NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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APPEAL HEARING

Advice on Afamelanotide for treating erythropoietic protoporphyria (ID927): Decision of the panel

Introduction

1. An appeal panel was convened on 18 May 2023 to consider an appeal against NICE's final evaluation document (FED), to the NHS, on afamelanotide for treating erythropoietic protoporphyria (ID927).

2. The Appeal Panel consisted of:

• Professor Peter Groves	Chair
• Jackie Fielding	Non-Executive Director, NICE
• Professor Kiran Patel	Health Service Representative
• Dr Paul Robinson	Industry representative
• David Chandler	Lay representative

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

4. The panel considered appeals submitted by Clinuvel (the company) and the International Porphyria Patient Network (IPPN).

5. Clinuvel was represented by:

• Lachlan Hay	Director of Global Operations, Clinuvel

• Sarah Love	Legal representative, Brick Court Chambers
• Tim Johnston	Legal representative, Brick Court Chambers
• Gareth Morgan	Legal representative, Pinsent Masons
• Anna Harley	Legal representative, Pinsent Masons

6. IPPN was represented by:

• Dr Jasmin Barman-Aksozen	Vice-President, IPPN
• Marten Pettersson	Strategic Affairs Officer, IPPN

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

• Dr Peter Jackson	Chair, Highly specialised technologies (HST) evaluation committee
• Sarah Davis	HST evaluation committee member
• Richard Diaz	Associate Director, NICE
• Victoria Kelly	Technical Adviser, NICE
• Helen Knight	Director of Medicines Evaluation, NICE

8. The appeal panel's legal adviser, Alistair Robertson DAC Beachcroft LLP, was also present.

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

Ground one: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

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

10. Dr Mark Chakravarty, NICE Lead Non-Executive Director for appeals, in preliminary correspondence had confirmed that:

- Clinuvel had potentially valid grounds of appeal as follows: Grounds 1a, 1b and 2
- IPPN had potentially valid grounds of appeal as follows: Grounds 1a and 2

11. The evaluation that is the subject of the current appeal provided advice to the NHS on afamelanotide for treating erythropoietic protoporphyria (ID927).

12. Erythropoietic protoporphyria (EPP) is a genetic disorder. It results from mutations in genes involved in the haem production pathway, such as ferrochelatase and delta-aminolevulinate synthase 2. The condition results in the accumulation of excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma and red blood cells. EPP is a cutaneous porphyria. The major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and artificial light emitted along the visible spectrum above 400 nanometres. The skin can rapidly become severely painful, swollen, itchy and red, and skin erosions can also occur. A phototoxic reaction typically lasts between 2 days and 3 days, but it can last 10 or more days, with severe pain and loss of sleep. These symptoms, along with persisting anxiety and social isolation because of sun and

light avoidance, can have a profound effect on quality of life. Over time, light exposure can cause thickening of skin on the knuckles and facial scarring. A small proportion of people with EPP may have important complications related to liver and gallbladder function. Patients lead their lives in a manner that avoids the impact of phototoxicity which can be severe enough to lead to second degree burns. Neuropathic pain sometimes develops and cannot be treated with painkillers. Sun block does not help. Bleeding and inflammation are internal and therefore not necessarily externally visible. Patients are often, therefore, accused of malingering, leading to further social isolation.

13. Afamelanotide activates the synthesis of eumelanin mediated by the MC1R receptor. Eumelanin contributes to photoprotection by absorbing light and serving as a filter. It also reduces oxidative stress by inactivating the superoxide anion and increasing the availability of superoxide dismutase.

14. Afamelanotide has a marketing authorisation in the United Kingdom under 'exceptional circumstances' and is administered as a dissolving subcutaneous implant. Afamelanotide is the first treatment that has been specifically developed for patients with EPP.

15. Before the appeal panel hearing commenced, the Chair confirmed the independence of the appeal panel and made introductory remarks. He explained that a bundle of papers had been circulated to appeal panel members prior to the hearing for their consideration. Some of these papers were publicly available and some were confidential in nature. He described the purpose of the hearing, to explore residual uncertainties in the minds of the panel members and to explore the legitimacy of each appeal point in turn in an exploratory, inquisitorial and non-adversarial manner. Throughout the hearing, questions would be asked of appellants and NICE representatives without any

intent to put people under duress but rather to help resolve residual uncertainties. He made clear that the panel had already met before the hearing to plan the nature of the proceedings together. He also explained that the panel would be meeting on another day to the hearing to deliberate and arrive at its final conclusions about the legitimacy of the appeal points considered.

16. For each valid appeal point, it was explained that the appellants would be provided the opportunity to present their appeal points in turn, following which there would be questions from the panel directed through the Chair. At the end of each appeal point discussion, the appellants would be provided the opportunity to raise any additional relevant points.

17. The Chair explained that the appeal panel conclusions and decisions about the legitimacy of the appeal points heard would be communicated to appellants and later published on the NICE website.

18. Before the hearing commenced, the Chair read out the following statement on behalf of NICE:

> ‘I understand from NICE that some documents which are relevant only to Clinuvel’s appeal points were omitted from the papers sent to IPPN in advance of the appeal. NICE apologises for that, and I can see how it would be unsettling for IPPN. NICE has now provided as many of the originally omitted documents to IPPN as possible (and also apologises for the late sharing of those documents). I have been advised there are now 48 pages of documents that are still omitted, and NICE has confirmed to me that they do not have any bearing on any of IPPN’s points. I do pass on NICE's apologies for this, but I hope that IPPN will be reassured that the documents in question do not relate to their appeal.’

19. The numbering of appeal points in this letter reflects those that were used during the hearing. Reference is also made to their corresponding number in the original appeal letters. The text of this letter does not represent a verbatim account of the proceedings nor a

documentation of the order of events that took place but rather, provides a brief summary of the appellant and committee submissions for the points that were discussed.

20. As part of Clinuvel's opening statement, Tim Johnston noted that NICE had shared a document with Clinuvel, then subsequently said that the document was subject to legal privilege and should be removed from the papers. Clinuvel confirmed that it would not refer to the document in the hearing, but noted that Clinuvel considered the document to be potentially relevant and that Clinuvel had been prejudiced by its late removal.

Appeal by Clinuvel

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

Appeal point 1a.1: The procedure followed by the committee was not sufficiently transparent

21. Tim Johnston, for Clinuvel, stated that the committee had changed its position repeatedly throughout the evaluation on what evidence it would take into account. Essentially, qualitative evidence was discerned as useful to help understand the effects of the condition but not good enough for quantitative analysis. A distinction was made between structured and unstructured qualitative data, but the nature of this difference was unclear to the company. It had been advocated by the committee that a vignette study would be useful, but Tim Johnston claimed that this had merely served to confuse the issue about what data was and what was not considered valuable by the committee. He went on to explain that the company had sought clarification from NICE about the justification for the request for a vignette study but had not received a substantive response. He also claimed that the approach that the committee had taken to the data it wished to consider had changed with time and that this had put the

company at a disadvantage since it felt that it was 'shooting at a moving target'. As a consequence, it was claimed that the company could not determine how to best engage with NICE during the evaluation.

22. Dr Peter Jackson, for NICE, stated there had been no change in the approach that the NICE committee had taken to qualitative data during the evaluation. He explained that a vignette study was considered to represent structured qualitative data in which it was possible to assign quantitative values to different clinical states but that it was exceedingly important to get the scenarios right at the outset. He explained that NICE advocated a mechanism of transforming qualitative data from spontaneous reports into numbers, and he apologised if there had been any confusion caused.

23. Dr Peter Jackson proceeded to provide further clarification about the difference between what was meant by structured and unstructured qualitative data. A vignette study was described as a very structured approach in which experts use their skill to understand how to arrive at a consensus and capture the essence and totality of the important issues to patients in each of the scenarios, so that those scenarios can then be scored. He also explained that vignette studies incorporate an element of quality control looking at the variability of numbers produced. He described the process of undertaking a vignette study as being a rigorous process.

24. Dr Peter Jackson then outlined how the availability of unstructured data had had a significant impact on the committee. He explained that comments from qualitative studies were very persuasive and made the committee consider whether the original model and estimates from the clinical trial data had truly captured all the benefits of treatment of this illness. He described, though, how the committee did

not have available to it any structured evidence to explore this further and therefore had called for the undertaking of a vignette study.

25. In response, Lachlan Hay, for Clinuvel, referred to the February 2022 evaluation consultation document. He expressed the views that Dr Peter Jackson's comments were not limited to one specific type of data; that there was no reference to the concept of structured or unstructured data; and that "structured" refers to a vignette and "unstructured" refers to any other form of data. He concluded that NICE appeared to have 'shifted the goalposts'.

26. In response Peter Jackson clarified that NICE had produced ample guidance on the hierarchy of evidence, what comes into structured and unstructured data and what NICE sees as appropriate evidence. Richard Diaz, for NICE, added that had NICE been asked to help clarify points about data description, it would have provided this but that it had not been asked. Letters had been sent to the Chief Executive Officer of NICE and not to the committee. He stressed that NICE had a very good track record of undertaking very complicated evaluations. In this case, NICE had hosted additional meetings with the company and patient group and had tried to explain what was needed, but it did not appear to have been successful for reasons that he was unable to explain.

27. The appeal panel concluded as follows. It reminded itself that this appeal point related to a question of whether the procedure followed by the committee had been sufficiently transparent and fair. It noted that the appellant had expressed concerns that the committee had not shared with the company a consistent and transparent approach to data it considered was or was not valuable and helpful in informing its decisions. The panel observed that the committee had drawn conclusions about why the available published qualitative data was not sufficiently robust to inform the economic modelling and analysis

and had communicated this clearly and transparently in the FED. It also noted that the committee had concluded that these data were likely to have under-estimated the extent to which EPP impacts on quality of life and had sought more robust data to better reflect this in recommending the undertaking of a vignette study. This had also been explained transparently in the FED in a manner that appeared to be procedurally fair to the panel.

