforts to take account of these limitations and incorporate other sources of evidence into their final decision.

120. The appeal panel therefore dismissed the appeal on this point.

Conclusion and effect of the appeal panel's decision

121. The appeal panel therefore upholds the appeal on the grounds IPPN 1a.1, CLINUVEL 1b.1, IPPN 1b.1, BAD 2.2, BAD 2.3, IPPN 2.2. The appeal is dismissed on all other grounds.

122. The evaluation is remitted to the evaluation committee who must now take all reasonable steps to address the following issues:

    i) The failure to include an IPPN representative at the second committee meeting (IPPN 1a.1).

    ii) The failure to demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act (CLINUVEL 1b.1 and IPPN 1b.1). 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.

    iii) The appeal panel's conclusion that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide (BAD 2.2 and 2.3, IPPN 2.2).

123. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.