

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY EVALUATION

APPEAL HEARING

Advice on sebelipase alfa for treating lysosomal acid lipase deficiency

Decision of the panel

Introduction

1. An appeal panel was convened on 25 April 2017 to consider an appeal against NICE's final evaluation determination (FED), to the NHS, on lysosomal acid lipase deficiency (LAL D) - sebelipase alfa (ID737).
2. The Appeal Panel consisted of:
 - Patrick Storrie Chair
 - Dr Rosie Benneyworth NICE Non-Executive Director
 - Professor Marios Adamou Health service representative
 - Dr Mercia Page Industry representative
 - John Morris Lay representative
3. None of the members of the appeal panel had any competing interest to declare.
4. The panel considered appeals submitted by:
 - Alexion Pharma UK
 - Birmingham Women's and Children's NHS Foundation Trust, London Guy's Hospital Genetic Centre, and Willink Unit, Genetic Medicine, Central Manchester University Hospitals NHS Foundation Trust (CMFT) - who appealed jointly
 - The Society for Mucopolysaccharide Diseases (MPS Society).
5. Alexion Pharma UK was represented by:
 - Heidi Wagner Senior Vice President, Global Government Affairs
 - Dr Emma Harvey Senior Medical Director
 - Adela Williams Arnold & Porter LLP – solicitors
6. The Birmingham Women's and Children's Hospital NHS Foundation Trust, London Guy's Hospital Genetic Centre, and Willink Unit, Genetic Medicine, CMFT, who appealed jointly, were represented by:
 - Dr Suresh Vijay Consultant, Birmingham Children's Hospital
 - Dr Simon Jones Consultant, Royal Manchester Children's Hospital

- Dr Anupam Chakrapani Consultant, Great Ormond Street Hospital
London

7. The MPS Society was represented by:

- Sophie Thomas Advocacy Support Team Manager
- Alexandra Morrison Clinical Data Lead
- Nicole Coleman Patient

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

- Dr Peter Jackson Highly Specialised Technologies (HST)
Evaluation Committee Chair
- Meindert Boysen Programme Director – Centre for Health
Technology Evaluation
- Sheela Upadhyaya Associate Director – HST
- Boglarka Mikudina Technical Lead
- Ian Watson Technical Advisor
- Sotiris Antoniou Highly Specialised Technologies Evaluation
Committee Member

9. NICE's legal adviser Stephen Hocking (DAC Beachcroft LLP) was also present, as was Dr Andrew Black, an appeal panel member in training.

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

11. 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
- b) Exceeded its powers.

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

12. The Vice Chair of NICE (Mr Andy McKeon) in preliminary correspondence had confirmed that:

- Alexion Pharma UK had potentially valid grounds of appeal as follows:
Grounds 1a and 2.
- Birmingham Women's and Children's NHS Foundation Trust, London
Guy's Hospital Genetic Centre, and Willink Unit, Genetic Medicine, CMFT,
who appealed jointly, had potentially valid grounds of appeals as follows:
Ground 2.
- The MPS Society had potentially valid grounds of appeals as follows:
Ground 2.

13. The evaluation that is the subject of the current appeal is the final evaluation determination of sebelipase alfa for treating lysosomal acid lipase deficiency published on 15 February 2017.
14. Before the appeal panel inquired into the details of the appeal points the following made preliminary statements: Heidi Wagner for Alexion Pharma UK, Dr Simon Jones for the joint appeal, Sophie Thomas for the MPS Society, and Dr Peter Clark for the committee.
15. Heidi Wagner, for Alexion Pharma UK, explained that this was an extremely rare genetic disease. When it presents in babies it presents as a medical emergency, the babies will die within months. For older patients only a proportion have a need for treatment. Sebelipase alfa is the only specific treatment for this condition and is showing impressive results.
16. The highly specialised technologies evaluation process was designed to accommodate treatments for these very small patient populations, but she felt this objective had not been achieved.
17. Heidi Wagner said there had been a lack of clarity about the evaluation process, particularly about what this process required and what the criteria for a recommendation for use were. She felt there was no guidance about the managed access agreement (MAA) (which seemed to be a requirement introduced after the first consultation), how this would be structured and what it should include. Furthermore, she found the negotiation with NHS England over an MAA fraught with difficulty with conflicting and circular requirements and an opaque procedure. NICE had not facilitated these discussions. The company has repeatedly made clear its desire to negotiate a successful outcome in what had been a fluid process, but could not do so because of a lack of support.
18. Heidi Wagner stated that the committee failed to recognise the severity of lysosomal acid lipase deficiency and failed to consult with clinical experts specifically as it related to infants. She also raised a concern about the approach to evidence presented particularly in the use of unrealistic utility rates presented by the Evidence Review Group (ERG). Alexion argued that a deficiency in procedure had led to sebelipase alfa not being approved.
19. Dr Simon Jones, for the joint appeal, stressed the clinical severity of the infantile presentation of LAL and found the whole evaluation process disappointing and disrespectful to the nature of the disease and the fact that this was a life-saving therapy. The appraisal was rushed, and seemingly done for the benefit of the process itself not the patients. He said that the use of quality-adjusted life-year (QALY) for this disease was not an appropriate measure or consistent with other similar conditions. His view was that given the benefit of sebelipase alfa to infants and the lack of a comparable therapy, it was hard to imagine not recommending a discussion about price. It seemed to him that clinical effectiveness was not the prime issue but cost and then went on to give examples of efficacy of sebelipase alfa in fourteen infants treated in the UK, ten of whom are still alive. He stated that the logical conclusion of this process was that children are at risk of