28. The panel further noted that NICE had offered support to the company and had hosted a stakeholder forum to facilitate a better understanding of the need and reasons for the acquiring of further quality of life data to inform utility values. The panel understood that in the context of a complex evaluation during which public consultation is undertaken, there is sometimes an understandable need for an evolving and changing approach by NICE to the need for additional data acquisition to resolve important uncertainties in the minds of the committee members. In this evaluation, the panel concluded that there had been transparency about this within the normal processes and that the committee had justified why a vignette study was requested but not mandated.

29. The panel deemed, however, that the committee could have explained better in the FED the difference between structured and unstructured qualitative data since this had clearly led to some confusion. The panel would suggest that the committee consider whether re-writing of the relevant sections of the FED may be helpful in providing this additional clarity.

30. The appeal panel dismissed the appeal on this point.

Clinuvel and IPPN

The following appeal points were considered together:

Appeal point Clinuvel 1a.3: NICE acted unfairly by reason of delay

Appeal point IPPN 1a.1: Pausing the appraisal during the pandemic and further delays in the evaluation of afamelanotide were unfair to patients with EPP in England and Wales.

31. Tim Johnston, for Clinuvel, stated that the delays during this evaluation had amounted to something very substantial, 8 years in total to date, meaning that no patient in England and Wales had received afamelanotide through the NHS, which was in contrast to Scotland. Concern had been raised in January 2020 by Clinuvel regarding the delays. Furthermore, he claimed that the delays could not be explained wholly by the COVID-19 pandemic and that the NICE committee had acknowledged the delays. Although he stated that he had no intention of re-iterating the details of all of the delays, he provided an example that following a NICE briefing in February 2020, there was a void until February 2021 when the company had written to NICE. Furthermore, NICE had stated in September 2021 that it would prioritise a response, but a further delay of at least 3 months ensued.

32. Tim Johnston went on to explain that the company had never been informed by NICE that there was a pause in the evaluation or that there would be an effect of the COVID-19 pandemic on HST evaluations. He further noted that some HST evaluations were seen to be progressing and therefore the company had wondered why this evaluation had been singled out to be paused.

33. Tim Johnston concluded that there had been long and protracted delays in the evaluation and that the time had passed for this topic to be re-considered by the NICE committee. Rather, he proposed that the appeal panel rewrite the FED and send it to the NICE guidance executive.

34. Dr Jasmin Barman-Aksozen, for IPPN, noted that afamelanotide was classified as ‘therapeutically not critical’ during the pandemic and that the evaluation was therefore paused by NICE. She explained that it had taken almost 3 years until the evaluation was re-started and that IPPN had learnt that other appraisals were ongoing, or had started during the pandemic, including 3 appraisals of technologies that had already been recommended in England and Wales. She outlined how the pause had led to consequences including preventing the meaningful exchange with the committee on what type of data would be acceptable to them; not learning about the date of the re-start and therefore preventing meaningful studies to be undertaken; and a loss of confidence by patients in England and Wales in the whole process. She further claimed that NICE had changed the narrative about the reasons for the delay and that although NICE had said that the delays had provided IPPN an opportunity to collect new evidence, this had proved difficult to do without knowing the extent and duration of the pause.

35. In response, Helen Knight, for NICE, stated that only work therapeutically critical to COVID-19 was continued during the pandemic and that NICE had continued about 60% of its work programme. She went on to explain that the 'therapeutically critical' work topics were those where mortality was affected. She acknowledged that there were other parts of appraisals that continued or were commenced too, but also there were many things that NICE were not publishing or taking to committees. She explained that the reason for this is that NICE committees comprise front line clinicians and that it was imperative that NICE did not take these clinicians away from hospitals during the pandemic. Additionally, NICE did not want to over-burden the NHS with new guidance which did not affect mortality.

36. Helen Knight accepted that the process had been lengthy. She explained that when NICE started to recover following the pandemic, it prioritised working with stakeholders to get to a point where NICE could see something more relatable to what patient experts were telling them about the impact of this disease. She also addressed the issues relating to the correspondence that had been sent by the company. She explained that most of this contained requests that NICE release the FED and complete the process, but NICE considered that it still needed to have useful conversations with stakeholders and that the delays had allowed useful data to be submitted by IPPN which had helped with a further understanding of the condition. She claimed that without those data, NICE would not have been close to a position enabling consideration of managed access (MA).

37. Richard Diaz, for NICE, added that after the first appeal it was clear the committee needed to re-evaluate everything from the beginning. To allow for that, the informal stakeholder workshop provided the opportunity to present an explanation of what NICE wished to achieve to get a resolution of the process. At this time, the company was assured that NICE would aim henceforth to get this evaluation completed within the normal timeframes for an HST and, he claimed, this had been achieved following the online stakeholder workshop. Finally, he added that the delay was not as deleterious as the company was claiming since further data had been generated by IPPN in the intervening period and the conclusions of the committee had, in the end, been similar to those when the original evaluation had been undertaken.

38. The appeal panel concluded as follows: It reminded itself that this appeal point related to whether it was procedurally unfair for there to have been delays in this evaluation and whether these delays were unfair to patients with EPP in England and Wales. The panel noted

that following the first appeal there had been long delays in this evaluation that appeared to have been driven by the complexity of the evaluation and which were only partially explicable by the COVID-19 pandemic. While it acknowledged the rationale behind the categorisation of afamelanotide as being 'therapeutically not critical' during the pandemic given the absence of any suggestion that it has an impact on patient mortality, it noted that other NICE appraisals had continued during the pandemic and there seemed to have been a lack of clarity and fairness in the communication with stakeholders about the nature and duration of the pause in this particular evaluation.

39. The appeal panel carefully considered the evidence as to the extent to which the delays, which it considered overall to have been procedurally unfair, had impacted on the outcome of the evaluation, or on the company or patients. In this regard, it noted the negative outcome of the evaluation that, it judged, was not a consequence of the delay. Indeed, it noted the fact that the delay had, if anything, provided the opportunity for further data acquisition, to help resolve uncertainties in the minds of the committee. It therefore concluded that there appeared to have been no negative consequences of the delays on the outcome of the evaluation or, therefore, on patient management, given the negative recommendations ultimately arrived at. The panel noted that the delays may have contributed to periods of uncertainty in the minds of patients and also in the minds of the company in regard to its future planning for example, on its approach to the issue of the limited period of time of market exclusivity remaining for afamelanotide. The panel also concluded that the evaluation process could have been expedited and that communication between NICE and stakeholders could have been better during the delay periods.

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

Appeal by Clinuvel

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

Appeal point 1b.1: NICE breached its duties under the Equality Act 2010

41. Tim Johnston, for Clinuvel, identified that this was the second time an appeal panel had had to consider compliance of this evaluation with the Equality Act 2010 (EA 2010) since 2018. He declared that the first time around, the committee failed to appreciate that the EA 2010 applied to the evaluation. The first appeal panel agreed that EPP patients were unique and that their substantial disadvantage required reasonable adjustments to be made accordingly to the evaluation process. With respect to the EA 2010, he expressed the intention to describe how the committee had fallen short of meeting their obligations in not applying reasonable adjustments to their processes and decision-making. He went on to explain that when a Provision, Criteria or Practice (PCP) (and in this instance, the HST process is a PCP), puts a disabled person at a substantial disadvantage i.e., more than minor or trivial, the obligation of the Act is to take such steps as is reasonable to have to take to avoid the disadvantage. Disadvantage is measured by reference to the position that would exist if the disabled person did not have the disability and the obligation is to do everything that is reasonable to avoid it. So, Tim Johnston explained, the committee should have asked itself 2 things. Firstly, what is the specific disadvantage experienced by patients with EPP? Secondly, what reasonable adjustments are we required to make to overcome that disadvantage?

42. Tim Johnston outlined that there are several disadvantages faced by EPP patients but that the most important of these, in the context of this evaluation, is that it is impossible in patients with EPP to build a

coherent base of evidence that captures the impact of EPP on quality of life and to demonstrate the wider extent of the adverse impact of the disease on them beyond just the phototoxic reactions. This is because of the difficulties that are driven by (a) the range of disbenefits (b) the small number of sufferers (c) the fact that it is ethically impossible to do a double-blind trial and (d) that it is scientifically impossible to quantify the effect of the disease and especially outside of a double-blind framework. This means the disbenefit is directly and causally tied to the reasons why it is not possible to capture the benefits of any treatment using Quality Adjusted Life Years (QALYs). Tim Johnston acknowledged that there are many categories of patients who suffer from a disability in the context of the EA 2010 but claimed that no other groups suffer from being unable to show the benefit of treatment. He described how the European Medicines Agency (EMA) had previously recognised these disadvantages and had licensed afamelanotide even though the benefits could not be captured by conventional methods. While in this evaluation the FED does recognise the challenges of measuring treatment effect, it claims that this is not unique to EPP. However, Tim Johnston, said that he is unaware of any other disease with the same features or similar difficulties with generating reliable cost effectiveness data and therefore that adjustments in approach are required by the committee that amount to more than just a 'tweak,' to meet the requirements of the EA 2010.

43. Tim Johnston then focussed his comments on the stated benefits of afamelanotide and explained that paragraph 4.47 of the FED said that it would have been reasonable to consider alternative methods to capture the wider benefits of afamelanotide but failed to explain how to mitigate the precise disadvantage encountered by EPP sufferers. In paragraph 4.50, he cited that the committee had taken account of EQ5D data analysis and that it considered the evidence extremely

uncertain and used analyses as part of their reasonable adjustments. The committee did not, he claimed, ask or answer what specific adjustments were necessary to ameliorate the specific disadvantage faced by EPP sufferers. The most obvious reasonable adjustment, he proposed, was to recommend this drug for routine commissioning. To justify this, he noted that one small study had led to a reduction in the Incremental Cost-Effectiveness Ratio (ICER) by a factor of 10, although it was then accepted that the ICERs were extraordinarily uncertain, and that it was extraordinarily difficult to capture the benefits of this drug.

44. Tim Johnston went on to suggest that alternative reasonable adjustments that could have been made included applying a QALY weighting to mitigate the disadvantage faced by EPP patients, recommending afamelanotide use through a Managed Access Arrangement (MAA) or accepting that this is a product that is unsuitable for analysis using QALYs, as demonstrated by the QALY figures for this drug being very wide ranging.

