Highly Specialised Technology

Olipudase alfa for treating Niemann-Pick disease types A and B [ID3913

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olipudase alfa for treating Niemann-Pick disease types A and B [ID3913]

Contents:

The following documents are made available to stakeholders:

1. **Appeal papers**
2. **Appeal outcome letter**
3. **EAG post appeal analysis**
4. **Post Appeal Company Addendum by Sanofi**
5. **EAG Critique of Company Addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies (HST)

Olipudase alfa for treating Niemann-Pick disease types A and B [ID3913]

Meeting of the appeal panel – 24th May 2024

Venue: Zoom webinar

Appellant: 1) Niemann-Pick UK

The following documentation is made available to the **Appeal Panel:**

1. **Appeals received and responses against the Final Draft Guidance (FDG) from:**
   a. Appeal letter from Niemann -Pick UK [redacted]
   b. Initial Scrutiny letter to Niemann-Pick UK [redacted]
   c. Niemann-Pick UK response to initial scrutiny letter [redacted]
   d. Final Scrutiny letter to Niemann-Pick UK [redacted]

2. **Final Draft Guidance issued for appeal on 27 February 2024** [noACIC]

3. **Presentation slides discussed at 07 December 2023 second Committee meeting prepared by; Yelan Guo and Thomas Jarratt**
   a. ECM2 Part 1 slides [redacted]
   b. ECM2 Part 2 slides [redacted]
   c. Email from RD responding to MT re: JD splenectomy and mortality statement [noACIC]

4. **Response to DG consultation received from:**
   a. Company response to DG consultation [redacted]
      i. Additional Model Results [redacted]

   Patient experts:
   b. Patient expert 1 [redacted]
   c. Patient expert 2 [redacted]
   Clinical expert:
   d. Clinical expert 1
   e. Clinical expert 2
   f. Clinical expert 2
   Professional group:
   g. Niemann -Pick UK [redacted]
   h. EAG critique to company response and responses to draft guidance [ACIC]

5. **Draft guidance issued on 26 October 2023**

6. **Presentation slides discussed at 05 October 2023 first Committee meeting prepared by; Yelan Guo and Thomas Jarratt**
    a. ECM1 Part 1 slides [redacted]
    b. ECM1 Part 2 slides [redacted]

7. **Assessment report / Evidence Review Group prepared by Peninsula Technology Assessment Group - University of Exeter [redacted]**

8. **Response to technical engagement**
    a. Niemann-Pick UK [noACIC]

9. **Full Submissions received from consultees before ECM1:**
    Patient experts:
    a. Patient expert 1 no ACIC]
    b. Patient expert 2 [no ACIC]
    Clinical expert:
    c. Clinical expert [redacted]
    Professional group:
    d. Niemann -Pick UK [no ACIC]
        i. Raebel [no ACIC]
    e. BIMDG, UK [redacted]

10. **Clarification letter and company response** [redacted]

11. **Evaluation scope and matrix** as issued to consultees:19th January 2022

12. **Guide to the technology appraisal and highly specialised technologies appeal process as issued to consultees with FED [noACIC]**

13. **Interim process and methods of the highly specialised technologies programme**

    NICE health technology evaluations: the manual

Documents referred to in the Niemann-Pick UK Appeal letter

Appeal point 1(a).2

Final Draft Guidance 27 February 2024, section 3.18, see document 2

Final Draft Guidance 27 February 2024, section 3.17, see document 2

Committee papers 05/03/24 - p46-47, p47-48

Final Draft Guidance 27 February 2024, section 3.19, see document 2

Footnote 2; - Fraser LK, Murtagh FE, Aldridge J, Sheldon T, Gilbody S, Hewitt C. Health of mothers of children with a lifelimiting condition: a comparative cohort study. Arch Dis Child. 2021 Oct;106(10):987-993. doi:10.1136/archdischild-2020-320655. Epub 2021 Mar 2. PMID: 33653713; PMCID: PMC8461446.

Final Draft Guidance 27 February 2024, section 3.20, see document 2

Footnote 3; - Song, Jieun & Mailick, Marsha & Greenberg, Jan & Floyd, Frank. (2019). Mortality in parents after the death of a child. Social Science & Medicine. 239. 112522. 10.1016/j.socscimed.2019.112522.

Appeal point 2.3

Final Draft Guidance 27 February 2024, section 3.20, see document 2

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19th March 2024

Dear Dr Chakravarty,

Final Draft Guidance Document – Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease) type AB and type B [ID3913]

In consideration of the acknowledged and high degree of unmet medical need in the ASMD community, Niemann-Pick UK (NPUK) would like to appeal the negative Final Draft Guidance decision on the above mentioned highly specialised technology.

We are disappointed by the Committee's decision to not consider further evidence or actions that could be taken to resolve areas of uncertainty and we therefore submit our appeal on the following grounds:

Ground 1:

(a) NICE has failed to act fairly.

Ground 2:

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

Ground 1(a): NICE has failed to act fairly.

1(a).1 The Committee's decision does not fully recognise the significant clinical and life changing benefits of treatment with olipudase alfa

We are concerned that the Committee has underestimated the clinical benefits of treatment and the evidence that it can overcome disease severity and reverse disease impact. Clinical data is overwhelmingly positive with statistically significant improvement in all measured clinical domains at 1 year in both paediatric and adult patients. Furthermore, those benefits were sustained with ongoing improvements noted in long term analysis. Olipudase alfa not only stabilised this degenerative condition but reversed the disease. The FDG (3.26) states that the QALY calculations are unlikely to have fully captured the impact of symptoms on patients' ability to function in their daily lives, and evidence from the clinical and patient experts supports this view. Our concern is therefore that this decision has been determined more by the high cost of treatment, rather than insufficient evidence for clinical efficacy.

We accept that the Committee's decision is limited by the appraisal process, which we believe does not provide a level playing field for first line, highly effective and innovative technologies such as olipudase alfa, against second- or third line – often more expensive and less effective – therapies which benefit from a shorter and less stringent appraisal process. In this case, a more flexible approach should be considered by taking into account the ten-plus years of real-world evidence, which strongly demonstrates a lack of functional decline in patients with longer term use of olipudase alfa.

1(a).2 The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities.

In a recently published study undertaken by Raebel and colleagues[1], it was found that olipudase alfa had a sustained and positive impact in many domains deemed important to patients and their families. Both the qualitative and quantitative data in this study suggest olipudase alfa had a meaningful impact on the physical, emotional, and mental health of patients and families, underlining the profound impact on physical symptoms, and demonstrating the impact of these symptoms on the broader QoL of patients, caregivers, and their families.

Whilst we did not agree with the company sourced disutility values from Pompe disease (3.18), neither did we agree with the EAG choice to utilise disutility information from meningitis. We recognise that this population may have significant care needs, however, it is not a progressive condition in the same way as ASMD, with the attached uncertainty, anticipatory grief, progression of disease and care needs.

The Committee's assumptions that carer disutility should be based on the health state of the person with ASMD irrespective of the treatment used is not reflective of the real-world

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[1] Raebel, E.M., Wiseman, S., Donnelly, C. *et al.* Real-life impacts of olipudase alfa: The experience of patients and families taking an enzyme replacement therapy for acid sphingomyelinase deficiency. *Orphanet J Rare Dis* **19**, 36 (2024). https://doi.org/10.1186/s13023-024-03020-4

evidence that ASMD patients and families experienced with olipudase alfa as reported by Raebel and colleagues.

Whilst we agree that ASMD patients experience different health states dependent on severity and rate of progression, available evidence shows the treatment used has a significant impact on carer disutility. The anxiety, stress, and mental health effects on carers, such as depression, and the impact on work and social life, is significant in this disease. Many parent-carers must cut back or stop working to attend to the daily needs of their child, including the regular attendance of medical appointments with multiple providers. Raebel's description of the real-world experience for ASMD carers details the significant improvements associated with olipudase alfa treatment including mental health improvements noted by 80% of carers.