treatment cessation, referring to children who have been started on treatment in good faith expecting therapy would be provided for as long as needed.¹

20. Sophie Thomas, for the MPS Society, expressed feelings of sadness at having to be at the appeals process because sebelipase alfa has compelling clinical evidence recognised by the EMEA which fast tracked approval of the medication. Through the HST process, clinical groups and patients have asked for openness and felt the patient population has been better determined and should have had input into the MAA and guidelines. Sophie Thomas felt that the committee did not recognise the severity of disease in infants and gave examples of its severity with 89% dying before one year and for those who survived to their first birthday all but one dying before age four. Three infants are diagnosed in England in each year and are likely to die within one year whilst of the clinical trial population all patients reached their first birthday with the oldest patient still thriving and developing. Quality-of-life data was presented to committee and the high uncertainty concerns of the committee about benefits from sebelipase alfa are unjust as LAL D is ultra-rare and the committee was reluctant to accept long-term benefits presented through patient experience. Sophie Thomas stressed very good outcomes being seen in infantile presentation LAL D taking sebelipase alfa, with the oldest patient so treated thriving and unburdened by illness. She concluded that she felt their hands were tied because whatever case they present would be negated by cost, this is devastating news for patients as people know there is treatment and they will not be having it.
21. Dr Peter Jackson, for the committee, explained that the HST evaluation committee was set up in 2013 to scrutinise seriously disabling rare diseases, which were not well served by a standard HTA process. The committee includes lay members, an ethicist, commissioners and public health clinicians. Each evaluation begins with a presentation from the manufacturer, a critique, patient evidence and one session is set aside for patients. The committee always hoped to recommend use but within a fixed budget system, every pound spent is a pound less for other patients. In terms of the decision making process for HST, he expanded that the committee have a mind-set to find ways to recommend the therapy and that the method of reaching decisions was deliberative with numerical values supporting but not leading the discussion. The benchmark is considered with regard to what treatments would be displaced in the highly specialised field if a specific treatment is approved.
22. Dr Jackson said that the committee understood the severe nature of LAL D particularly in infants and listened to patients and parents and took note. This is facilitated by HST tending to consider a single technology assessment on one day so patients and experts can expand more than in an HTA, and also the company has more time. Dr Jackson was confident in that the clinical expert account of the natural history of the illness and long-term likely effects of treatment were received and he checked that the committee had not misunderstood evidence. In fact the evidence was scrutinised and where factors

¹ In order to avoid causing confusion to the NHS, or distress to patients and their carers, it is necessary to state immediately that the appeal panel understand and the committee confirmed that NHS treatment for existing patients should be unaffected by this evaluation, see below

were of particular influence, they were discussed to ensure all plausible considerations were included in deliberations. This for example included considering population subgroups such as infants with severe disease which would benefit more from treatment but might cost more to treat. The committee considered that there was uncertainty in short and long-term efficacy (and the long term natural history of infant patients is unknown), and there was high cost. It therefore did not feel able to recommend the treatment. In terms of the MAA, the committee provided feedback to the company on points that could be addressed to help satisfy the concerns of the committee, but the committee's concerns remained. In conclusion he felt the process was followed and any deviation was in the interests of patients who might benefit from sebelipase alfa.

23. The hearing then considered the appeal points individually. (At the hearing the ground two appeal points were considered first and appeal points were grouped thematically to assist in the conduct of the hearing. However for ease of reference to other appeal documentation they are set out here in the order they are raised in the appellants' appeal letters.)