45. Lachlan Hay, for Clinuvel, expressed the opinion that there is considerable evidence that shows a complete lack of regard by NICE and the HST committee to its responsibilities under the EA 2010. At the appeal hearing in 2018, he said that the HST Chair, Dr Peter Jackson, had demonstrated a lack of awareness that EPP was a disability since it was not a visible disability. He also claimed that Dr Peter Jackson in at least 2 meetings had specifically asked the company what it was about EPP which makes it unique and that, in his capacity as HST committee Chair, he had never apologised for the admission that he did not see EPP patients as having an invisible disability.

46. Lachlan Hay also raised an issue pertaining to the validity of the Equality Impact Assessment (EIA) documentation. He claimed that

the document appears to have been updated after sign off and that the EIA was not made until approximately 2 years after the appeal panel realised that NICE had a duty to comply. Lachlan Hay also referred to privileged and confidential documentation that could not be discussed at the appeal hearing which, he claimed, demonstrated the lengths to which a public body will go to in order to avoid meeting its obligations.

47. Dr Peter Jackson, for NICE, responded to a number of points that had been made by the Clinuvel representatives. He clarified that all HST treatments share the fact that there is no validated tool to measure their benefits and explained that the adjustments that NICE make for various disorders are part of routine management of topics within the NICE HST programme. Dr Peter Jackson went on to explain that in relation to the EMA's assessment, this was undertaken many years ago and what might not have been possible then, is likely possible now. For example, considering the evidence provided by IPPN, there is the suggestion that the response to treatment and burden of this disorder was measurable.

48. Dr Peter Jackson explained that the committee had specifically considered the disadvantages suffered by people with EPP and the one that stood out to them was the one having the biggest impact on the evaluation i.e., the difficulty in measuring the burden of disease on quality of life (QoL). He claimed that the committee had made a number of adjustments in its procedures which he detailed as follows: i) the NICE reference case uses a model presented on the basis of cost and QALYs. While the model that the committee was presented with initially was not of that form, it took account of it and worked around data driven by Disability Adjusted Life Years; ii) the committee also considered indirect proxy conditions and the Evidence Review Group (ERG) added a second and a third proxy condition to the one already proposed; iii) the committee took particular note of the

testimonies of patients and clinical experts; iv) the committee asked for further information and analysis to determine the extent to which clinical trials might have underestimated treatment benefits; v) NICE also explored the impact of increasing the time horizon in the economic model (referred to later in this letter); vi) to allow for all of these adjustments to be made, NICE extended deadlines to allow further data to be generated and submitted if possible and also held a workshop to help stakeholders provide further information; vii) the committee worked with IPPN and considered data that routinely, on the advice of the External Assessment Group (EAG), would normally not be incorporated to any extent into committee decision making. In the absence of any further assistance from the company or permission to share the company's model wider, NICE worked with the data provided by the IPPN to produce exploratory estimates even though it is not conventional practice for NICE to work on generating models since this is usually the role of the manufacturer.

49. Dr Peter Jackson explained that by making all of these adjustments, the committee considered that it had put patients with EPP on at least an equal footing with other people who came before the HST evaluation committee with other rare and disabling disorders. The committee therefore felt it had gone to reasonable lengths to make reasonable adjustments.

50. Following questioning from the panel, Dr Peter Jackson stated the adjustments that he had enumerated in his previous answer probably were not laid out and described in the FED in the same detail as articulated at this hearing but that the purpose of the FED is to describe some but not necessarily all of the elements of the committee processes.

51. Richard Diaz, for NICE, provided clarification about the EIA documents in response to the concerns that had previously been

raised by Lachlan Hay. He stated that the EIA form covers the entire period of the evaluation and that this explains why a previous NICE employee's signature appears in earlier parts of the documents when she was responsible for oversight and sign-off but that he had then taken over this responsibility and his signature appeared later. He claimed that this is standard operating procedure and that there is no real discrepancy or cause for suspicion.

52. Richard Diaz further responded to earlier points that had been raised by the Clinuvel representatives: i) he stated that during the course of this evaluation, methods have moved forward such that it is now not impossible to calculate QoL for patients with EPP. The data might still be uncertain but be of sufficient robustness for a committee to use the evidence to inform its decisions e.g. if the evidence is collected around vignettes; ii) although the company had said that the committee had not explicitly explained the particular disadvantages of this condition, the company had not done so in a sufficiently robust way that could be formed into a quantitative value to inform committee decision-making; iii) while the EA 2010 mandates that positive action be undertaken to eliminate the impact of disability, this does not necessarily mean that NICE should completely abandon the principle of finding value for money across the whole population; iv) abrogating the use of the ICER and making a positive recommendation for use regardless of what the evidence says is not reasonable, particularly when there is a pathway to finding out what QoL is for this population or at least getting close to it; v) the FED is not a legal document but is a means by which NICE aims to provide clear, concise and useful guidance to the NHS in implementing what is recommended.

53. Tim Johnston reiterated the claim that the adjustments that had been built into the HST processes had been insufficient and were not what the EA 2010 requires. He explained that the question the committee should have asked itself was what adjustments should be made in

relation to a particular disadvantage. The matter in question was not one of treating everyone equally or the same but rather what the particular disadvantages are and have we managed to mitigate them all.

54. Following questioning from the panel, Dr Peter Jackson clarified that the 13 examples of disadvantages in patients with EPP that were identified by the company in their appeal letter were mainly characteristics but that the committee had considered precisely what the disadvantages were with EPP. In doing so, they had concluded that the real difficulty in measuring the burden of the disease and response to treatment were paramount. Dr Peter Jackson also explained that these are situations that are shared with other HST evaluations, and that the committee use a lexicon of methods to deal with such situations which represent methods of indirectly gauging the response to treatment. Dr Peter Jackson also made the point that while there are things that NICE itself can do to overcome these challenges, there are things that NICE requires help from others to do and in this instance, help was either not forthcoming or was slow in coming.

55. Tim Johnston suggested that the legal obligation doesn't apply to Clinuvel and that while it was absolutely right that Clinuvel engaged (and Lachlan Hay had stated there were many examples which referred to the company seeking to engage NICE) the legal obligation applied to the public authority. It appeared that the major reasonable adjustment from NICE was whether or not Clinuvel should have conducted a vignette study. That was not the correct approach in the opinion of the company although it agreed that it was extraordinarily difficult to capture the disbenefits of this disease.

56. Following questioning from the panel about how the committee had advanced equality of opportunity in the course of its obligations, Dr

Peter Jackson responded that the committee had made adjustments, which they thought would allow a proper assessment and may enable them to reach a positive conclusion.

57. Dr Peter Jackson explained that the committee was very conscious that it not only had duties under the Equality Act, but that it also had duties under the Health and Social Care Act (HSCA) to balance the costs and benefits of treatment. Apart from getting further evidence, it seemed difficult to see what further adjustments the committee could make in its processes without failing in its duties under the HSCA.

58. Richard Diaz added that if the committee followed the Clinuvel argument, any unique treatment should be waved through without any other consideration.

59. Tim Johnston stated that it was not their submission that any new product should be waved through but rather that the right questions needed to be asked and the right adjustments made. In this case, the decision not to flex ICERs is what it really came down to. He claimed that NICE was prepared to look at other studies, but not flex ICERs because it was considered that this would never be reasonable, it seemed. Furthermore, he submitted that NICE should have been prepared to be sufficiently flexible to enable recommendation to a MAA. There appeared to be no recognition in the FED that this was even considered a possibility.

60. Dr Peter Jackson stated that of the plausible ICERs the committee considered, the flexing of the ICER which would have been required could mean denying treatment for 90 people awaiting routine NHS care. It was that kind of magnitude of flexibility required, with an ICER of £1.8m, which was the underlying cause for concern for the committee.

61. Helen Knight, for NICE, added that NICE had understood from the start that trials did not capture the benefits of this treatment. NICE was presented with the most optimistic ICER. The committee deliberated, heard all of the evidence and all of the challenges. She acknowledged that the FED might not have been written in the most perfect way, but the committee had given everything careful and due consideration and the committee concluded that more information needed to be generated in order to get close to making a positive recommendation. Had the most plausible estimate of cost effectiveness been closer to £100k the situation may have been different, but £133k was the most optimistic number the committee had seen, and this was associated with uncertainty and not low enough to 'get over the line'.

62. The appeal panel concluded as follows: It reminded itself that this appeal point related to whether or not NICE had breached its duties under the EA 2010 and exceeded its powers in not making a positive recommendation for the routine commissioning of afamelanotide. The panel considered that the committee had accepted during this evaluation that patients with EPP have a disability and that their decision-making needed to consider the provisions of the EA 2010. Furthermore, the panel considered that the committee had recognised that patients with EPP have substantial disadvantages arising from the application of NICE's usual processes and that they had considered precisely what these were and what their relevance was to this assessment. In this regard, there appeared to be general agreement between the company and the committee, that the real difficulty in measuring the burden of the disease and response to treatment are paramount in this regard. The panel noted that the committee had identified that the provisions of the EA 2010 require that reasonable adjustments should be made to their processes and decision-making in order to put patients with EPP in the same position

as those without. The panel concluded that the panel had considered and undertaken a range of adjustments to their processes with the hope and intention of making a positive recommendation in this evaluation. The panel noted that the expectation of the company and its representatives in their submissions were that this should have extended to providing such flexibility that acceptance of ICERs above the normally acceptable range either to support a positive commissioning recommendation or to enable a MAA should have been applied. It also noted, however, the submissions of the NICE representatives in explaining the degree to which the most plausible ICER was substantially greater (an order of magnitude) than the normally acceptable threshold of cost effectiveness as well as the wider legal and societal duties of NICE in only recommending treatments that are plausibly cost effective. The panel also took account of the efforts that had been made by the committee to propose an approach, through the undertaking of a vignette study, to provide QoL data that would better inform quantitative measures of utility in EPP patients, although this had not been accepted by the company.