We note the statement "The patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD" (3.17), which we feel is a misrepresentation of the patient expert in this case, and since the health state of ASMD patients is profoundly impacted by receiving treatment with olipudase alfa. In lay language 'health state' was interpreted as state of health at that time (i.e. a good or bad day) not 'Health State' as measured by spleen size and lung function. The carer evidence submitted does not agree that Health State defined in this process by spleen and lung markers determines carer effort (see Committee papers 05/03/24 for a list of symptoms needing care p46-47 pt1 and for carers input for symptoms p47-48 pt3). We therefore make the point that many other symptoms of ASMD are present and require carer input, even when spleen and lung markers are lower.

The FDG states (3.19) "It also noted that ASMD severity is on a spectrum, so caring needs would differ between the less and more severe health states and an average of 1 would be reasonable. The committee concluded that an average of 1 carer was appropriate for decision making." Again, this assumes that lower spleen and lung markers remove or negate other symptoms reported and experienced by patients and therefore the need for carer support, which is not the case. We ask that the Committee reconsider the reported patient expert view that an average of 1.5 carers would be more reasonable. This is based on our belief that HRQoL is reduced across the whole family and that there is a need to properly consider not only carer burden, but the impact on carer quality of life. This is further evidenced by a study undertaken by Fraser and colleagues[2] which found that mothers of children with a life-limiting condition such as ASMD have significantly higher incidence of depression, anxiety, and serious mental illness than other mothers.

Patient expert evidence stated that as symptoms are variable and severe, and dependent on disease progression, carer involvement can be all-consuming. Whilst we appreciate that the Committee considered the impact of a patient's death on carers qualitatively in their decision making (3.20), we question whether this was sufficiently understood, and why it was not also taken into account quantitatively. We do not feel that the Committee's approach fully recognised the profound effect of bereavement and feelings of guilt for passing on a genetic disease (also described by Raebel), or in the case of siblings, the guilt

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[2] Fraser LK, Murtagh FE, Aldridge J, Sheldon T, Gilbody S, Hewitt C. Health of mothers of children with a life-limiting condition: a comparative cohort study. Arch Dis Child. 2021 Oct;106(10):987-993. doi: 10.1136/archdischild-2020-320655. Epub 2021 Mar 2. PMID: 33653713; PMCID: PMC8461446.

for being unaffected. This can result in long-term impacts on their mental health and ability to participate in everyday life and society. A study by Song and colleagues[3] found that parents who had experienced the death of a child had a 32% higher likelihood of early mortality than their peers who did not have any deceased children.

We would like to highlight the well-known challenges in measuring paediatric HRQoL and in capturing what matters most, particularly in a trial for an ultra-rare condition such as ASMD, with very small numbers of children self-reporting. The perspective of parent-carer proxy reports may be very different, meaning children's views are underrepresented and not truly reflective of their experience. In addition, both paediatric and adult patients reported being used to a reduced quality of life prior to treatment, and only realising how reduced this was following treatment.

We also raise the point that patient experts attempting to inform the Committee of their experience in this area were cut short or stopped from making their comments during Committee meetings. There was little time given to hear or reflect on patient expert comments, or for the Committee to ask questions. We therefore question the value placed on patient expert testimony throughout this process.

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

2.1 The Committee did not give due consideration to the proposed MAA (3.24) and the potential to address uncertainties in clinical benefit, patient, and carer disutilities.

The statement "It would need to be shown that olipudase alfa was plausibly cost effective in the context of a highly specialised service. But the committee recognised that, at the price the company had chosen to charge, olipudase alfa was not plausibly cost effective. So, it concluded that a recommendation with a managed access agreement was not appropriate for addressing the uncertainties in the evaluation." (3.24). Due to the proven clinical benefits of this technology, the small population and limited availability of data, we feel that the Committee's decision to discount a managed access agreement is unreasonable as it removes the opportunity to address their outstanding questions and uncertainties. In addition, the decisions made by authorities in Scotland and the EU provide evidence that a managed access approach is possible and likely beneficial.

It is our opinion that a five-year, outcomes-based managed access agreement could address the Committee's outstanding uncertainties, gain enhanced QoL data and address questions about uncaptured benefits, whilst enabling patient access to this innovative technology. We understand the need to consider cost and believe that a managed access agreement could also support further commercial negotiations.

The statement "People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop." (1.2) is

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[3] Song, Jieun & Mailick, Marsha & Greenberg, Jan & Floyd, Frank. (2019). Mortality in parents after the death of a child. Social Science & Medicine. 239. 112522. 10.1016/j.socscimed.2019.112522.

appreciated; however, the negative FDG decision causes extreme distress for patients and their families by endangering access for those currently in compassionate use and expanded access programmes and removing funding support for clinical monitoring, hospital, and home care infusions. Whilst the company has indicated a willingness to continue providing free of charge supply, our concern is that hospital trusts will not be able to honour their agreement to support the financial costs related to treatment in light of the negative FDG decision.

As stated in the FDG (3.7) the impact of ASMD on QoL of patients and carers is underestimated in the model as the standard instruments (EQ-5D and SF-36) were not sensitive enough to capture the impact of symptoms or the improvements seen by patients over time. This was supported by RWE and stressed by patient and clinical expert testimony, which also confirmed that not all symptoms or impacts were fully understood at the start of this study. Therefore, we would like to challenge the EAG's belief that the severity and impact of symptoms were fully captured in the vignettes, and the FDG statement they have been suitably considered, as the vignettes are not measurable, repeatable markers.

We do not support the Committee's conclusions regarding the plausible ICER and maximum acceptable ICER thresholds and feel that these are unreasonable considering the acknowledged clinical benefits of olipudase alfa.

The assumption that data from the International Niemann-Pick Disease Registry (INPDR) will be available to address the Committee's uncertainties outside of a managed access agreement is unfounded. The result of the negative FDG decision on olipudase alfa will prevent access for patients in England, Wales, and Northern Ireland, and impact the ability of the INPDR to capture treatment effect data that is of statistical significance or specific to patients in these countries.

We firmly believe that clinical data collected via a managed access agreement and linked to patient and carer reported outcome measures (collected through the INPDR) could inform the Committee's uncertainty regarding HRQoL and help to address the limitations in evidence due to the small ASMD population.

In Raebel's study, patients and families reported life-changing effects with olipudase alfa based on their experience, consistently expressing the view that all patients with ASMD need access to olipudase alfa. We feel that this information, in addition to the clinical evidence, and the impacts of removing / denying treatment, provide a compelling case for reconsideration of the managed access agreement option.

Conclusion

NPUK strongly supports immediate and full approval of olipudase alfa and fair patient access as deemed the standard of care by expert treating clinicians (Geberhiwot 2023[4]).

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[4] Geberhiwot, T., Wasserstein, M., Wanninayake, S. *et al*. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann–Pick disease types A, B and A/B). *Orphanet J Rare Dis* **18**, 85 (2023). https://doi.org/10.1186/s13023-023-02686-6

Olipudase alfa is the only disease modifying treatment option for ASMD patients and has shown significant clinical benefit, halting progression, reversing the debilitating symptoms of ASMD, whilst improving the lives of patients and carers.

This decision, which leaves no option except complex and costly best supportive care, has caused significant distress for the ASMD patient and carer community as it will undoubtedly lead to unnecessary morbidity and preventable death. This decision raises many concerns including the Committee's perpetuation of health inequalities experienced by people affected by ultra-rare conditions.

We ask, in recognition of the challenges we face as an ultra-rare disease in navigating the HST process, in the availability of data in our small population, and the fact that there is no other disease modifying treatment option on the horizon for ASMD, that a pragmatic approach to approving this transformative treatment may be considered.