Appeal by Alexion Pharma UK

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

1.1 The failure to follow a clearly defined procedure in this HST evaluation is unfair

24. Adela Williams, for Alexion Pharma UK, stated that to be fair, a process must be properly defined so that stakeholders know what they must do to get a positive outcome. On this occasion, NICE has fallen far short of its usual standards. She claimed that the process which had been followed was not reflected in the interim guide. Rather it developed as it went along producing a mismatch between the understanding of stakeholders and the committee. She also claimed that there was a casual approach to providing guidance, and when this was provided for asfotase alfa NICE merely communicated over the phone that the same approach would apply for sebelipase alfa.

25. As regards the MAA, NICE's process does not require an MAA at all. An MAA was first mentioned in a phone call to the company part way through the process. There was no indication what an MAA should contain or how to create one, only a partly redacted MAA for another product that was offered as a guide.

26. For MAAs in other appraisals NICE had facilitated discussion between stakeholders. The company asked for this assistance but was refused. The company has submitted a patient access scheme but heard nothing more about that after August 2016. It was told to negotiate with NHS England, but NHS England replied that it would not negotiate until there was an "in principle" recommendation on clinical grounds from NICE. Yet they were told that to get that recommendation they had to have submitted an MAA agreed with NHS England. Ms Williams stressed that an MAA was not a document that the

company could produce without input from others. The company was in a bind whatever it did.

27. As a result of its own efforts the company did produce a consensus MAA agreed with clinical specialists, but this still did not satisfy the committee, for reasons that remained opaque.
28. Dr Peter Jackson, for the committee, explained that its guidance to the company had been that the MAA is a useful tool for a company to respond to committee concerns but it was not considered to be essential or to be the only way to do so. The process guide does not refer to an MAA and the template produced by the committee was a means to communicate its concerns to the company and facilitate the company's response.
29. Meindert Boysen, for the committee, commented on NICE facilitating engagement and envisaged a formal step of 'reconsideration' as referred to on section 18 of the Interim Process and Methods of the Highly Specialised Technologies Programme. Professor Marios Adamou asked the committee what would happen if the MAA was used "correctly" by Alexion Pharma UK and Dr Jackson said he believed that concerns would have remained.
30. Dr Emma Harvey from Alexion Pharma UK stated the company did not have feedback and received incomplete guidance when constructing the MAA. This was not something the company could do by itself. It also requested assistance to involve other stakeholders. Heidi Wagner added that they were told not to reach out to stakeholders and that NICE would do this.
31. Adela Williams said that the company was aware that an MAA would potentially be a route to obtain approval for the product, but needed assistance because this was not an "Alexion" MAA and procedures did not specify what has to go into an MAA. Adela Williams stated that Alexion were given advice piecemeal, and were never given a complete list of the attributes which an MAA would need to have to satisfy the committee.
32. Meindert Boysen admitted this is a process in development but did not accept it was made up as they went along. He added that the committee cannot force NHS England to do anything.
33. The appeal panel's legal adviser Stephen Hocking asked about the MAA and the strength of the advice that one was required, and Alexion Pharma UK said they were "strongly advised" to address concerns in the MAA, and understood it to be "just short of a mandate" that one was submitted.
34. The appeal panel concludes as follows.
35. It agrees that a company must know, during an appraisal, what all of the material drivers of a decision are. The key moment to consider is the moment at which the committee takes its final decision: at that point, has the company been made aware of all of the material drivers, has it had a chance to address them, and has whatever submission it has made informed the committee?