63. The panel concluded that in this evaluation, the committee had made reasonable adjustments in its processes in a manner that was maximalist and recognised its wider legal and societal obligations. The panel was satisfied that the committee had taken all the steps it was reasonable to take to put people with EPP into the position they would be in if they did not have that condition. Furthermore, it considered that in its deliberations and decision-making, the committee had advanced equality of opportunity in accordance with the EA 2010. The panel therefore concluded that NICE had not breached the EA 2010 and had not exceeded its powers in not making a positive recommendation for the use of afamelanotide.

64. The appeal panel therefore dismissed the appeal on this point but suggests that the committee consider re-writing the FED to better describe the details of its relevant considerations on this appeal point that were outlined in this hearing.

Appeal by Clinuvel

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

Appeal point 2.1: The committee's decision-making did not follow the relevant NICE Principles

65. Sarah Love, for Clinuvel, stated that a failure to apply NICE principles and standards had been alluded to throughout the hearing. She claimed that the approach to Principle 7: value for money, had been questionable. She described how the panel had heard that ICERs may not always be robust but there were no other alternatives to ICERs proposed. She claimed that there was no acknowledgement of any broader considerations beyond ICERs in the FED conclusions and discussion of whether or not to recommend afamelanotide. She submitted that costs and benefits alone were not enough to make a recommendation and that the relevant sections in the FED, 4.42 and 4.58, provided only a brief and superficial discussion of other factors that had been considered by the committee. Sarah Love also claimed that applying NICE principle 7 paragraph 22 requires that consideration of cost effectiveness needs to take a broad view since this is a lifelong condition with significant and multiple impacts and all factors with potential impact had not been considered by the committee adequately in this evaluation.

66. Richard Diaz, for NICE, explained that the ICER was not the only measure used in this evaluation. In this case, there was a path to

measuring cost effectiveness through the recommendation of undertaking a vignette study. Nonetheless, he stated that the ICER is the best measure of health and its use by NICE in evaluations has been consulted on, accepted and is underpinned by the health economic expertise on the HST. The committee can consider other factors and, in this case, had indeed done so. He acknowledged that the committee could perhaps have done a better job in drafting the FED in describing these but, in his opinion, it was fairly comprehensive in this regard and had been written in a manner that explained the committee's thinking in sufficient detail. He concluded by saying that if there were areas that could have been explained more clearly, NICE was happy to do so.

67. Following questioning from the panel, Sarah Love clarified that people in England and Wales were referred to when reference had been made in submissions about populations.

68. Following questioning from the panel, Dr Peter Jackson, for NICE, stated that the fact that afamelanotide is the only licensed treatment for EPP is not unusual in the work of the HST evaluation committee. Indeed, he explained that there being no other alternative treatment or the fact that available treatments are highly ineffective are requirements for entry into the HST programme.

69. Dr Jasmin Barman-Aksozen, for IPPN, noted that HST 4 and HST 5 were both evaluations in which existing therapy was tested against a new approach or replacement therapy and was considered to have the same efficacy and safety as the newer version.

70. Helen Knight, for NICE, informed the panel that the HST programme is for very rare and usually very severe conditions. The fact that there are no other standard treatments available for EPP is therefore not an unusual situation in an HST evaluation. Routing technologies into the HST programme inevitably means that other services with the

potential to achieve more health in the wider patient population are displaced. She further explained that the intention in this evaluation was to make sure that all additional clinical benefits were captured.

71. The appeal panel concluded as follows: The panel reminded itself that this valid appeal point related to the extent to which the committee's decision-making had reasonably adhered to NICE principles with particular regard to the range of factors that had been considered by the committee to inform its conclusions about the benefits and costs of afamelanotide in patients with EPP. During the hearing, the panel, in considering this appeal point, had already considered Clinuvel appeal point 2.2 (see later), which had also required an exploration of the full range of factors that had been considered by the committee in reaching its recommendations. The panel noted the HST evaluation committee's primary objectives are to assess clinical and cost effectiveness and these are undertaken through a focus on the consideration of ICERs which themselves are informed by the results of the clinical studies. Whilst ICERs are not the only measure of an assessment, they are central to the conclusions about cost effectiveness. In this evaluation, the panel were persuaded, following the discussion of this appeal point and Clinuvel appeal points 2.1 and 2.2 (see later), that the committee had followed NICE principles in the manner in which it had considered the validity and weight of a range of evidence of effectiveness measures that included but went beyond just the ICERs. The panel understood the challenges posed by the uncertainties associated with the ICER calculations in this evaluation and the concerns that these had not fully captured the treatment benefits of afamelanotide. It noted the proposals that had been made by the committee to enhance the capturing of data to better understand the impact of afamelanotide on the lives of patients with EPP. The appeal panel were convinced that the testimonies of EPP patients had been considered by the committee and had been

impactful on their holistic understanding of the disease. Nonetheless, it was persuaded that while the committee had acknowledged the innovative nature of this treatment and the potentially life-changing benefits for patients with EPP, the degree of uncertainty that remained in the minds of the committee members about the plausibility of cost effectiveness limited the extent to which any additional factors could drive a positive recommendation.

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

Appeal by Clinuvel

Appeal point 2.2: It was unreasonable for the committee to conclude that afamelanotide could not be recommended for funding on the basis of the ICERs falling outside the normal range in the HST Process Guide

73. Sarah Love, for Clinuvel, stated that in 2018 the committee considered ICERs ranging between £1.2m and £1.8m. By the time of the second FED in 2023, the range of plausible ICERs had now come down to as low as £133k. She went on to say that if one considered the price at which Clinuvel would make afamelanotide available, this figure came down further to £121k. The committee accepted that this lower end ICER was plausible. She further submitted that even before consideration of a MAA and further data collection, the committee were at the point where a 17.5% reduction would get NICE within the acceptable ICER threshold. She added that one small exploratory study had led to a huge improvement in the ICER and there is a possibility that an ICER of £121k may even be pessimistic since it might not have captured all the treatment gains from afamelanotide. Under these circumstances, she proposed that the committee should have made a structured judgement, as outlined in paragraph 55 of the HST methods guide, that refers to the degree of certainty, the captured benefits, the degree of innovation and other special considerations or non-health benefits that are relevant to the

evaluation. She questioned whether the committee had looked beyond ICERs and considered that cost effectiveness was possible and realistic even if the ICERs were over £100k. She concluded that ICERs were not the sole mandatory touchstone of cost effectiveness and claimed that little flexibility had been applied by the committee when the ICER was above £100k.

74. Dr Peter Jackson, for NICE, stated that the starting point in the evaluation was to calculate the QALY-based ICERs, as outlined in the HST Methods Guide. If the ICER was below £100k, unless there was heavy uncertainty, a positive recommendation would have been fairly straightforward. He went on to explain that with an ICER above £120k, other factors were unlikely to overturn the discrepancy, but if the ICER was close to £100k, the committee would consider other factors to see if any of them are particularly strong with this technology that would suggest that an additional allowance should be given in applying the ICER acceptability threshold.

75. Dr Peter Jackson outlined that in this evaluation and after consultation, the ICER remained the primary tool for committee decision making. NICE did acknowledge the new price adjustment which reduced the ICER, but the manufacturer base case still showed a £280k/QALY gain which was considerably above the acceptable threshold. Dr Peter Jackson illustrated this by noting that the opportunity cost of a positive recommendation under these circumstances would mean the possibility that 90 patients awaiting routine NHS care would be displaced to provide similar benefit to one patient with EPP undergoing NHS treatment with afamelanotide. The committee concluded that this would represent a poor use of NHS resources if a positive recommendation was made. Dr Peter Jackson also explained that the committee had considered the range of ICERs both in regard to whether or not to make a positive recommendation and also the appropriateness of enabling an application for a MAA.

76. Lachlan Hay, for Clinuvel, explained that the company was not satisfied it understood what the most plausible ICER was in the minds of the committee, nor the process for flexing the ICER or how ICERs were used in this evaluation. The company had raised the point that ICERs should be based on the uniform price (in this case the price was confirmed as £13,209). This was therefore a process point and a substantive complaint because if any meaningful weight had been given to non-health related quality of life, the committee may have reached the view that the right answer was to flex the ICER.

77. Sarah Davis, for NICE, clarified that the ICER threshold for HST is £100k. There is no £120k threshold in NICE methodology. In this case, the committee looked at the threshold and then looked at how far away the plausible ICERs were. Sometimes it was really clear but sometimes the scenarios were uncertain. In this case, if the FED did not provide a very clear statement of the most plausible ICER it was because there was so much uncertainty that the committee did not have a most plausible ICER in mind. Rather, there was a range and within that range, it was clear that the lower ICERs were optimistic and only existed because NICE had done further analyses based on data that was not provided by the company. Sarah Davis further explained that the risk of giving a positive recommendation based upon the calculated ICERs was too high due to the high level of uncertainty involved. The description about an “order of magnitude” captured the difference between the most optimistic ICER and where the committee's preference lay in terms of the most plausible ICER. Because of the magnitude of difference between the committee’s preference and the threshold, it did not feel that a reasonable adjustment would be possible in regard to flexing the acceptable ICER range in this instance.

78. Lachlan Hay responded by stating that the company had been very consistent in its approach to pricing since one uniform price existed

for this product, the price at which Clinuvel would make afamelanotide available to the NHS. If it was understood that the £121k ICER was only for the MAA consideration, then one could draw the conclusion from the discussions that had been had with NHS England that there was no concern about displacement costs because the budget for MAA was ringfenced.

79. Following questioning from the panel, Dr Peter Jackson confirmed that for a MAA, separate funds are available to avoid an impact on routine commissioning but that a recommendation for routine commissioning is linked to a lost opportunity to fund treatments for other patients. He clarified, therefore, that the consideration of displacement costs refers to a decision for routine commissioning.

80. Helen Knight, for NICE, emphasised that even when considering MAA, the product in question must have the potential to be cost effective.