In deliberating the most effective use of NHSE funds, we would like to see these challenges, the uncertainties raised by the Committee plus the significant clinical and societal benefits of treatment fully explored through the opportunity of a five-year outcomes-based managed access agreement.

NPUK supports either an oral or written appeal process.

Yours sincerely,

[redacted]

[redacted], Niemann-Pick UK

Making a difference to the lives of those affected by Niemann-Pick

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Tuesday 26 March 2024

Dear [redacted]

Re: Final Draft Guidance – Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease) type AB and type B [ID3913]

Thank you for your letter of 19 March 2024, lodging an appeal against the above Final Draft Guidance (FDG). Dr Chakravarty is temporarily unavailable and so in accordance with paragraph 3.1 of NICE's Guide to the technology appraisal and highly specialised technologies appeal process, I am conducting initial scrutiny on this occasion.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to provide an initial view on whether they are within the permitted grounds of appeal ("valid") and are at least arguable. The permitted grounds of appeal are:

- 1(a) NICE has failed to act fairly, or
- 1(b) NICE has exceeded powers;
- (2) the recommendation is unreasonable in the light of the evidence submitted to NICE.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information, are arguable, and fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn.

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

Appeal point 1(a).1: The Committee's decision does not fully recognise the significant clinical and life changing benefits of treatment with olipudase alfa

Following careful consideration, I am not minded to refer this appeal point to the Appeal Panel. I understand your argument to be that the Committee has underestimated the clinical benefits of treatment and the evidence that it can overcome disease severity and reverse disease impact. In support of this, you refer to paragraph 3.26 of the FDG, in which the Committee acknowledges, as part of its consideration of whether olipudase alfa is an innovative treatment, that the QALY calculations probably did not fully capture symptoms, and so the benefit of olipudase alfa may be underestimated. It is clear, however, that the committee took this issue into account in its decision-making, concluding that olipudase alfa is innovative in treating ASMD. I cannot see a basis on which the Committee's consideration of this issue was arguably unfair.

You have also argued that the Committee should have taken account of "*the ten-plus years of real-world evidence, which strongly demonstrates a lack of functional decline in patients with longer term use of olipudase alfa*". Again, I cannot see any arguable unfairness in the Committee's approach. The Committee concluded that olipudase alfa improves clinical outcomes associated with ASMD and that treatment effect can continue into the longer term, but becomes more gradual as the person's condition moves nearer to full-health. The committee did take evidence of longer term effectiveness into account in its decision making, driving its conclusion that a 27.6 QALY gain was considered most plausible.

Appeal point 1(a).2: The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities.

I am minded to refer this appeal point to the Appeal Panel, on the basis that it is arguable that the Committee has acted unfairly if it:

- misrepresented the patient expert's position by stating in paragraph 3.17 of the FDG that "[T]*he patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD*" and/or

- "*cut short*" patient experts with the consequence that the Committee did not receive sufficient patient testimony to enable the Committee to understand their position.

There are a number of other points made under this appeal point in your letter, which do not seem to me to demonstrate arguable unfairness:

- You refer to a recently published (2024) study by Raebel and colleagues. If this study was not available to the Committee, it was not unfair for the Committee not to have had regard to it.

- You note the Committee's conclusion that an average of 1 carer was appropriate for decision making, and ask that the Committee reconsider the reported patient expert view that an average of 1.5 carers would be more reasonable. It is clear from paragraph 3.19 of the FDG that the Committee did consider that view, but reached a different conclusion. The Committee did not fail to consider it, and so its approach was not arguably unfair. If you consider that the Committee's conclusion on this point was unreasonable, you may re-state this appeal point as a ground 2 point, with an explanation of why you consider the conclusion to be unreasonable (with reference to the rationale for the Committee's conclusion provided in paragraph 3.19 of the FDG).

- You note that the Committee considered the impact of a patient's death on carers qualitatively but not quantitatively and question whether the Committee sufficiently understood the impact. Again, the FDG is clear that the Committee did consider the patient expert evidence on this point and reached a view having considered that evidence. The Committee's approach was therefore not arguably unfair. If you consider that the Committee's conclusion on this point was unreasonable, you may re-state this appeal point as a ground 2 point, with an explanation of why you consider the conclusion to be unreasonable (with reference to the rationale for the Committee's conclusion provided in paragraph 3.20 of the FDG).

- You refer to a study by Song and colleagues. I note that the EAG provided the Committee with specific consideration of this study (see page 431 of the Committee Papers dated 23 October 2023, at page 80 of the EAG's report beginning at page 352 of those papers). Again, therefore, I cannot see an arguable case that the Committee acted unfairly by failing to consider that study.

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

Appeal point 2.1: The Committee did not give due consideration to the proposed MAA (3.24) and the potential to address uncertainties in clinical benefit, patient, and care disutilities.

I am not minded to refer this appeal point to the Appeal Panel. The Committee can consider a recommendation with managed access only when all three of the following criteria are satisfied:

- the medicine has the plausible potential to be cost effective at the currently agreed price, but the evidence is currently too uncertain, and

- new evidence that could sufficiently support the case for recommendation is expected from ongoing or planned clinical trials, or could be collected from patients having the medicine in clinical practice, and

- these data could feasibly be collected within a reasonable timeframe (up to a maximum of 5 years) without undue burden.

  (The Manual, paragraph 6.4.6)

One of the mandatory criteria is therefore that the technology must be plausibly cost effective *at the currently agreed price*, if evidential uncertainties can be resolved. In this case, the Committee explained in paragraph 3.24 that "*at the price the company had chosen to charge, olipudase alfa was not plausibly cost effective*". It was therefore not open to the Committee to make a positive recommendation with managed access. I appreciate that the pricing data is confidential to the Company and therefore may not be available to NPUK; however, without some basis for considering that the proposed data collection would resolve evidential uncertainties with the effect that the technology would become cost effective at its current price, the criteria for a positive recommendation with managed access cannot be met.

Conclusion

The above sets out my initial views on all of your appeal points.

In respect of your points which I am not minded to refer on you are entitled to submit further clarification and/or evidence to me within the next 10 working days, and I will then give a final decision on the points to put before an appeal panel. For the point I am already content to refer on, an oral appeal will be held which is likely to be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information please ensure you have provided a version with this information redacted by 18 April 2024.

Ordinarily appeals are conducted on the basis of the appellants' written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let the NICE Appeal team know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than 3 May 2024. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Yours sincerely

Sharmila Nebhrajani OBE

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11th April 2024

Dear Dr Nebhrajani,

Appeal against Final Draft Guidance Document – Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease) type AB and type B [ID3913]

Thank you for your letter dated 26th March 2024, in which you set out your initial views in relation to the admissibility of the points we raised in our letter of appeal dated 19th March 2024:

Ground 1(a):
NICE has failed to act fairly
Appeal point 1(a).1: The Committee's decision does not fully recognise the significant clinical and life changing benefits of treatment with olipudase alfa
Appeal point 1(a).2: The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities.

Ground 2:
The recommendation is unreasonable in the light of the evidence submitted to NICE.
Appeal point 2.1: The Committee did not give due consideration to the proposed MAA (3.24) and the potential to address uncertainties in clinical benefit, patient, and care disutilities.

Thank you for your consideration of our appeal points, and for confirming that you will refer appeal point **1(a).2** to the Appeal Panel

In addition, we are grateful for your detailed justifications regarding the appeal points you are not minded to refer to the Appeal Panel. Thank you for the opportunity to provide additional detail in relation to these; we provide our comments and observations below.