36. Although the panel understands and has some sympathy with the company's frustration with what it saw as a process that was being "made up as it went along", (or as Meindert Boysen has it, that was "in development"), this mutability is not sufficient to make out the ground of appeal. The panel notes that the HST process is relatively new, and also that of its nature it may be expected to vary more between evaluations than the normal HTA process. A degree of flexibility to accommodate the different nature of treatments likely to be referred to the HST process is not unwelcome. The panel agrees both that the process followed is not fully set out in the interim guide and that it appears to have developed as it progressed, but the question is: that being so, was the final decision arrived at unfairly?
37. The panel also has sympathy with the company concerning the way in which some of NICE's communications were made. It is not ideal neither if important communications were taking place by telephone conversation rather than in writing, nor if NICE was relying on communications made in relation to the asfotase alfa evaluation to guide the company in this evaluation. (Equally, the panel does not feel that was wholly unreasonable. No doubt the company would have been surprised if a radically different approach had been adopted in the two evaluations.) However looked at as a question of fairness the panel felt the company had (in good faith) made rather too much of these complaints. The panel was satisfied that rather than imposing requirements in an opaque or retrospective way, NICE was offering guidance and assistance. It should not be discouraged from doing so. Cross referencing to asfotase alfa did create a somewhat casual impression, however the panel was satisfied that the company was in fact informed as it needed to be of matters relevant to this evaluation.
38. Aspects of the company's complaint under this ground are the other side of the same coin, namely that in some respects NICE did not offer enough assistance, particularly around the creation of an MAA. Again the panel had some sympathy with the company and the catch-22 situation that they thought they perceived. However the panel was satisfied that the company was mistaken in this analysis. It was clear to the panel from all the evidence that the most important issue in this particular evaluation was cost effectiveness. All sides had appreciated the extreme clinical need of infant patients and the need of other patients (as to which see below) and all sides had appreciated that this drug was efficacious, albeit the long term outcome of infant patients was inevitably unknowable at this stage. However it seemed all parties agreed there were really significant health benefits, albeit stakeholders argued that these were greater than the NICE Evidence Review Group accepted. The issue was the high cost of those benefits, and that was clear some time before the finalisation of the FED. It follows that the company was aware that to secure a positive recommendation it would need to improve its value proposition, and that it knew the drivers of the value proposition.
39. Typically a patient access scheme would be one way to make this improvement, but for reasons that the panel were unaware of it seems that the Department of Health had not progressed the scheme offered. That must be a matter for it rather than for NICE. An MAA offers another way to present an improved offer. The panel were satisfied that an MAA was not presented by NICE as an absolute

requirement or as the only way to make an improved value offer, and that the committee did not have any hidden detailed expectations of the form or content of a particular MAA. The panel understands the company's frustration at its dealings with NHS England but NICE did not require (though it may have welcomed) NHS England engagement. It may be that NICE had been more helpful in another appraisal but it would be wrong to use that fact to impose obligations to assist in every case. The true question is fairness in this evaluation.

40. It is significant that the company did manage to submit an MAA. While the content of that MAA did not persuade the committee to recommend the product, the reason was not any defect in the form of the MAA, or the way in which it was created. Rather the value offer was still considered insufficient, which is a matter of substance rather than fairness.
41. Overall, the panel agreed that this was a process in development, where it may be that in some areas the company had misunderstood suggestions and guidance from NICE as requirements, and in other areas the company had not had assistance which it would have welcomed. Clarity on what is a requirement and what is advice, and on what matters, NICE will offer assistance and what is left to a company could usefully be improved. However the panel were satisfied that by the time of the committee meeting that settled the FED, if not before, the company knew what the material drivers of the decision were, had had a fair chance to address them, and that this informed the decision made. Accordingly the process followed was fair.
42. Therefore the panel dismissed this appeal point.

1.3 The committee's assessment of value for money is unfair and fails to consider the population of patients eligible for treatment within the managed access agreement

and

1.4 The committee has provided no adequate reasons for its conclusions regarding the determination of the population of patients eligible for treatment within the proposed managed access agreement

43. Alexion Pharma UK made the point that the relevant patient population would be the MAA population, which it had designed to be the patients most likely to benefit from treatment. It presented analyses that showed a weighted average QALY gain of 23.0 whilst the committee's preferred analysis was associated with a total quality-adjusted life year (QALY) gain of 17.15, compared with 10.52 QALYs for best supportive care (incremental QALY gain of 6.64 probabilistic result).
44. Dr Emma Harvey, for Alexion Pharma UK, stated that the FED does not show that the committee recognised and included the improved QALY gains for the MAA population. There is a lack of transparency in the FED in how QALY gains were awarded and it is not clear how value for money conclusions were reached. Adela Williams added that the MAA was not created by the company alone but

agreed by clinical experts, and the reason for not accepting their views were not clear in the FED.