81. The appeal panel concluded as follows: it reminded itself that this appeal point related to the reasonableness of the decision that was made by the committee to not make a positive recommendation for afamelanotide on the basis of the ICERs falling outside of the normal range, as stated in the HST process guide. In arriving at its decision, the panel understood the paramount importance that the committee gave to most plausible ICERs and their proximity to the threshold of cost effectiveness acceptability. In this evaluation, the panel was persuaded that the committee had considered a wide range of ICERs but had concluded that the most optimistic of these was above the acceptable threshold and was associated with considerable uncertainty. The panel also noted that the committee had struggled to define a most plausible ICER but that the ICER range that it considered to be most plausible was described as 'an order of magnitude' higher than the acceptable threshold. In reaching its

decision to not make a positive recommendation, the panel were satisfied that the committee had taken into consideration a range of factors beyond just the ICER levels. It noted that the range of benefits and costs, the certainly of the evidence, degree of innovation, the magnitude of incremental benefits as well as the health-related benefits, had been considered by the committee. The panel considered that the committee's conclusion that none of these was sufficiently compelling to provide adequate support for a positive recommendation in the face of most plausible ICERs that were well above the acceptable threshold for cost effectiveness was reasonable.

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

Appeal by Clinuvel

Appeal point 2.3 The reasons in the FED for refusing to recommend an MAA were illogical

83. Sarah Love, for Clinuvel, stated that the purpose of managed access was to give faster access to promising new treatments that might not otherwise be recommended because of uncertainty over clinical effectiveness or cost effectiveness. More evidence is collected during the period of managed access to resolve the uncertainties and there is a financial arrangement in place for that period. She submitted that the committee accepted that the medication worked but stated that there was uncertainty over the extent of clinical effectiveness and cost effectiveness. The company had raised concerns about access to the MAA due to a perceived lack of flexibility from NICE and since June 2022, the main route to MAA has been the Innovative Medicines Fund (IMF), but this did not exist when this evaluation began. Sarah Love explained that the IMF principles impose significant financial

requirements on companies such as a requirement to continue treating patients after the MAA who start during MAA. Although there was an assumption of risk for the company, she explained that this was accepted by Clinuvel since they considered that they had no choice but to do so. She further submitted that qualification for the IMF does not require there to be evidence that a treatment is cost effective. No requirement, for example, exists to point to an ICER under £100k she claimed, and this is made very clear in principle 3 of the IMF. The discussions about the MAA, had, however, focussed on the ICER getting close to £100k. In summary, she submitted that the committee had conceded that Clinuvel's data collection proposals could have generated utility values; that Clinuvel had agreed to the IMF principles; and that Clinuvel had put forward risk-sharing proposals.

84. Saran Love went on to explain that the results of one small study had reduced the ICERs down to £121k and that there was a very strong risk that none of the studies and therefore the ICERs had fully captured all of the patient benefits of afamelanotide. The company therefore deemed it inappropriate to focus on the ICERs alone in considering the question of a MAA.

85. Lachlan Hay, for Clinuvel, expressed concern that it was clear from his discussions with NHS England (NHSE) that they were only interested in the price of the product. He expressed the view that this was because NICE had briefed NHSE that there was no route to cost effectiveness.

86. Richard Diaz, for NICE, clarified that in regard to the MAA, the budget impact was not the test being applied by NICE but rather cost effectiveness and value for money for the NHS. The prerequisite for entering a MAA is that the treatment needed to be plausibly cost effective. In this case the most optimistic ICER was still above the

threshold and while a 17.5% reduction would have brought it down to the threshold, uniform pricing for afamelanotide made that impossible. Additionally, the company proposal for data collection was insufficiently detailed to allow the committee to determine whether uncertainty would be resolved at the end of the MAA. Furthermore, he pointed out that the company had not reached a commercial agreement with NHSE either. He explained that although NICE had tried its best to move its position significantly, having accepted the newly submitted evidence from IPPN that enhanced the committee's understanding around this condition, the committee had no option but to not recommend a MAA.

87. Following questioning from the panel, Dr Peter Jackson, for NICE, explained that the wording of the IMF principles does not give the committee a high degree of flexibility in applying criteria for cost effectiveness. It is made absolutely clear that the committee need to believe there is a plausible ICER of below £100k and in this regard, there is less flexibility for MAA than there is for recommending routine commissioning.

88. Lachlan Hay responded that the company perceived the biggest barrier to a MAA was NICE's representation to NHSE being unfavourable despite the company putting forward innovative approaches to help manage risk, presenting a budget impact and accepting that uncertainties needed to be addressed.

89. Sarah Love challenged the view that NICE could not make a recommendation unless the ICER was below £100k. Principle 3 referenced cost effectiveness and she questioned whether NICE interpreted that as meaning that there needed to be plausible ICER of below £100k and explained that this did not resonate with the stated barrier to a MAA being the need for a better proposal for data collection to resolve uncertainties.

90. Helen Knight, for NICE, responded on behalf of the committee. The committee had not stated that they had seen plausible potential for cost effectiveness in this case. The decision making ICER for a MAA was around £133k and even factoring in other elements outside of the ICER, the committee did not feel there was sufficient evidence to conclude that there was a plausible potential for cost effectiveness. She explained that the committee had been hopeful that there may have been a commercial arrangement negotiated which could provide the potential for value for money and allow a period in the MAA IMF. Helen Knight also reflected on the fact that NICE had previously successfully supported access with other companies who had entered into discussions with NICE and in this case, NICE had also tried to work with the company.

91. Following questioning from the panel, Helen Knight confirmed that newly submitted data from IPPN had had a big impact on estimates of cost effectiveness but, she explained, there were challenges with these data. Although new ICERs were calculated by NICE by inputting the IPPN data into the model, the committee were not comfortable that this package demonstrated plausible cost effectiveness that could be considered for inclusion in the IMF.

92. Richard Diaz clarified that no additional data had been submitted by the company and that the data from IPPN had been entered into the model by NICE in an attempt to find a constructive way forward. Furthermore, he explained that NICE could not share the model with IPPN in the absence of agreement from the company.

93. Helen Knight explained that the list price had been considered in this assessment because that was all that was possible to do. The only other commercial arrangements NICE could consider would be those agreed with NHSE. If there was only a list price and no other

commercial arrangement, NICE were obliged to take the list price into consideration in its assessment.

94. Following questioning from the panel, Richard Diaz provided clarification on the normal sequence of evidence submission and consideration. Usually, the company makes a submission and creates their base case; then this is evaluated by the ERG who interrogate it and come to their own conclusion as to their preferred assumptions; ultimately, the committee then decides what their preferred assumptions are in informing its decision-making. He went on to explain that in this case, there had been a challenge in getting the process to happen in this way. NICE had had to extend consultation periods to enable the company to provide a response; NICE had been as flexible as possible to guide the company through the process and the commercial considerations; but because of communication difficulties this process had not always worked.

95. The appeal panel concluded as follows. It reminded itself that this appeal point related to whether the reasons stated in the FED for refusing to recommend afamelanotide for a MAA were illogical or unreasonable. The panel concluded that the possibility of a MAA had been carefully and appropriately considered by the committee but that they were unable to recommend this predominantly because of the absence of an ICER that demonstrated plausible cost effectiveness. The panel also noted that there were concerns expressed by the committee that the data collection plans that had been submitted by the company were of insufficient detail to be confident that they would resolve uncertainties within a MAA. The panel noted that although the most optimistic ICERs that were generated were £133k, these were not considered by the committee to be the most plausible and were associated with considerable uncertainty. The panel also noted that the company had been prepared to accept the financial risks and conditions of the IMF but had applied uniform pricing to

afamelanotide. The panel also noted that a commercial agreement had not been reached in discussions between the company and NHSE. The panel concluded that it was reasonable for the committee not to recommend a MAA and that an explanation for this was outlined in the FED. The panel considered, however, that the wording of paragraph 4.54 of the FED could be clearer in explaining that the need for the resolution of substantial residual uncertainties related to their ability to make a positive recommendation for routine commissioning of afamelanotide rather than as a mandate for a MAA.

96. The appeal panel therefore dismissed the appeal on this point but recommends that the committee consider re-wording paragraph 4.54 in the FED.

Appeal by Clinuvel and IPPN

The following appeal points were considered together:

Appeal point Clinuvel 2.4 The emphasis placed by the committee and NICE on the importance and usefulness of a vignette study to inform the QALY was irrational

Appeal point IPPN 2.2 It is unreasonable for the committee to assess the EQ-5D feasibility study as less scientifically valid than vignette studies

97. Sarah Love, for Clinuvel, highlighted that the EMA in their assessment had concluded that there were no available scientific instruments to fully measure the benefits of afamelanotide in EPP. The committee agreed that it was not re-examining those conclusions. She explained that the questions posed for the EMA were not the same as those for the HST committee. The finding of no available scientific tools is a very important one when considering how the committee went about evaluation. The committee, she claimed, had viewed a vignette study as a pre-requisite for access to the MAA. A vignette would have

provided a new qualitative exercise involving a small number of patients with sufficient quality issues. She questioned what exactly a vignette study would show that other studies would not and whether there was there a cogent reason to place so much weight on a vignette study. The company, she submitted, could not comprehend why such a study was being held out as the only way to plug gaps in knowledge and the company had been accused of not being willing to undertake a vignette study.

98. Sarah Love went on to explain that three things emerged very clearly for the company. Firstly, this really was not just a preference, but a very strong preference for a particular form of evidence. In reality it appeared to be a requirement. Secondly, a requirement was being imposed even though the EMA said that there was no satisfactory tool to assess this condition. Thirdly, the fact that the company did not do a vignette study was held against it, despite conveying its reasons and the concerns shared by others e.g. patient groups.

99. Sarah Love further submitted that in terms of other evidence, the IPPN had submitted 5 peer reviewed studies. The committee evaluated these as described in 4.29 and 4.30 of the FED and said that none could inform the economic model. The committee was looking for any other evidence possible to feed into an economic model. Two difficulties arose in her opinion. Firstly, uncertainty required more data to make it less uncertain. This could then hopefully be backed up by better data in a MAA. Secondly, the company considered that a vignette study was not the only evidence and may not even have been the most reliable so it was unclear why it was it preferred over any other form of evidence.