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

Appeal point 1(a).1: The Committee's decision does not fully recognise the significant clinical and life changing benefits of treatment with olipudase alfa

Your initial view
Following careful consideration, I am not minded to refer this appeal point to the Appeal Panel. I understand your argument to be that the Committee has underestimated the clinical benefits of treatment and the evidence that it can overcome disease severity and reverse disease impact. In support of this, you refer to paragraph 3.26 of the FDG, in which the Committee acknowledges, as part of its consideration of whether olipudase alfa is an innovative treatment, that the QALY calculations probably did not fully capture symptoms, and so the benefit of olipudase alfa may be underestimated. It is clear, however, that the committee took this issue into account in its decision-making, concluding that olipudase alfa is innovative in treating ASMD. I cannot see a basis on which the Committee's consideration of this issue was arguably unfair.

You have also argued that the Committee should have taken account of "*the ten-plus years of real-world evidence, which strongly demonstrates a lack of functional decline in patients with longer term use of olipudase alfa*". Again, I cannot see any arguable unfairness in the Committee's approach. The Committee concluded that olipudase alfa improves clinical outcomes associated with ASMD and that treatment effect can continue into the longer term, but becomes more gradual as the person's condition moves nearer to full-health. The committee did take evidence of longer term effectiveness into account in its decision making, driving its conclusion that a 27.6 QALY gain was considered most plausible.

Our response
We respectfully acknowledge your views and the Committee's recognition that the benefit of olipudase alfa may be underestimated. However, we stand by the concerns raised in our appeal letter, and maintain that the decision is unfair, as:

- the final decision appears to be based on cost as opposed to clinical benefit, and;
- NICE does not provide an equitable assessment process for novel treatments for conditions in which no disease modifying therapy is available, when compared to the assessment process for new treatments for conditions that already have a licensed therapy.

Regarding the Committee's conclusion "that olipudase alfa improves clinical outcomes associated with ASMD and that treatment effect can continue into the longer term, but becomes more gradual as the person's condition moves nearer to full-health." We respectfully make the point that there is no evidence for the assertion "treatment effect becomes more gradual". It is our understanding, based on clinical evidence, that all patients continue to move towards normal or stay normal.

In light of the Committee's conclusion that olipudase alfa is innovative in treating ASMD, a consideration of an adjustment in their approach to the evaluation of highly specialised technologies such as this was anticipated, with flexibility in regard to a further QALY increase that reflects the true clinical and societal value of this technology. Whilst the Committee's conclusion that a 27.6 QALY was considered most plausible demonstrates some recognition of the significant impacts of ASMD, it does not, however, fully recognise:

- That there is no alternative therapy for ASMD patients in England
- The high societal cost of complex best supportive care, involving many different specialities
- The ability of treated patients and their families to participate in life and contribute to society following treatment with olipudase alfa

Appeal point 1(a).2: The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities.

Your initial view
I am minded to refer this appeal point to the Appeal Panel, on the basis that it is arguable that the Committee has acted unfairly if it:

- misrepresented the patient expert's position by stating in paragraph 3.17 of the FDG that "[T]*he patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD*" and/or

- "*cut short*" patient experts with the consequence that the Committee did not receive sufficient patient testimony to enable the Committee to understand their position.

Our response
Thank you for confirming that you will refer this appeal point to the Appeal Committee.

Your initial view
There are a number of other points made under this appeal point in your letter, which do not seem to me to demonstrate arguable unfairness:

- You refer to a recently published (2024) study by Raebel and colleagues. If this study was not available to the Committee, it was not unfair for the Committee not to have had regard to it.

Our response
The Raebel manuscript was made available to the Committee in report form and as a pre-print, provided as additional information to each of our submissions and we would like to request confirmation that this was taken into consideration. This peer-reviewed manuscript, which captures the patient voice and perspective in relation to the benefits of treatment with olipudase alfa, is unique. The information described is not captured in the literature, and we therefore feel that the Raebel manuscript is essential to support the Committee's understanding of the patient experience, and to substantiate the views of the patient experts.

Your initial view
- You note the Committee's conclusion that an average of 1 carer was appropriate for decision making, and ask that the Committee reconsider the reported patient expert view that an average of 1.5 carers would be more reasonable. It is clear from paragraph 3.19 of the FDG that the Committee did consider that view, but reached a different conclusion. The Committee did not fail to consider it, and so its approach was not arguably unfair. If you consider that the Committee's conclusion on this point was unreasonable, you may re-state this appeal point as a ground 2 point, with an explanation of why you consider the conclusion to be unreasonable (with reference to the rationale for the Committee's conclusion provided in paragraph 3.19 of the FDG).

Our response
Thank you for the opportunity to restate this appeal point as a ground 2 point. Our comments are included under this appeal point.

Your initial view

- You note that the Committee considered the impact of a patient's death on carers qualitatively but not quantitatively and question whether the Committee sufficiently understood the impact. Again, the FDG is clear that the Committee did consider the patient expert evidence on this point and reached a view having considered that evidence. The Committee's approach was therefore not arguably unfair. If you consider that the Committee's conclusion on this point was unreasonable, you may re-state this appeal point as a ground 2 point, with an explanation of why you consider the conclusion to be unreasonable (with reference to the rationale for the Committee's conclusion provided in paragraph 3.20 of the FDG).

Our response
Thank you for the opportunity to restate this appeal point as a ground 2 point. Our comments are included under this appeal point.

Your initial view

- You refer to a study by Song and colleagues. I note that the EAG provided the Committee with specific consideration of this study (see page 431 of the Committee Papers dated 23 October 2023, at page 80 of the EAG's report beginning at page 352 of those papers). Again, therefore, I cannot see an arguable case that the Committee acted unfairly by failing to consider that study.

Our Response
We acknowledge your rationale for not including this point as admissable.

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

Appeal point 2.1: The Committee did not give due consideration to the proposed MAA (3.24) and the potential to address uncertainties in clinical benefit, patient, and care disutilities.

Your initial view
I am not minded to refer this appeal point to the Appeal Panel. The Committee can consider a recommendation with managed access only when all three of the following criteria are satisfied:

- the medicine has the plausible potential to be cost effective at the currently agreed price, but the evidence is currently too uncertain, and
- new evidence that could sufficiently support the case for recommendation is expected from ongoing or planned clinical trials, or could be collected from patients having the medicine in clinical practice, and
- these data could feasibly be collected within a reasonable timeframe (up to a maximum of 5 years) without undue burden.

(The Manual, paragraph 6.4.6)
One of the mandatory criteria is therefore that the technology must be plausibly cost effective *at the currently agreed price*, if evidential uncertainties can be resolved. In this case, the

Committee explained in paragraph 3.24 that "*at the price the company had chosen to charge, olipudase alfa was not plausibly cost effective*". It was therefore not open to the Committee to make a positive recommendation with managed access. I appreciate that the pricing data is confidential to the Company and therefore may not be available to NPUK; however, without some basis for considering that the proposed data collection would resolve evidential uncertainties with the effect that the technology would become cost effective at its current price, the criteria for a positive recommendation with managed access cannot be met.

Our response

We acknowledge and accept your rationale for not including this point as admissable, and also the Committee's explanation in paragraph 3.24 that "at the price the company had chosen to charge, olipudase alfa was not plausibly cost effective".

You are correct that pricing data is not available to NPUK. What is available is the lived-experience of our patient community, and the extreme disadvantage placed upon them by the decision to deny access to not only a life saving treatment, but the only treatment available.

We were highly disappointed by the breakdown of commercial negotiations and the failure to reach a favourable agreement on price. NPUK want to see effective treatments approved for use in all types of Niemann-Pick diseases, at prices that are affordable for our health system, but with the appropriate flexibility within that system to take into account the highly complex nature of developing medicines for our ultra-rare diseases.

In our role as patient advocates, we must remind the Committee (and indeed the Company), that their actions and decisions have severe consequences for our patient community. We must question why their lives are not a priority and why they are caught in the void between clinical effectiveness and agreeable cost.