45. Dr Peter Jackson, for the committee, stated that they looked at the treatment criteria in the MAA and compared them to the inclusion criteria for the clinical trials which established clinical effectiveness of treatment to sebelipase alfa. They were largely similar. It was therefore difficult to understand how restricting the patient group broadly to those who would have been in the clinical trials would give a better result than seen in the clinical trial. The experts did not explain why they thought this subgroup was better. Dr Jackson also commented that the company's numbers reflected an expectation that under the MAA a greater percentage of children would be treated. The change in QALY gain was circa 4%. The committee had considered that change but it did not fundamentally change their view. Dr Jackson drew the attention of the appeal panel to the slide set where this was flagged to the committee. The committee needed an explanation of how the MAA identified those who were more likely to benefit from treatment. He felt that the committee's concerns had been explained in the FED at paragraph 5.10.
46. Dr Emma Harvey, for Alexion Pharma UK, said that the MAA did define patients more likely to benefit from treatment and as a consequence there were redefined QALY gains attributable to that population, but the FED does not show that the committee recognised these gains. She also said that this was the first time she heard that the issue was that the MAA and clinical trial criteria were not different enough.
47. Adela Williams acknowledged that the committee was concerned that the MAA did not restrict treatment to those who would gain most benefit, but said no reasons were given for these concerns. The MAA proposals were made by experts. As Alexion was not able to revise the MAA by itself this was unfair.
48. Dr Peter Jackson said every opportunity was given to clinicians to define who would benefit most in terms of the value proposition.
49. Sophie Thomas, for the MPS Society, stated that there are uncertainties in all MAAs for rare conditions and start-stop criteria and quality of life assessments are needed.
50. The appeal panel concludes that the committee did fairly consider the QALY gains that would be attributable to the MAA patient population, but was unpersuaded by them. It notes that as the company were asserting that this population would achieve greater benefit then it was for the company to provide the reasons to believe that would be so. The committee's concern that the MAA population and the trial population are similar is credible and should be obvious. The committee is entitled to consider but not then to be persuaded by expert opinion. The committee's observation that in any event the QALY gains would have made little difference to its analysis reflects a view that the main driver of the value proposition was not clinical benefit, and that issue seems clear from the evaluation overall. It is not unfair for the committee not to address more extensive reasoning to a factor which it did not consider to be the principal barrier to a

positive recommendation. The panel was satisfied that the reasoning in the FED was adequate, and dismissed both of these appeal points.

1.5 The committee has failed adequately to take into account the benefits of sebelipase alfa in infants with rapidly progressing LAL D

51. Dr Jane Harvey, for Alexion Pharma UK, said that there were quality of life gains unique to the infant population. Global regulators realised this life saving potential in an otherwise fatal disease and granted accelerated approval. This necessarily truncated the regulatory dataset that could be submitted to NICE. Dr Harvey acknowledged that it was not very clear what the long-term outcomes will be, but the company have seen survivals of 3 to 6 years and the patients still doing well. They reported QALY gains exceed 27 and the FED did not recognise those QALYs. If the regulatory authorities were satisfied that the treatment was efficacious why were NICE not?
52. Dr Peter Jackson, on behalf of the committee, said that in section 5.23 of the FED he recognised higher incremental QALYs and did see the predictions of continued benefit. He also commented that the infants needed higher dose and the cost was considerably higher with this high QALY group and hence the committee was unable to give a positive recommendation.
53. The appeal panel is aware that the regulatory authorities are satisfied that the product is sufficiently safe and efficacious to permit marketing. Indeed no party to the appeal had argued other than that this was an effective drug in a population at high (in some cases very high) need. However NICE's remit is clinical and cost effectiveness. These are understood to be different issues to the grant of marketing authorisation. To those versed in the field, such as consultees and clinicians, there is no inherent contradiction that calls for an explanation in concluding that a drug may be both clinically efficacious and yet not cost effective.
54. The panel were satisfied that the committee had taken account of the benefits of treatment in infants, but that it had nevertheless concluded that, because of high cost, treatment was still not cost effective in this group. That conclusion was not procedurally unfair, and the appeal panel dismissed the appeal on this point.

1.6 The exclusion of a clinical expert from the meeting of the committee in November 2016 was unfair and is likely to have prejudiced the evaluation

55. Adela Williams, for Alexion Pharma UK, commented that this is a complex and rare disease. NICE rightly invited clinical experts to give evidence, among them Dr Jones. Dr Jones indicated in advance that he could not attend the November 2016 committee meeting in person, and asked if he could attend by telephone. On the day the telephone line failed, and NICE made no further attempt to contact him. It was therefore without essential expert input to understand new evidence being presented.
56. Dr Jones added that meetings were convened at fairly short notice, not always six weeks. He was supported by NICE to attend by phone but this failed. He did

not consider this to be anyone's fault but he could have been called on another number.

57. Sheela Upadhyaya, for the committee, explained that Dr Jones had notified NICE that for family reasons he could not attend the meeting and arrangements had been made for him to attend by phone. The project manager spoke to him on the day of the meeting to notify him of the time that he would be called. NICE dialled the agreed number twice but he could not be contacted. He subsequently called back but the meeting was under way.

58. The appeal panel was prepared to assume that, having identified Dr Jones as an expert whose input could assist the committee, fairness required NICE to make meetings of the committee available to him. It was not prepared to assume that fairness required NICE to ensure that he attend, or that it was unable to proceed without him. NICE had made reasonable arrangements for Dr Jones to attend which had unfortunately failed. The panel noted that Dr Jones considered no one to be at fault for that, and it concluded that that was a fair assessment. Faced with a situation where Dr Jones could not be reached on the agreed number without fault on NICE's part it was not unfair to proceed without him, any more that it would have been unfair to proceed if he had planned to attend in person and had been delayed on public transport.