100. Sarah Davis, for NICE, responded that IPPN had produced a survey of 18 patients with assessment of QoL using EQ5D. This was a very small sample size compared to that which one would normally expect

in studies considered by the committee. It was indicative of what the utility values could be, but not robust enough for NICE to have confidence in it. NICE also had concerns about how patients were selected for this study since limited details about this had been provided. The submitted feasibility study data also led to concerns in the minds of the ERG and committee about robustness since asking patients to think back to their previous health state is challenging and introduces the potential for recall bias in influencing the estimates produced.

101. Dr Jasmin Barman-Aksozen, for IPPN, explained that the IPPN had accepted the challenge of evaluating QoL in patients with EPP but had stated that EQ5D assessments, directly administered to patients was their preferred option in terms of generating further data. Hence, the IPPN had conducted a feasibility study and had expressed strong reservations about a vignette study. If members of the public were involved in generating quantitative QoL data, one would need be sure that key aspects of EPP would need to be understood and IPPN had experience of people not understanding EPP. Dr Jasmin Barman-Aksozen submitted that that the IPPN EQ5D study was now complete and provided utility values comparable to patients in a treatment arm compared to the normal population. In summary, the IPPN study was considered by them to have higher validity since it considered that the data is superior to those that could be produced with a vignette study and such data has already been accepted in other situations as valid.

102. Sarah Davis stated that NICE's duty is to make an assessment of value in order to make a recommendation that reflected a fair value for money for all patients in the NHS. To do this, NICE needed to make an assessment of QALYs. The company's estimate of QALYs was probably too small because it was based on Randomised Controlled Trial (RCT) data. The company's arguments that it was not possible to perform calculations based on RCTs in this case was

accepted by the committee. She went on to explain that EPP-QOL was favoured by the committee to reflect QoL in EPP but it was not possible to generate QALYs from those data. NICE therefore explored the use of proxy conditions that were proposed by the company and the ERG but neither of these reviews generated a favourable QALY. She outlined that the committee considered that a vignette study would therefore be helpful based on experience from other HST evaluations. The big benefit of this approach, she explained, is that vignettes enable one to bring together rich qualitative data from patient groups and then produce utility estimates derived from the general population. Vignettes were a strong preference for NICE since they avoid issues of patient adaptation to the condition and sometimes the non-patient population may see benefits that patients don't.

103. Sarah Davis also discussed suggestions that the company had made regarding what they would do if a MAA went ahead. e.g., map from EPP-QOL. The difficulty that was perceived with this approach was that a larger group of patients would be required than was possible given the disease rarity, so it would be difficult for the company to achieve sufficient results in the time available. She explained that the committee did not feel, having considered what the company proposed for data collection in an MAA, that it would meet NICE's requirements but made it clear that the performance of a vignette study was not mandated by the committee although a more detailed proposal would have been helpful and would have been considered by NICE.

104. Following questioning from the panel, Dr Peter Jackson, for NICE, explained that a vignette study is the kind of study most likely to be successful in a short time period, using a small number of patients at minimal cost and was, therefore, considered by the committee to be

the best route available to the company to generate new and useful additional QoL data.

105. Following questioning from the panel, Lachlan Hay, for Clinuvel, stated that there had been extensive discussion on vignettes during the course of this evaluation which were, for example, detailed in evaluation committee meeting 4 and 5. He claimed that after the third committee meeting and a subsequent delay, it was explained during the stakeholder workshop that a vignette study would be required before any MAA could be agreed to improve the value for money assessments. In this regard, it was considered that NICE had mandated a vignette study prior to consideration for a MAA. He explained that no other country had demanded such a new study before approving the drug. He reminded the panel that the EMA had deemed there were no instruments to assess this treatment beyond what we had already and that the company had proposed methods of data capture in a MAA that were closely aligned to NICE's preferred methodology. He therefore submitted that the company disputed that it had not engaged in attempts to generate further data but had considered that conducting a post authorisation safety study and mapping from EPP-QOL, was a more effective way of doing this.

106. Furthermore, Lachlan Hay challenged the overall remit of NICE and questioned whether NICE was perhaps seeing itself as a *de facto* regulatory authority.

107. Following questioning from the panel, Lachlan Hay stated that the company understood this disease and worked closely with expert physicians and patients. It disputed that a small qualitative study was the best way to arrive at new evidence although NICE was insisting on this, so the company questioned the expertise, remit and ability of NICE to design such a study.

108. Dr Jasmin Barman-Aksozen explained that they had asked NICE whether it would be acceptable to conduct a vignette study in an academic centre, but these proposals were not met with any interest. She claimed that patients knew their condition, so it was best to ask them about their own QoL rather than use members of the public and that this is what had been achieved with the additional QoL data submitted. She went on to explain that IPPN acknowledged that the additional studies had been small but pointed out that vignette studies were also very small, sometimes having as few as five experts participating. In the studies submitted, the IPPN data was generated by patients with involvement of an academic centre; data was collected in a scientifically valid way and published in peer reviewed journals; while there were some limitations, these were discussed in these publications including the issue of recall bias which, she claimed, was minimised through the collection of prospective data. Finally, she stated that NICE had set a precedent to accept proxy condition utilities in HST16, in which IPPN had been a stakeholder.

109. Sarah Davis stated the preferred method proposed by NICE was to get lots of members of the public to assign QoL values in a vignette study. It was proposed that 100 to 200 people could provide data points and, she explained, it was more acceptable to have a large number of members of the public than a small number of clinicians involved in the process. She went on to outline how NICE had reviewed a wide variety of other potential approaches to obtaining estimates of utility values and by considering IPPN's data, NICE had demonstrated flexibility in considering unpublished data and datasets with small numbers of patients. She explained that the ERG had looked at several sources of evidence, some of which did not generate cost effective ICERs. NICE had arrived at the conclusion that a vignette study would be the best means of acquiring useful QoL data on the basis of expert advice after having considered other

alternative ways of measuring benefits with this treatment. In this regard, she referenced the Decision Support Unit (DSU) report that had been published after the EMA had undertaken their assessment of afamelanotide and which, therefore, had identified new approaches to assessing QoL data.

110. Dr Peter Jackson, for NICE, explained that the committee did not mandate the undertaking of a vignette study but gave a strong steer in this direction. He explained that without these data, the committee considered that it did not have sufficient information to overturn a negative recommendation in the face of high ICERs and the absence of any other reliable data sources. He further explained that EQ5D data was considered by the committee but that it had identified serious limitations in these and concluded that the data were nowhere near a standard that would support a positive recommendation.

111. Richard Diaz, for NICE, further explained that the DSU report is a technical document that is used to support the evaluation process, tackling difficult and emerging areas in health economics. The DSU report helps to drive improvement and development of methods in this area which are widely shared and peer reviewed and also sit alongside NICE's other methods.

112. Sarah Love confirmed that Clinuvel's approach was based on EPP-QOL as required by the EMA and that this was intended to be a lot closer to NICE's reference case. She also explained that the ERG had said that it preferred using EQ5D data in accordance with the NICE reference case.

113. Dr Peter Jackson confirmed that the first stage of a vignette study is getting clear scenarios to describe different health states. This tended to be an iterative process, between clinical experts and patient experts, to define the scenarios and be sure they captured everything that was really important to patients. He explained that providing QoL

scores for the scenarios can be undertaken by members of the public but also by clinical experts and this therefore incorporates the input of those that know the disability associated with EPP. He explained that NICE has accepted vignette studies conducted in this way in the past.

114. Helen Knight, for NICE, confirmed that the committee had considered all of the data that was available to it and would have been willing to make a recommendation for MAA based on the IPPN data. It wanted to ensure, however, that during MAA there would be further studies undertaken, including a form of vignette study. She went on to explain that the committee wanted to see evidence that would provide a higher degree of certainty to support value for money of afamelanotide, and vignettes were considered to be a good method of doing this and were relatively easy to conduct. She emphasised that a product can only go into a MAA if there is an agreed approach to resolving uncertainties and that the committee has a duty to ensure information is obtained that will resolve those uncertainties. She explained that while the committee was open to having discussions about the vignette study and how it might be delivered, it wanted to be assured that there would be research undertaken in the MAA period that would effectively resolve uncertainty.

115. Sarah Davis added that for each evaluation, NICE needs to look at all factors, e.g. vignettes compared with trial data. In this case, it was considered that a vignette would allow an assessment of treatment versus off treatment QoL benefits. Dr Peter Jackson explained that the committee had already considered alternative methods such as the use of proxy conditions and would also have considered alternative methods had these been proposed such as mapping from EPP-QOL to EQ5D or preference weighting for EPP-QOL. Nonetheless, he explained that the advice of experts was that these would have been much more costly to undertake.

116. Sarah Love stated the company was still confused as to whether the further study had to be completed before a MAA was considered or whether NICE could recommend a MAA as long as there was an acceptable proposal for research to resolve uncertainty.

117. Dr Peter Jackson stated that having a plan for data collection (of an acceptable form) is not the only issue for qualification for an MAA but that there is a requirement that there is a proposal that is potentially cost effective. One of the ICERs seen by the committee has to be potentially cost effective at the outset for recommendation for a MAA.

118. Richard Diaz pointed out that there is no Patient Access Scheme (PAS) in place for this drug.

119. Lachlan Hay stated the company had put forward proposals to NICE about data collection based on post authorisation data collection and including the PAS that is in place in Scotland. He claimed that NICE was given this information many times, the last occasion being in September 2022. He challenged, therefore, the suggestion that the company had not come forward with alternatives to vignettes and considered that there is a very well-established data collection study in place.

120. The appeal panel concluded as follows. It reminded itself that these appeal points relate to the extent to which it was unreasonable or irrational for the committee to place an emphasis on the importance and usefulness of a vignette study to inform the QALY as well as the extent to which it was unreasonable for the EQ-5D feasibility study to be considered by the committee to have been scientifically less valid than vignette studies. The panel noted that the committee had given careful consideration to the new QoL data that had been submitted by IPPN that had included the EQ-5D feasibility study and had incorporated those data into revised cost modelling calculations. The panel noted, however, the concerns that had been expressed by the

ERG and supported by the committee about considerable uncertainty associated with the newly submitted data. These uncertainties were as a result of the small numbers of patients included, the lack of clarity around patient selection, the possibility of recall bias by the patients included and the absence of a control. The panel concluded that it was reasonable for the committee to question the scientific validity of the newly submitted data because of these legitimate concerns and to seek alternative forms of QoL data that may better inform the quantitative estimates of cost effectiveness.