The Committee's understanding "that there is an unmet need for treatments that improve outcomes and quality of life for people with ASMD" (section 3.3 FDG), their conclusion "that olipudase alfa improves clinical outcomes associated with ASMD" (section 3.6 FDG) and their recognition (section 3.26 FDG) that olipudase alfa is innovative in treating ASMD" clearly reflects their preparedness to recommend olipudase alfa for routine commissioning should they be presented with a plausible cost effective option.

We therefore question why, if the Company were not minded to provide a plausible cost-effective option, supported by their economic model, did they pursue an appraisal process in which patient experts were asked to give their time and experience in support of a process that had no opportunity of success.

Appeal point 2.2: The Committee's conclusion that an average of 1 carer was appropriate for decision making is unreasonable

Your initial view

- You note the Committee's conclusion that an average of 1 carer was appropriate for decision making, and ask that the Committee reconsider the reported patient expert view that an average of 1.5 carers would be more reasonable. It is clear from paragraph 3.19 of the FDG that the Committee did consider that view, but reached a different conclusion. The Committee did not fail to consider it, and so its approach was not arguably unfair. If you consider that the Committee's conclusion on this point was unreasonable, you may re-state this appeal point as a ground 2 point, with an explanation of why you consider the conclusion to be unreasonable (with reference to the rationale for the Committee's conclusion provided in paragraph 3.19 of the FDG).

Our response

Section 3.7 of the FDG states that: "The EAG noted that it is likely that standard instruments such as the EQ-5D or SF-36 are not sufficiently sensitive to show improvements in clinical outcomes in ASMD." These are, however, standard tools applied by NICE and NHSE to model QALY's, even though NICE is aware that they have a number of limitations in capturing many aspects of ultra-rare diseases. We would like to better understand how the Committee interpreted the utility benefits taking into consideration the limitations as corroborated by the EAG, and specifically, does the Committee have confidence that the modelling has captured all the benefits seen in clinical practice and reported directly by the patients, parent and carers.

We note the statement in the FDG (3.7) "The committee understood that the evidence on olipudase alfa's treatment effect on HRQoL from the clinical trials was mixed, but there were limitations in the evidence given the different study designs, the small sample sizes, and the relatively short duration of trial follow up." There is no mention of the valuable insights given by the community or patient experts. PRO reports and registry data have proven to be credible measures of the true impact of treatment for patients. It appears that these are considered of secondary importance as "anecdotal evidence", placing doubt on the value, involvement, and commitment of patients, families, clinicians and patient experts.

Section 3.19 of the FDG states "During its first meeting, the committee noted that the impact of the disease would be wider reaching than just the carer of the person with ASMD and would impact their wider social network. But it also considered that ASMD is not likely to produce such a profoundly large carer burden that 2 or more carers are needed to commit full-time efforts towards caring duties." In addition, the Committee considered the views and evidence provided by patient experts that 1.5 carers was preferable for decision making. Due, however, to the precedent in other highly specialised technology guidance for ultra-rare diseases, also referred to within section 3.19 of the FDG, this was not upheld.

We maintain that this approach is unreasonable, and that in this case the Committee should break with precedent and take full consideration of the patient evidence and viewpoint that 1.5 carers would be more appropriate for decision making.

Appeal point 2.3: The Committee's conclusion regarding the impact of a patient's death on carer disutility is unreasonable.

Your initial view

- You note that the Committee considered the impact of a patient's death on carers qualitatively but not quantitatively and question whether the Committee sufficiently understood the impact. Again, the FDG is clear that the Committee did consider the patient expert evidence on this point and reached a view having considered that evidence. The Committee's approach was therefore not arguably unfair. If you consider that the Committee's conclusion on this point was unreasonable, you may re-state this appeal point as a ground 2 point, with an explanation of why you consider the conclusion to be unreasonable (with reference to the rationale for the Committee's conclusion provided in paragraph 3.20 of the FDG).

Our response

We question whether the Committee had a sufficient understanding of the impact of bereavement on parents and carers to support their decision making. In our appeal letter, we highlighted patient expert evidence that stated symptoms are variable and severe, and dependent on disease progression, carer involvement can be all-consuming. We also

highlighted the long-term impacts on carer mental health and ability to participate in everyday life and society.

We are concerned that the Committee's approach did not fully recognise the profound effect of bereavement and feelings of guilt for passing on a genetic disease, or in the case of siblings, the guilt for being unaffected. Whilst we appreciate that the Committee considered the impact of a patient's death on carers qualitatively in their decision making (3.20), we question how this was considered, whether the evidence was robust and sufficiently understood, and why it was not also taken into account quantitatively. We feel the current approach is unreasonable, and we question the appropriateness of applying this.

Conclusion

We thank you once again for considering our submissions in this appeal, and particularly for upholding point appeal point 1(a).2.

We hope that the information provided in this letter has clarified our appeal points and that you can consider these for referral to the Appeal Panel.

It is our profund hope that a pragmatic approach to approving this transformative treatment may be considered, or at least that an agreement to treat clinically vulnerable patients can be reached.

Yours sincerely,

[redacted]

[redacted]
[redacted]Niemann-Pick UK

Making a difference to the lives of those affected by Niemann-Pick

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease) type AB and type B

1 Recommendations

1.1 Olipudase alfa is not recommended, within its marketing authorisation, for treating acid sphingomyelinase deficiency (ASMD; Niemann-Pick disease) in people with type AB or type B.

1.2 This recommendation is not intended to affect treatment with olipudase alfa that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

ASMD (type AB and B) is a genetic disorder that severely affects the quality of life of people with the condition, and their families and carers. It also increases the risk of death. There is no licensed treatment for the underlying causes of ASMD. Best supportive care, such as improving nutrition and breathing, and treating infection, aims to manage the symptoms.

Clinical trial evidence shows that, 1 year after starting treatment with olipudase alfa, lung function is improved and the size of the spleen is reduced in adults and children

with ASMD. The improvements may continue in the longer term, but become more gradual as the condition stabilises.

There are uncertainties in the economic model. Also, the available cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources for highly specialised technologies, even after taking into account the decision to apply additional weight to the effect of olipudase alfa on quality and length of life. So, olipudase alfa is not recommended.

2 Information about olipudase alfa

Marketing authorisation indication

2.1 Olipudase alfa (Xenpozyme, Sanofi) is indicated 'as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B'.

Dosage in the marketing authorisation

2.2 The dosage schedule available in the summary of product characteristics for olipudase alfa.

Price

2.3 The cost for olipudase alfa is £3,612.00 per 20-mg vial (excluding VAT, BNF online accessed October 2023).

2.4 The company has a commercial arrangement, which would have applied if olipudase alfa had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Sanofi, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Niemann-Pick type AB and B

3.1 Niemann-Pick disease is caused by a genetic mutation that means certain cells in the body do not metabolise a substance called sphingomyelin (a type of fat) correctly, leading to a build-up of this in cells. The clinical manifestations of the disease depends on the location of the affected cells but, over time, the accumulation of this fat causes cells to die, resulting in damage to multiple organs. There are about 40 to 50 people diagnosed in England in total with type A, B or AB. Both type AB and type B involve primary symptoms that include an enlarged spleen, low platelets, an enlarged liver and liver disease, delayed growth and puberty, and a blood lipid profile that increases the likelihood of atherosclerosis (hardening of the arteries). Type AB can also include slowly progressive neurodegeneration, which is not present in type B. The disease is associated with increased risk of death, with the leading cause being respiratory or liver failure. Type AB and B, together with type A which is not included in this evaluation, are also known collectively as acid sphingomyelinase deficiency (ASMD). Other forms of Niemann-Pick disease include types C and D, but these are not classified as ASMD nor covered in this evaluation.