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

1.8 The committee has failed to consider the status of children with juvenile-onset LAL D in accordance with the provisions of the Human Rights Act 1998

60. The appeal panel was grateful for the written legal submission it had received on this point.

61. Essentially the same point had arisen in the appeal concerning dintuximab for treating high risk neuroblastoma. The panel adopts the same view of the law which it took in that appeal. In the interests of brevity it does not repeat that discussion here.

62. The appeal panel upheld the appeal on this point.

63. Of course the panel accepts that the committee will have been aware that many patients (in particular the infant group) were children. It also accepts that in an HST it is more difficult to refer to a "usual approach" and the possible need for a departure from it. What is absent and is needed is an explicit consideration and conclusion, which need not be lengthy, on the question of what extra or different accommodation if any is necessary in light of the fact that there is an identifiable group of patients who are children.

1.9 In reaching its conclusions the committee has failed to take into account relevant evidence

64. Adela Williams, for Alexion Pharma UK, remarked that the committee had accepted that not all benefits of treatment had been taken into account in the

ERG's approach to utility values, but then gave no weight to this consideration. This was sloppy decision making and left consultees unable to verify the decision. The company did not know if the committee had accepted their conclusion on QALY gain, and the committee did not seem to have acknowledged that their calculations were likely to be pessimistic.

65. Dr Peter Jackson replied that the committee had not settled on one set of utility values or another. It noted that the company was optimistic and the ERG pessimistic. It did not settle on intermediate values as those would have lacked supporting data.

66. Adela Williams replied that FED paragraphs 5.21 and 5.22 gave the impression that the ERG values were the driver of the decision.

67. The appeal panel accepted Dr Jackson's description of the committee's approach. It has in the past held that fairness does not require a committee to settle on a "right" value for any particular parameter and the approach described of considering both sets of values but with reservations as to each was not unfair. The panel also felt that consideration and explanation should be proportionate to salience. Utility is an important consideration, but in this evaluation cost appears to have been more significant. If no plausible utility values would have rendered the product acceptably cost effective in the committee's eyes, then fairness does not require an extended consideration of utility values.

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

Appeal Ground 1(b) NICE has exceeded its powers

69. No appellants raised points under this ground.

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

Appeal by Society for Mucopolysaccharide Diseases (MPS Society)

And

Appeal by Birmingham Women's and Children's NHS Foundation Trust, London Guy's Hospital Genetic Centre, and Willink Unit, Genetic Medicine, CMFT (joint appeal)

70. The subject matter of these sets of appeals was interwoven, and so they are discussed thematically below.

MPS Society: 2.3 The committee's reservations on the long-term health benefits of sebelipase alfa not being achieved and the benefits being highly uncertain due to the limited data available (para 5.22) are invalid and subjective

and

Joint appeal: 2.4 It is unreasonable for the committee to make a recommendation against funding based on the uncertainty of long-term outcome for the infantile-onset sub group

71. Sophie Thomas, for the MPS Society, invited the panel to look at the survival of the patients who had been in the clinical trial: all lived to their first birthday, and the oldest UK patient was now close to his/her fifth birthday. All were developing well and hitting usual milestones. It was inevitable that they could only have survived for as long as the trial had been underway, and so the period covered by data was short. Sophie felt there was clear evidence that longer term effects were life changing. QALYs were an inappropriate tool to use in rare diseases.
72. Dr Jones, for the joint appeal, added that the committee had not been specific about the concerns it had, or about how long term “long term” was. He said that the ERG's concern that other therapies may have developed between the treatment of patients in the historic control group and the trial patients was ill founded. He and colleagues had looked after almost every child in the UK with this condition and none of them were aware of any improvement in treatment (other than this product) that extended life by more than one to two weeks. There were no long term data because as yet there was no “long term”. Clinicians know the evidence is incomplete but they will provide long term data if given the time.
73. Alexandra Morrison, for the MPS Society, added that given the choice not all patients will accept treatment. She did not understand what the committee's issues with the MAA were, as it had stopping criteria and allowed for the collection of long term data.
74. Dr Vijay, for the joint appeal, said that from the perspective of the disease's natural history, long term for a child with infant onset disease is weeks or months. The product is the best treatment that has been investigated. Children are living to school age. This is a lifesaving and life changing product.
75. Dr Jackson replied for the committee. He explained that HSTs do not use ICERs, although they do calculate incremental costs and incremental QALYs.
76. Dr Jackson said that there was different uncertainty in two different patient populations. In older patients there was uncertainty because of the short trial duration compared to possible lifelong treatment, but also because of the use of surrogate markers for disease progression. Extrapolating from those markers produced uncertainty. The ERG would have had it that those markers gave no evidence of benefit but the committee rejected that as too conservative. (Dr Vijay later responded that these surrogate markers are in fact used in clinical practice and are considered more sensitive to clinical states than clinical markers would be.)
77. In the infant group the absolute number of patients was very small. It was necessary to extrapolate well into the future, and was impossible to have data about the natural history or outcomes for these patients after the first few years. Also these patients receive a higher dose than their adult counterparts and it was