121. In this regard, the panel were persuaded that the committee had acted reasonably in recommending the undertaking of a vignette study. It noted that this approach was consistent with the recommendations of the published and widely accessible DSU report that guides NICE practice in generating utility values from QoL data in the absence of compelling published data. The panel were persuaded that while the committee had given a firm recommendation about the undertaking of vignette studies, this was not mandated. It also accepted that in the absence of more robust QoL data to inform utility values there would be continued residual uncertainty surrounding the ICER estimates used to inform judgements about cost effectiveness.

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

Appeal by Clinuvel

Appeal point 2.5 The failure to place any (or any adequate) weight on treatment adherence data was irrational

123. Sarah Love, for Clinuvel, stated that this evaluation had collated significant evidence and that treatment adherence data was being presented as a proxy marker for efficacy. The committee, as it is required to, said it would consider all of that evidence but adherence

data, despite being as high as 98.5% was not deemed to be a marker of effectiveness. She explained that the company were concerned that adherence data was disregarded as not being a direct marker of efficacy. She submitted that adherence data provide information in areas such as cost and showed something about the value of treatments to patients. Indeed, in this case, even though patients travelled vast distances for implants at specialist centres across Europe, adherence was high. She also proposed that the use of adherence data would enable a judgement of the magnitude of treatment benefit even though it does not always quantify the size of benefits. The committee concluded that the treatment was effective but were unable even to hazard a guess at the magnitude of benefit. She claimed that if the committee had not irrationally dismissed adherence data, then the conclusion might have been different.

124. Lachlan Hay, for Clinuvel, added that clinical demand for the drug existed after clinical trials since patients and expert physicians had asked to continue the drug. He explained that that had been a major factor driving the company to continue to engage with NICE. In doing so, the company had sought to provide the vast amount of adherence data available, and it was unclear to the company why NICE had been so dismissive of adherence data when there was precedent for it being considered in other HSTs (Fabry's disease, Gaucher's disease and SCS HST).

125. Dr Peter Jackson, for NICE, said that NICE agreed that adherence appeared to be high, when compared with adherence rates with other treatments such as oral treatments for preventing disease and treatments for conditions such as prostatic malignancy. In terms of individual patients, the relationship between magnitude of benefit and adherence was deemed less certain, however. He explained that the committee concluded there was no discernible direct link between adherence and magnitude of benefit, numerical or qualitative, which

might have enabled an adjustment leading to a positive recommendation.

126. Following questioning by the panel, Dr Peter Jackson explained that if the ICER figures had been very close to the threshold of acceptability, rather than twice the threshold, consideration of the additional information from adherence data may have helped address areas of uncertainty. On the other hand, this was not possible since the ICER was an order of magnitude too high. He further outlined that NICE had considered the adherence data but could not be certain about how big an effect it demonstrated. When the committee saw how high the ICERs were above the acceptability threshold, the committee looked at other factors and asked whether any of those could overcome the difference between the calculated ICER and the threshold ICER. If there had been only a small discrepancy, he explained that adherence data would have carried weight alongside other data to 'push it over the line.' With such a large discrepancy, however, it was unlikely that any of these other factors could have 'pushed it over the line'.

127. Following questioning by the panel, Dr Peter Jackson explained that the extent to which additional data sources such as adherence data are influential in the minds of the committee in informing decisions about cost effectiveness depends on the extent to which the most plausible ICERs are or are not close to the acceptable threshold. He stressed again that the committee would have used the adherence data alongside other factors had the ICERs been closer to the threshold. For example, 20% above the threshold is the area where the committee might very much focus on these additional factors, bearing in mind their responsibility to balance cost and effectiveness. The committee had wanted to recommend the use of afamelanotide in this evaluation if possible so that patients could access this treatment but had concluded that it was unable to do so because of the high

levels of uncertainty associated with cost effectiveness that the committee did not wish to magnify.

128. Following questioning from the panel, Dr Peter Jackson explained that the literature about the link between adherence and benefit is very uncertain. He explained that the committee had not, therefore, spent a huge amount of time discussing this and had accepted that no strong link exists between adherence and magnitude of benefit. He acknowledged that adherence had been considered in previous evaluations but mainly to inform estimates of cost effectiveness. In this regard, he explained that if patients are not adherent, they no longer carry the costs associated with treatment which can be substantial for a HST. Stopping rules and adherence can therefore have a major impact on cost effectiveness and the ICER. He went on to emphasise, however, that in these previous evaluations, adherence had not been a marker of benefit but merely of cost effectiveness.

129. Lachlan Hay responded for the company and asked at what point all these considerations had been taken into account. The company was informed that adherence data was not relevant and if that was the case, there was no purpose of putting it into the model at all.

130. Sarah Love also expressed concerns that none of these considerations were articulated in the FED. The hearing had been informed that there were potentially situations where it could have been a ‘tipping over the line factor’ and it was important to understand therefore whether adherence data was considered to be relevant or not. She considered that there appeared to be no uncertainty about the adherence data and what it showed but noted that the hearing was being told the relationship between the data and magnitude of benefit and ICER were a concern. She reminded the panel that there is an ICER of £121k so raised the question as to whether this issue should not be re-considered.

131. Sarah Davis, for NICE, provided further clarification on the committee's use of adherence data. She explained that NICE does not and did not use adherence data to denote efficacy. In this case she explained that the data were important in showing that patients valued the treatment; that adherence data added to the picture but could not be used to generate an impact on QALY data; and that comparison with other conditions is not relevant. She also clarified that although the existence of an ICER of £121k was debated, the committee had had to consider current list price, which was reflected in the £133k figure. The previous price was no longer relevant if the list price had changed.

132. Lachlan Hay responded that the company were concerned on 2 fronts. Firstly, that despite the list price being consistent throughout the entire review (Clinuvel having stated the lower price was given to NHS England), NICE had decided to use the Scotland list price. Secondly, NICE was required to consider all the evidence and the HST Chair had now stated in the hearing that some evidence would only have been considered if the ICER had been closer to the acceptable ICER threshold. He claimed that such information was never given to the company in any of the committee hearings or in the FED.

133. Dr Peter Jackson noted that the discussion was drifting to consider ICERs based on the new information provided by the IPPN, which the committee was willing to consider when thinking about an MAA but did not think was of a sufficiently robust nature to allow it to make formal recommendations. There was a difference between the ICERs considered in making a formal recommendation for use, and those considered to determine whether it might be possible recommend a MAA. He explained that in relation to an MAA, the wording of the requirements are based on the ICER alone, and not on the ICER alongside qualitative surrounding factors.

134. Helen Knight, for NICE, reinforced the fact that the committee had considered adherence data and had looked at all the evidence presented to it. The difficulty was in discerning what weight the committee could give to adherence data. The committee looked throughout at the magnitude of clinical benefit and concluded that adherence data did not add anything to the other information that was considered.

135. The appeal panel concluded as follows. It reminded itself that this appeal point relates to whether it was reasonable for the committee to have failed to place any (or any adequate) weight on adherence data. The panel were persuaded that the committee were aware of the high adherence rates with afamelanotide and had considered these in their decision-making. The panel noted that the high adherence rates were considered a reflection of the value that patients gave to the treatment and indicated a high level of compliance and acceptability of the treatment. The panel were not surprised by this since this is the only treatment available for EPP and one would anticipate high adherence rates (particularly in a clinical trial setting where adherence rates are higher than in real world data), particularly since afamelanotide does not appear to have any significant adverse effects. The panel were convinced by the argument that there is insufficient evidence to support the use of adherence rates as a direct marker of clinical effectiveness, although they may be used in some circumstances to influence details of models of cost effectiveness such as by reference to treatment stopping and duration. Overall, the panel concluded that in this evaluation, and in light of the high ICERs that the committee considered to be most plausible, it was reasonable that the committee did not give substantial weight to adherence rates in influencing its decision-making and in making a negative recommendation for the use of afamelanotide, and that they had acted logically and reasonably in this regard. Furthermore, the panel considered that the

reasoning had been adequately described in the FED given that this was not a factor that had played a central role in its decision-making.

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

Appeal by IPPN

Appeal point 2.1 Using a shorter than usual time-horizon for the economic model was unreasonable given that EPP is a lifelong chronic condition and the justification for the decision discriminates against patients aged 70 years and older.

137. Dr Jasmin Barman-Aksozen, for IPPN, stated that QALYs are calculated as a product of benefit and time over which that treatment is used and that NICE prefers a lifetime horizon. She had conducted a review of concluded HST evaluations and found that these had used a median of 100 years and a maximum time horizon of 125 years. In this case, a time horizon of 60 years was used for afamelanotide, so it seemed that patients had been disadvantaged. She understood that the committee had determined that a longer time horizon would mean a decline in utility, but IPPN were concerned to know whether this reflected the normal approach of NICE in calculating age adjustments. She went on to explain that NICE had explored a time horizon of 70 years and that patients with EPP usually start this treatment at 22 years of age (the median age of diagnosis). She emphasised that although the EMA had indicated that this treatment is available for patients up to an age of 70 years, it also says that it can be used over the age of 70 years if this is guided by extra laboratory tests and careful vigilance. IPPN deemed that it would be unfair to exclude patients over 70 years of age from receiving this treatment.

138. Victoria Kelly, for NICE, stated that the committee ran a scenario to extend the time horizon from 60 to 70 years. This led to a very slight increase in the most optimistic ICER. She explained that increasing the time horizon increased the undiscounted QALYs gained, and this was validated by an academic group and presented to the committee. On the other hand, she also explained that the ICER increased very slightly because utility declined with advancing age while the cost remained constant. She outlined the fact that the rationale for not extending the time horizon in this evaluation was primarily because it slightly increased the ICER; that it had a negligible effect on undiscounted QALY gains; and that it did not reflect recommended use in the older patient population. The committee had highlighted that because of limited data for treatment in older people, afamelanotide is not recommended for people over the age of 70 years. She pointed out that this reasoning was clearly described in the FED.