Burden of the condition

3.2 ASMD is an inherited metabolic disorder caused by enzyme deficiencies within the lysosome, known as lysosomal storage disease. Both type AB and type B ASMD have a considerable impact on quality of life, not just for the person with the condition but also for their carers, family and wider social network. Build-up of sphingomyelin can restrict lung capacity, causing extreme fatigue and limiting the ability to exercise and take part in everyday life. Patient experts also explained that the effect on energy levels means that the frequent trips for appointments can result in the person being unable to function properly for days afterwards, and that considerable planning is needed in the days running up to appointments.

An enlarged spleen can cause anaemia, limit the ability to eat usual size meals, and cause nausea and vomiting. This poses a substantial risk of malnutrition. The potential for contracting infections (which can be hard to recover from) and the risk of physical injury from contact with enlarged organs can make people afraid of normal activities such as using public transport and engaging in social activities. In children, symptoms such as delayed growth or puberty, and abdominal swelling from enlarged organs, can have a profound psychological impact (particularly in people aged 10 to 16) and can lead to bullying and social isolation. These clinical manifestations considerably impair the ability to perform daily tasks. Children with ASMD in particular often need a carer to support activities of daily living. There is also a significant impact on the quality of life of carers and siblings of people with ASMD. Caring duties can be very time consuming and can inhibit the carer's ability to maintain employment and considerably impact their personal relationships and social lives. Psychological strain in the form of anxiety, depression and stress are common, along with fatigue resulting from the level of care needed and from the child's poor sleep. Also, when a carer is the biological parent of the person with ASMD, there may be feelings of guilt and responsibility for passing on the genetic disease. Siblings of children with ASMD may also be affected, for example, through limited attention from parents because of their caring responsibilities. This may lead to feelings of exclusion, resentment, embarrassment and anxiety. The committee understood that ASMD is a debilitating and life-limiting disease, which has a substantial impact on quality of life for both the person and their carers.

Clinical management

Existing treatment

3.3 The clinical experts explained that there is no licensed treatment addressing the underlying causes of ASMD. Best supportive care involves supportive or palliative treatment to support nutritional needs (with or without feeding tubes), respiration (including supplemental oxygen and

treatment of infections), liver disease (including consideration of a liver transplant), blood products and treatment for low bone mineral density. The patient experts explained that the current treatments do not bring the disease under control to a sufficient degree, and many people still need carers. Day-to-day care for people with ASMD is done at home with the help of carers, but the complex and wide-ranging nature of ASMD means that frequent hospital visits and visits to specialist centres throughout the country are needed to manage the condition. The committee understood that there is an unmet need for treatments that improve outcomes and quality of life for people with ASMD.

A new treatment option

3.4 Both the clinical and patient experts noted that olipudase alfa represents a transformative addition to supportive care for ASMD. The patient experts explained that the treatment can greatly reduce the burden of the disease by addressing the key clinical manifestations. Importantly it reduces the size of the spleen and liver, and increases lung capacity. They explained that this could have a life-changing impact on quality of life for people with ASMD, because they may regain the ability to perform everyday tasks and this would reduce the time needed for their carers' responsibilities. This may allow the carer to return to work and improve their quality of life. It may also reduce the number of people who die from ASMD. The clinical experts agreed and noted that the side effects are relatively minor, especially compared with the symptoms of ASMD. They also noted that the neurological manifestations of ASMD would not be addressed by olipudase alfa. The committee understood that olipudase alfa represents a potential new treatment option for people with ASMD type AB and B.

Clinical effectiveness

Data sources and representativeness of the trial populations

3.5 Clinical-effectiveness data for olipudase alfa came from several clinical trials. ASCEND (n=36) is a phase 2/3, double-blind randomised controlled

trial comparing olipudase alfa with placebo in adults with ASMD. After having the randomised treatment for 52 weeks, everyone had olipudase alfa in the extension period of the trial, which is ongoing and reported data for an additional year at the time of submission. ASCEND-Peds was an open-label single-arm trial in which 20 children and young people under 18 years had olipudase alfa with 52 weeks follow up. DFI13412 was an open-label trial in which 5 adults had olipudase alfa with a 26-week follow up. Finally, LTS13632 is an open-label extension study including people from the ASCEND-Peds and DFI13412 trials. This extension study is also ongoing and reported data for 7 children and 5 adults at a follow up of 4 years and 6.5 years, respectively. The EAG noted that the inclusion and exclusion criteria of the trials were stringent and was concerned that people with a milder or more severe condition may have been excluded. The clinical experts explained that those with the most severe ASMD and a group of adults with mild ASMD, for example those with mildly reduced lung capacity, were excluded from the trials. Each of these exclusions accounted for about 20% of the ASMD population in practice. But the clinical experts explained that usually people with the most severe disease are children, and data from the early access programme suggested that they could also benefit from the treatment. The EAG noted that the baseline body weight in these trials was lower than would be expected in the UK. The clinical and patient experts explained that some people with ASMD have reduced height and weight, but after some time on the treatment, they could catch up to the general population in both respects. The EAG also noted that although the marketing authorisation for olipudase alfa is for people with either type AB or type B disease, it is unclear how many had type AB or B in the trials. The EAG explained that people with type AB disease sometimes have neurological symptoms that are unaffected by olipudase alfa. This means that the level of representation of type AB in the overall cohort is potentially important, because olipudase alfa may have differential effects on key outcomes and quality of life in people with type AB compared with type B. Baseline

characteristics show that roughly 25% of people in ASCEND and 40% of people in ASCEND-Peds had neurological symptoms consistent with type AB disease. But the clinical experts explained that these may be because of developmental delays resulting from non-neurological manifestations of the disease (such as poor nutrition), and not necessarily indicative of type AB disease. For this reason, it is challenging to differentiate between type AB and B in practice, particularly in young people. A more certain diagnosis may only be reached in adulthood, after there has been time for those with developmental delay to catch up with their peers, and for the cause of the neurological symptoms to become clearer. Also, although the proportion of people with type AB disease is unknown, the high proportion of people with neurological symptoms in the trials suggests that people with type AB may be over-represented. This may result in a conservative estimate of the efficacy of olipudase alfa. During the second committee meeting, the clinical experts explained that populations in the trials are representative of those seen in the NHS. But they noted that there will be some children who were too young to be included in the trial, and that all adults present at the earliest stage of their disease in practice, most without fibrosis. The committee noted the variable clinical manifestations associated with ASMD and the spectrum of the disease. It concluded that the populations in trials are representative of those seen in the NHS.

Clinical effectiveness in trials

3.6 Evidence from the clinical trials shows that olipudase alfa improves various key outcomes. Evidence from ASCEND showed that olipudase alfa was associated with a greater improvement from baseline in mean percentage predicted diffusing capacity of the lungs for carbon monoxide (DLco) compared with placebo at both 26-week (14.14; 95% confidence interval [CI] 5.85 to 22.44) and 52-week follow up (19.01%; 95% CI 9.32 to 28.70). The differences were statistically significant. In ASCEND-Peds, evidence showed that the percentage predicted DLco increased by a mean of 33% (95% CI 13.4 to 52.5) from baseline for olipudase alfa. A

responders analysis done by the company also showed that 5 out of 18 adults on olipudase alfa in ASCEND had a clinically significant improvement (defined by the company as an improvement of 15% or higher) in lung diffusion capacity at week 52. The EAG noted that there could be further improvements after 52 weeks but there is uncertainty because no further responder analyses were done. It also noted the high rates of missing outcome assessments at the 2-year follow up (50% for DLco). Spleen volume reduced for people taking olipudase alfa. In the ASCEND trial, 94% of people taking olipudase alfa had a reduction of 30% or more in spleen volume at 12 months, whereas no change was seen in the placebo arm. The EAG noted that again there were a lot of missing outcome assessments at 2 years for this outcome (30% and above). But, clinical advice to the EAG suggested that it is plausible that the reduction would be maintained at this level at least in the months after the trial. Data from the extension study LTS13632 also showed that at 78 months there was a mean reduction in spleen volume for adults (59.5%, n=5) and children (the data is confidential so cannot be reported here). Liver volume also showed a large decrease at both 6-month and 78-month follow up (the exact result is confidential so cannot be reported here). A treatment effect largely in the same direction was also seen for other clinical outcomes, including platelet counts and liver function. The committee noted the improvements in clinical outcomes associated with olipudase alfa, but also noted the relatively short follow up periods in the trials. It questioned the treatment effect of olipudase alfa in the longer term. The clinical experts explained that olipudase alfa was associated with significant improvements in the first 6 to 12 months, and that the improvement could continue after 2 years. During the second committee meeting, the clinical experts also explained that in their experience, patients could still benefit from the treatment after years of taking it, with continuous improvement in spleen volume and lung capacity but at a slower rate of change compared with the earlier stages of treatment. The patient experts explained that treatment has a profound effect on key