not known what dosage they would need as adults. For adult patients, the committee accepted long term survival was probable, but for infants this was unclear. He understood and sympathised that it was difficult to produce data to reduce these uncertainties but the committee had to consider the impact of its advice on the NHS.

78. It was in responding to this appeal point that Dr Jackson helpfully confirmed that the committee's understanding was that no patient currently receiving treatment in the NHS should be removed from treatment as a result of the committee's recommendation.
79. Dr Jones, for the joint appeal, responded that the evidence for elosulfase alfa was less clear, the drug less effective and there was the same length of data, but the committee had recommended use with an evidence review at five years, although he conceded he could not comment on the cost of that drug. Dr Vijay agreed, and stressed that without treatment the outcome for infants is certain death.
80. The appeal panel understands that both the committee and the appellants were in a difficult position. For a treatment that has only been available for a limited period and which may be taken by most patients for the rest of their lives, the available data will not cover the possible treatment period and extrapolation is needed. That extrapolation will introduce uncertainty. In the panel's view it would be unreasonable to treat that uncertainty as necessarily a bar to a recommendation, (because on that basis no treatment such as this will ever be recommended until many years have passed), and it would be unreasonable to expect the committee to ignore uncertainty entirely (because the panel accepted that the uncertainty was real). The panel considered that the committee had to reach a reasonable understanding of what uncertainty was present, and that its treatment of that uncertainty also had to be reasonable. In reaching that judgement the committee should be aware that, as Dr Vijay had made clear, the alternative to treatment is death. That requires a particularly careful approach from the committee.
81. The panel was satisfied that the committee had done so. The uncertainties identified appeared to be real. The approach to uncertainty described, for example, at the end of FED paragraph 5.22 was also reasonable: the committee had not regarded the mere existence of uncertainty as a bar, and by considering what its decision would have been even on more optimistic treatment assumptions the committee had performed a sensible check on its decision. Given the high stakes in this decision that approach was highly advisable. The panel acknowledges (as the committee did) that uncertainty is inevitable in such cases and that reducing uncertainty may be difficult. However it noted that the committee did not regard the uncertainty per se as unacceptable, but as unacceptable in light of "very high" cost. The committee was not therefore setting up uncertainty as an absolute bar to recommendation merely as a bar to recommendation at a particular cost.
82. The appeal panel therefore dismissed the appeal on this point.

MPS Society: 2.4 [formerly 1.2(a)] The committee have failed to recognise the severity of the disease in the infant population

This point is taken together with:

Joint appeal: 2.1 The severity of the infantile presentation and the significance of its alleviation with this therapy have not been fully recognised and therefore the recommendation at least for infantile patients is unreasonable

Joint appeal: 2.2 In particular, the degree of systemic inflammation and immune dysfunction which are seen in infant-onset patients has not been considered in the FED

83. Dr Vijay, for the joint appeal, explained that infantile onset patients present in extremis, with a few days to live. They have systemic problems, which are not limited to the liver. While there were children who died on the trial, it could be said retrospectively that their condition had already deteriorated too far for treatment to be effective. This product is the only treatment that can be offered.

84. Sophie Thomas, for the MPS Society, supported the evidence of Drs Vijay and Jones. She gave an example of the first child on the trial, who had been profoundly ill at three months and was now five years old and had been symptom free for two years.

85. Dr Jones stressed that these were some of the sickest patients he looks after. Graphs and the like could not convey how transformative the treatment is. The committee's conclusion must show that they did not grasp this, if they were uncertain about clinical effectiveness.

86. Dr Jackson responded that the committee had grasped the severity of the condition and had described this in the FED. The committee also acknowledged this is a multi-organ disease in the FED. They acknowledged the treatment is life-saving in infants. The uncertainty is in what percentage of infants will the treatment be life-saving and for how long. With nine patients treated and three deaths it is unclear what percentage respond to treatment, and that point is made independently of concern about extrapolating treatment into the future. Inflammation had not been mentioned in the evidence submission and so was impossible to consider.