139. Following questioning from the panel, Sarah Davis, for NICE, explained that cost-effectiveness analysis does not look at different ages specifically. The requirement is to use a time horizon which captures all benefits. NICE will look at different horizons to see if it they change the outcome. The committee were satisfied that use of 60 years was sufficient to capture all costs and benefits since a time horizon of 70 years did not materially change the output and in fact increased the ICER. This was explained by the fact that the average person at age 75 years is less healthy than the average person at age 70 years since there is a natural decline in QoL with old age. As patients get older, the relative cost of an extra year of treatment is greater so that as average health declines with age, QoL gain diminishes with age.

140. Dr Jasmin Barman-Aksozen asked for clarification about whether age adjustment was the usual approach adopted by NICE and why other

technologies had been appraised with longer time horizons. She further explained that there was a theoretical difference that a longer time horizon could make in terms of the total number of QALYs gained which could potentially drive the need for QALY weighting. She claimed that people over 70 years benefitted a lot from treatment since they had time to be outdoors and could really make use of that time. If the time horizon was shorter there would be less time to accumulate QALYs.

141. Sarah Davis explained that if a cost effectiveness model attempted to estimate lifetime gains and selected a short horizon, then they might be too short to demonstrate a QALY gain of greater than 10. In this case, with a time horizon of 60 years, there was a QALY gain of 10 in one of the scenarios and with a time horizon of 70 years, it did not change. So, she explained, that a 60-year horizon was not detrimental but indeed beneficial when considering the issue of QALY weighting. She confirmed that if the committee had selected a 70-year time horizon, it would not have changed the decision nor made any difference to the recommendation.

142. Dr Jasmin Barman-Aksozen sought further clarification about whether an extension of the time horizon to 100 years, as seen with other NICE evaluations, would be appropriate and whether it had been explored.

143. Sarah Davis explained that such an extension was a technicality in extending the models out to the end of the life tables. As one extends into the future, discounting becomes more relevant but so as long as the horizon is long enough to capture all the benefits one did not need to extend it further.

144. Helen Knight, for NICE, added that it was standard practice to have age adjusted utilities in analyses. Most often a lifetime horizon is used, and this would impact, for example, on a life-saving treatment.

Which time horizon is used depends on the circumstances with analyses having different impacts according to the technology considered. She explained that in this evaluation, the company had originally presented a 35-year horizon. NICE extended this because it needed to be long enough to capture all of the significant costs and benefits. In the end, a time horizon of 60 years was adequate to capture all costs and benefits and it produced the most favourable ICER.

145. Helen Knight explained that NICE did accept that this had been quite difficult for the patient group to assess since IPPN did not get access to the company's economic model since these data were considered to be confidential. She also provided clarification on the fact that the 60-year horizon did not preclude the possibility of patients over 70 years of age from receiving treatment since NICE did not include or exclude particular age groups.

146. The appeal panel concluded as follows: The panel reminded itself that this appeal point related to whether it was reasonable for NICE to have used a 60-year time horizon and whether this had discriminated against patients aged 70 years and older. The panel were persuaded that the committee had considered carefully the most appropriate time horizon on which to base its decisions. It noted that the original time horizon submitted by the company of 35 years was judged to be too short to capture all of the relevant benefits and costs and it considered that it was reasonable for NICE to have extended this further to 60 years. The panel were also persuaded that a longer time horizon of 70 years had been explored by the committee and considered that it had been reasonable that this was not felt appropriate since the outcome had been a small increase in the most optimistic ICER with a negligible effect on undiscounted QALY gains. The panel were satisfied that the use of a 60-year time horizon in this evaluation would not have precluded the use of afamelanotide in

patients aged 70 years or older and could not have introduced any discrimination.

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

Appeal by IPPN

Appeal point 2.3 It was unreasonable for the committee to not apply a QALY weighting in the case of afamelanotide

148. Dr Jasmin Barman-Aksozen, for IPPN, accepted that some aspects of this appeal point had already been covered in previous discussions. She said that from the FED, she understood that only discounted QALY gain was considered, and argued that undiscounted QALY gain should have been used. She observed that partial QALY weighting is sometimes applied by NICE when there are uncertainties in the data. In this case, she submitted that the clinical trial data for afamelanotide showed better QALY gains and cost per QALY outcomes than other comparable conditions. She therefore concluded that all of the evidence suggested this was an effective treatment and that QALY weighting should have been applied.

149. Sarah Davis, for NICE, explained that the NICE Methods Guide states that there needs to be compelling evidence of a significant QALY gain i.e. the score needed to be above 10 to apply QALY weighting. She pointed out that the committee had considered undiscounted QALY gain use in line with its usual practice so that there was no inconsistency in this regard. She explained that only one scenario had provided a QALY gain over 10 and this related to the use of the newly submitted IPPN QoL data that resulted in an ICER of £133k. The committee considered how compelling the evidence was that informed this scenario and noted that the data were derived from 2

small IPPN studies. One of these was a treatment survey of less than 20 patients and the second was a small feasibility study. She explained that the committee was left with significant reservations about the quality of both studies. She pointed out that the upper utility value was higher than the general population values for people without health conditions while the lower value was extremely low when considering the limitations inflicted on patients with this type of condition. NICE had accepted utility values under 1, but considered that 0.331 utility for untreated patients was very low particularly with questionable clinical face validity. She explained that the committee had therefore concluded that the QALY gains were insufficiently robust to represent compelling evidence that was needed to support the application of QALY weighting.

150. Following questioning from the panel, Sarah Davis explained that in HST evaluations, QALY weighting is applied when there is a significant gain identified in QALYs. She outlined how this serves to increase the acceptability threshold. She provided the example that if 15 QALY gains existed, the acceptability cost effectiveness threshold could be increased to £150k per QALY. On the other hand, she made clear that NICE could only apply QALY weighting if there is compelling evidence to support the QALY gains.

151. Dr Peter Jackson, for NICE, added that with HST evaluations, there is always uncertainty about the long-term extrapolation of results, but that in this case, the advice the committee received from the EAG was that the additional evidence was insufficiently strong or robust. He explained that in the past, HST had sometimes applied a reduced or partial weighting, by up to 50%, if there was some degree of uncertainty about the QALY gains, but in the present evaluation, the advice from the EAG was very strong that the data should not be relied upon. The uncertainty was therefore regarding the newly submitted IPPN data but there was also a discrepancy between

clinical trial data and what patients were telling the committee and this had created additional uncertainty.

152. Helen Knight, for NICE, confirmed that the committee had used undiscounted QALYs when considering if QALY weighting should be applied in line with their standard practice in all such evaluations.

153. Dr Jasmin Barman-Aksozen said that the FED stated that a discounted QALY gain was used. She then described how the IPPN study had used a generic instrument, so that it could be applied in different conditions. She explained that the lowest utility value stated was for the toxic burn reactions which are actual burn injuries. A comparison of these values with those in people who do not have acute burn injuries is not an indicator of unreliable data she claimed. Furthermore, she explained that it is not surprising that higher utility values in patients on treatment with afamelanotide are seen than in the general public without health conditions since the treatment is regarded by patients as a miracle. Dr Jasmin Barman-Aksozen went on to explain that she has been on the drug for ten years and she sees every day as a miracle.

154. Sarah Davis stated that the committee accepted that patients experienced a significant improvement in QoL from this treatment, but untreated utility was very low, and patients did not have toxic reactions all the time. The committee appreciated that EPP is a severely disabling condition and therefore allowed the utility into the model to consider what ICERs would result, but the committee did not consider the data on which these values were based were sufficiently robust to apply further QALY weighting.

155. Richard Diaz drew the attention of the panel to the reference in paragraph 4.44 of the FED to the consideration given by the committee to the economic analysis and the undiscounted QALYs.

156. Marten Petterssen, for IPPN, expressed concern about the comment that EPP patients do not have reactions all the time. He explained that the reactions are so grave and traumatic that it was quite clear that large proportions of the general population are unable to grasp the severity of EPP. He gave a personal account of his own traumatic reactions and described the lengths that he has to go to, to avoid visible light. Consequently, he considers that there are no safe spaces for him and although he might successfully avoid a reaction on certain days, this did not mean that he was safe. There was the additional matter of accumulated exposure to consider since the accumulation of very small doses of light exposure can lead to a reaction. Consequently, this condition dominates patients' lives and life adaptations are significant.

157. Following questioning from the panel, Dr Peter Jackson confirmed that individual patient testimonies had been very important to the committee in this evaluation. The committee was struck very powerfully by accounts like that of Marten Petterssen of IPPN, in appreciating just how dire the disorder was both during attacks and between attacks and the benefits people perceive with afamelanotide treatment. He explained that that was the reason why the committee had tried so hard to seek ways of getting close to cost effectiveness.

158. The appeal panel concluded as follows. The panel reminded itself that this appeal point relates to the reasonableness of the committee decision not to apply a QALY weighting in the case of afamelanotide. The panel were persuaded that the committee had given this issue due consideration in its decision-making. It was convinced that the committee had considered the impact of the newly submitted IPPN QoL data and the extent to which this had generated a scenario that resulted in an undiscounted QALY gain of greater than 10. Nonetheless, the panel accepted the concerns of the committee in regard to the uncertainty associated with these newly submitted QoL

data and considered that it was reasonable for them to have concluded that they did not represent compelling evidence of substantial QALY gains with afamelanotide. Having taken note of the criteria that are required for the committee to be able to apply QALY weighting, the panel concluded that it was reasonable for them not to have done so in this evaluation.

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

Conclusion and effect of the appeal panel's decision

160. The appeal panel therefore upholds the appeal of Clinuvel on Appeal point 1a.3 and the appeal of IPPN on appeal point 1a.1 on the grounds that NICE acted unfairly by reason of delay. The appeal is dismissed on all other grounds.

161. The appeal panel draws to the attention of NICE to paragraphs 29, 64 and 96 of this letter in which specific areas are discussed where rewording of the FED might be considered by the committee.

162. 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.