clinical outcomes, improving the ability to function in everyday life, including regaining the ability to exercise regularly, which can further improve people's wellbeing. The EAG noted that although there were improvements in clinical outcomes, some effects of the disease did not resolve completely (for example, spleen volume remained several times larger than usual). The clinical experts explained that although people with ASMD with more severe damage, such as lung or liver fibrosis, are unlikely to return to full or near-full health, there will still be a considerable treatment benefit. They noted that people with apparently considerable lung fibrosis on scans subsequently improved after taking olipudase alfa. The committee concluded that olipudase alfa improves clinical outcomes associated with ASMD and the treatment effect can continue into the longer term, but becomes more gradual as the person's condition moves nearer to full-health. The committee took this into account in its decision making.

Treatment effect on HRQoL

3.7 The ASCEND and ASCEND-Peds trials collected health-related quality of life (HRQoL) data using the EQ-5D and the SF-36. Results showed that there was no difference between arms in ASCEND. Both the company and EAG agreed that these results are inconsistent with the key outcome data from the trials and testimony from experts that suggests the improvements in key clinical outcomes have direct effects on quality of life. The EAG noted that it is likely that standard instruments such as the EQ-5D or SF-36 are not sufficiently sensitive to show improvements in clinical outcomes in ASMD. Also, given the relatively short follow up of the ASCEND trial and the small sample size, it was unlikely to see statistically significant differences in quality of life measured by EQ-5D or SF-36. The company suggested that because ASMD is a chronic condition, people may have adapted to it over time, which the instruments may not be sensitive enough to pick up. A positive benefit was shown in children in ASCEND-Peds, with 8 to 18 year olds having mean improvements in HRQoL that were above the threshold for minimally important differences

at 6 months and had increased further by 12 months. Children aged 5 to 7 had an increase near the minimally important difference threshold by 12 months. The EAG explained that ASCEND-Peds was open-label and so there is a risk of bias when interpreting the evidence. But it noted that other studies not included in the submission seem to also show a benefit, meaning the improvement in quality of life from baseline in children may be genuine. In the second committee meeting, the committee queried why some outcomes, particularly fatigue, showed limited improvement in the trial. The clinical experts explained that fatigue and quality of life were not well captured in the trial. They also reiterated the importance of many people with ASMD having got used to their reduced quality of life before starting treatment, which leads to higher than expected baseline scores and limits the sensitivity of tests to show the benefit of treatment. The patient experts agreed with this, noting that it was only after treatment that they realised how severely reduced their quality of life had been before treatment. They also noted that treatment has a transformative effect on quality of life. The committee understood that the evidence on olipudase alfa's treatment effect on HRQoL from the clinical trials was mixed, but there were limitations in the evidence given the different study designs, the small sample sizes, and the relatively short duration of trial follow up.

Economic model

Company's modelling approach

3.8 The company constructed a state transition model with 9 health states to model the disease course of ASMD for olipudase alfa and best supportive care. The model had a time horizon of 100 years. Health states were categorised by both spleen volume and DLco, with 3 levels of severity for each outcome. Spleen volume groups included less than 6 multiples of normal, 6 to 15 multiples of normal, and 15 and above multiples of normal. DLco states included a mild reduction (80% and above predicted value), moderate reduction (40% to 80%) and severe reduction (40% and below). The 10 health states modelled were 9 different combinations of the spleen

volume and DLco health states, plus an additional health state for death. Movement between the health states was determined by transition probabilities informed by data from the clinical trials (see section 3.5), along with additional data from the SPHINGO-100 trial (see 3.11) and a pooled chart review analysis. The committee concluded that the model structure was appropriate for decision making.

Modelling long-term treatment effect

3.9 The company and the EAG had different approaches to modelling long-term treatment effect. In its base case presented at the first committee meeting, the company assumed that everyone on olipudase alfa treatment would transition to the least severe health state (defined by spleen volume less than 6 multiples of normal and DLco 80% or above predicted value) from year 10, and would remain there for the rest of the modelled time horizon or death. The EAG was concerned about the uncertainties in treatment effect in the longer term and preferred to freeze the treatment effect from year 3 onwards in its base case, meaning that people stayed in the same health state after 2 years treatment. The committee considered that freezing the treatment effect after 2 years may be pessimistic, but was also concerned with the lack of justification for the company's approach. So, the committee asked the company to explore the scenario of a treatment effect that continues for 9 years and is then frozen from year 10.

In response to the draft guidance, the company interviewed 6 clinicians, exploring olipudase alfa's treatment effect in the longer term. Three of the clinicians felt unable to predict treatment effect waning, while another 3 estimated there would be none. But the EAG noted the limitations relating to the methods of the interviews, including lack of transcripts or quotes, and uncertainty in the methods used to analyse the qualitative data. In the company's revised model, health states were frozen from year 10, but people taking olipudase alfa got gradually healthier up until this point, so everyone was in the least severe health state by year 10. The EAG noted

that the company's revised approach was even more optimistic than its previous modelling of the long-term treatment effect because it saw people getting healthier at an earlier timepoint. It highlighted that the company presented no further data cut from clinical trials supporting olipudase alfa's treatment effect in the longer term. The EAG instead recycled the treatment effect seen in the clinical trials by maintaining constant transition probabilities from year 2 to year 10, with the health state of the patient frozen from year 10 onwards. The EAG considered that this approach aligned with the scenario the committee requested. The patient experts explained that the modelled health states were too simplistic, and by focusing on spleen volume and lung function the systemic nature of the condition was not properly captured, including the effects on malnutrition, fatigue, functioning and pain. They also advised that the ability to function in everyday life is a key area of improvement. They believed that these symptoms may not have been fully captured in the company's vignette study to inform the utility values of health states in the model. This was partly because the symptoms of ASMD are not fully understood. The clinical experts explained that in their experience spleen volume rapidly improved in the first few years then continued to improve but at a slower rate. They also noted that most people can be expected to move into the mild category for impaired lung function. They stated that around 10% to 20% of people will have neurological symptoms and so have residual disease after treatment, but otherwise patients' quality of life becomes near normal. Considering there may be an ongoing but more gradual improvement in the longer term, the committee agreed that it preferred the EAG's updated approach, which it considered to be in line with what would be expected. It noted that although spleen volume and lung function do not encapsulate the totality of the disease, they are still important outcomes, as well as being proxy indicators of other outcomes and overall health state. The committee concluded that the EAG's approach for modelling long-term treatment effect was appropriate for decision making. It acknowledged that health states defined by spleen

volume and lung function may underpredict the benefits associated with olipudase alfa and took this into account in its decision making.

Disease-related mortality in children

3.10 The company's original and final base case both included disease-related mortality in children, meaning some children would die as a direct consequence of the disease. The EAG considered this inappropriate, noting that in the SPHINGO-100 trial, although 3 out 30 children died during the 11-year follow-up period, the primary cause of death in all 3 children was pneumonia. The clinical experts explained that they have experience with children dying as a result of the disease for both ASMD type B and AB, and this is in line with the published literature. The committee concluded that it is appropriate to include disease-related mortality in children in the model.