87. Dr Vijay explained clinicians were still learning what the inflammatory process is, there was much to learn as patients did not used to survive.

88. Dr Jones added it had not been possible to recruit more than nine patients as the disease was so rare.

89. The appeal panel was satisfied that the committee had reasonably appreciated the severity of the disease in infant presentation. The FED records survival of less than 12 months and a median life expectancy of 3.7 months. The discussion of infant onset disease in FED 4.1-4.3 and 5.1-5.2 is brief but sensitive and correctly acknowledges the effect on parents as well as the child. FED 5.3 record

the evidence that this treatment is needed by all patients presenting before 6 months and it is the only treatment that can prevent early death. The panel is in no doubt that the committee knew that these infants are very gravely ill indeed, that the treatment would save at least some of their lives, and that it was reasonably concerned not that the illness was not severe but that it was unclear what percentage of patients treated might be saved.

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

Joint appeal: 2.7 The significance of treatment effect in older children with LAL deficiency has not been fully appreciated in the guidance

91. Dr Jones, for the joint appeal, said that this was a heterogeneous patient group. The FED contained relatively little discussion on older children, but concentrated on infants and adults.

92. Dr Jackson responded that this group was not brought to the committee's attention as needing specific consideration. His understanding was that the majority of cases referred to as "older children and adults" were in fact older children.

93. Nicole Coleman explained her experience of life as a patient with this illness, who had not been diagnosed as a child.

94. The panel were satisfied that the committee had given this group a reasonable level of attention, given that it had not been suggested to them that the group required a higher level of individual consideration.

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

Appeal by Alexion Pharma UK

2.1 The committee's criticism of Alexion for failing to incorporate collection of non-invasive measures for liver damage in the proposed managed access agreement are unreasonable in circumstances where such measures have not been validated in LAL D

96. Dr Harvey, for Alexion Pharma UK, explained that paragraph 5.11 of the FED was inaccurate. The MAA does include non-invasive measures of liver damage. The committee's apparently preferred measure, fibroscan, was not validated in this condition and would have been considered as an experimental tool only.

97. Dr Jackson, for the committee, replied that it depended what was meant by "direct measure of disease progression". A biopsy is the gold standard, but would not be reasonable on a repeated basis. The committee's concern was that there was no more direct measure than, e.g. blood tests. The committee has little concern about the lack of validation as the patient group was so small and validation in parallel diseases would be acceptable.

98. The panel was satisfied that the committee had not intended to be critical of the company, and that in referring to a lack of direct measures it intended to say a lack of more direct measures than the measures proposed. While the committee may wish to consider making this sentence clearer, the panel was satisfied it did not demonstrate any unreasonableness.

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

2.2 The committee's explanation for preferring the ERG's utility values does not justify the values selected

100. Heidi Wagner, for Alexion Pharma UK, said that the committee acknowledge that the ERG utility values were likely to underestimate benefits. The ERG proposed an alternative approach that capped utility values put forward by the company: the company did not feel this was reasonable but was prepared to accept it. However the committee rejected even this approach and used utility values that were too low without reason or justification.

101. Dr Jackson said the committee were presented with two sets of utility values. Each had benefits and drawbacks. Neither was likely to be "right". The committee preferred the Crossan values as they used NICE's preferred tool (EQ5D) and had a significant UK population input. The company values suggested that LAL D patients enjoyed better health than the general population. The ERG values might not be right and might underestimate but were closer to the committee's assessment of what would be the actual figure.

102. Ms Wagner replied that the capping proposed by the ERG addressed this concern, but Dr Jackson said he had not understood the ERG to agree that capping solved the concerns about the company's numbers.

103. The panel felt this was a case where the committee had to work with two sets of numbers neither of which was "the answer". It was a reasonable approach to choose one, and to have well in mind the limitations of it and make the necessary mental adjustments. In this case the committee chose the more pessimistic figures, but kept in mind that they were pessimistic. While it may be that it could equally have chosen the more optimistic figures and kept in mind that they were optimistic, what it had done was not unreasonable. There was no need to offer further explanation of why it had adopted one approach over another, when the purpose of either approach would have been the same: to begin from an imperfect start point and try to more closely approximate the correct position.

104. The appeal panel therefore dismissed this appeal point.

Conclusion and effect of the appeal panel's decision

105. The appeal panel therefore upholds the appeal on the ground raised in Alexion's appeal point 1.8. The appeal is dismissed on all other grounds.

106. The evaluation is remitted to the evaluation committee who must now take all reasonable steps to consider whether the fact that there is a group of child

patients affected by this disease calls for any modification of their consideration or conclusions.

107. 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.