Modelling mortality

3.11 The original company base case modelled mortality using the SPHINGO-100 trial, an observational study of 58 people with ASMD type B in North America over an 11-year period. Based on this study, the company estimated a standardised mortality risk (SMR) of 4.3 for people with ASMD compared with the general population, and for severe disease (defined as involving severe splenomegaly) an SMR of 43.1 was applied. The EAG commented that there were several limitations associated with this method. These included the low number of deaths occurring during follow up (9 people died, 8 related to ASMD) in the study, and categorising severe disease simply as whether the person had severe splenomegaly or not. After technical engagement, the company revised its approach to modelling mortality by using a parametric approach based on a pooled analysis of a chart review of 270 people with ASMD. Mortality was modelled for the olipudase alfa arm by applying a hazard ratio of 0.1 to best supportive care mortality. The EAG highlighted severe limitations in the company's revised approach. This included:

- extensive missing data on baseline severity markers such as spleen volume, liver volume and DLco in the chart review
- a lack of details on the methods
- the source of the hazard ratio used to model the olipudase alfa arm
- a lack of analysis and reporting on the checking and suitability of chosen survival curves.

Given the lack of details and reporting of the analysis and methods used, the EAG preferred to maintain the company's original approach in its base case, but noted there were also uncertainties with this. During its first meeting, the committee noted that the company's revised approach was based on a natural history study in an ASMD population, which might be a more appropriate data source because the shape of the hazard would not follow that of the general population. But the committee also recognised the severe limitations in the reporting of the company's approach. So, it asked the company to present additional information and analysis for its parametric approach. After the first meeting, the company revised its parametric approach, and provided further information and analyses used in this approach. It also used a different source of data (McGovern 2013) to inform mortality estimates for children having best supportive care. This was a prospective cohort study of 61 children with type B disease. The company explained that in the interview with the 6 clinicians (see section 3.9), 5 agreed that they preferred the parametric approach to modelling mortality because the curve was more likely to be generalisable to the natural history of the disease (high mortality in children, followed by a plateau and another increase in mortality in people in their late 50s and above). They had no major concerns about the generalisability of the chart review study to the UK population. The EAG maintained its preferred approach, noting that there were still issues relating to the use of the parametric approach. These included the limited justification for using a 0.1 hazard ratio to model olipudase

alfa mortality relative to that in people having best supportive care, the particularly the low rates of mortality attributable to ASMD (10 out of 42 deaths) in children and young people, and the low mortality in adults (6 deaths, 2 related to ASMD). During the second committee meeting, the company explained that its original SMR approach did not capture mortality in children and young people. The clinical experts explained that children and young people with ASMD are more likely to die than adults, but that both are exposed to an increased risk. They also noted that the cause of death may not be accurately recorded for children with ASMD, and death in childhood in this group is likely to be ASMD related. The committee was aware that most participants in the chart review were children and young people at baseline, and the shape of the parametric curves for mortality aligned with the clinical experts' testimonies and the natural history of the condition. The committee concluded that the company's parametric approach was preferred for modelling mortality, noting that both adults and children are exposed to an increased risk of mortality.

Discounting rate

3.12 In its base case, the company presented cost-effectiveness results assuming a 1.5% discount rate for costs and benefits, rather than 3.5% as used in the NICE reference case and as preferred by the EAG. The NICE health technology evaluations manual states that a rate of 1.5% may be considered if the committee is satisfied that the following 3 criteria are met.

Criterion 1

3.13 The first criterion for a 1.5% discount rate is that the treatment must be for people who would otherwise die or have a very severely impaired quality of life (see section 3.1 and 3.2). The committee recalled testimony from patient and clinical experts outlining the considerable impact the disease has on quality of life. The committee noted that despite some uncertainty, both adults and children with ASMD are exposed to an increased risk of

dying compared with the general population (see section 3.10 and 3.11). So, this criterion is met.

Criterion 2

3.14 The second criterion for a 1.5% discount rate is that the technology is likely to restore people to full or near-full health. After technical engagement, the company presented results from an online survey and semi-structured interviews with 10 children or their carers before and after treatment with olipudase alfa. This showed that the treatment improved all non-neurological symptoms. The EAG agreed that this survey showed important improvements associated with olipudase alfa, but the small sample size of the study and unclear methodology limited the confidence in the findings. Also, the EAG highlighted that clinical evidence showed that organs were still enlarged after treatment (at around 6 multiples of normal for spleen volume) and that meant that DLco at 52 weeks was around 70% of the predicted value, which may indicate that people are not restored to full health. The committee was concerned about the persistence of a significantly enlarged spleen and whether this prevents people returning to full or near-full health. During the second committee meeting, the patient experts explained that although an enlarged spleen is still possible after treatment, the reduction in size will be considerable and it is still likely that a person can live with near to normal quality of life despite having a spleen several times larger than normal size. The clinical experts also noted that, although lung capacity may still not be normal compared with the general population, all patients they see moved to mild impairment with improvements in cardiovascular function, exercise tolerance and fitness. The committee noted that people with type AB disease with neurological symptoms would not return to full health after treatment, and that it is often not possible to correctly differentiate between type AB and type B disease in childhood (see section 3.5). It agreed that most people would return to full or near-full health. So, this criterion is met.

Criterion 3

3.15 The third criterion for a 1.5% discount rate is that the benefits must be sustained over a long period of time. The company noted that the extension of trials provided data up to 4 years for children and up to 6.5 years for adults. It also explained that there is evidence in Gaucher disease that the effects of enzyme replacement therapy are maintained up to 20 years after starting treatment. One of the clinical experts noted that some people in the extensions of phase 1b trials have had olipudase alfa for up to 10 years without evidence of treatment effect declining. The patient experts also supported this, with their experience indicating that the effect is sustained in the long term. The EAG highlighted the small number of people with data available at the longer-term follow-up time points in the clinical trials. The committee recalled its discussions on the treatment effect of olipudase alfa in the longer term (see section 3.6 and section 3.9). It concluded that it is highly plausible the treatment effect may be maintained in the longer term, although the improvements may become more gradual over time as people's conditions stabilise. Considering the entirety of the evidence and the clinical and patient expert testimonies, the committee concluded that olipudase alfa met the criteria to be eligible for a 1.5% discount rate to be applied to both costs and benefits.

Patient weight

3.16 The company and EAG modelled the body weight of people with ASMD differently. The company modelled adult weight as being constant over time, whereas for children it fluctuated over time by applying a z-score function estimated from the SPHINGO-100 study and applying this to UK growth weight charts. The EAG noted that the average weights for both adults and children seemed lower than the UK average if using other sources. The EAG preferred to use the 2019 Health Survey for England report to model weight, and also applied a z-score function to the adult population, estimated from 18 year olds in the SPHINGO-100 study. The

patient and clinical experts agreed that it is common for people with ASMD to be shorter than their peers. Weight would be reduced because of this shorter height, although the difference compared with their peers is not as pronounced because the condition causes enlarged organs, which add weight. But the clinical experts noted that after several years of treatment, patients' weight would return to within the average range seen in the UK, but not to the extent of overweight or obese. The committee concluded that the EAG's approach was more appropriate, and that weight for both children and adults was likely to be within the normal range, but lower than the average of the UK general population. So, the starting weight should be at the lower end of the UK average in the model.

Carer disutilities

Applying carer's disutility

3.17 The company and EAG both included disutilities for carers of people with ASMD as part of their base cases, but differed on a number of assumptions. The company only applied disutilities to carers in the best supportive care arm, assuming that there are no carer needs for people taking olipudase alfa. The EAG preferred that disutilities be based on the health state of the patient, irrespective of the treatment arm. It noted that carers for people with severe health states would have reduced quality of life regardless of the treatment used. The patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD. The committee concluded that carer's disutility should be based on the health state of the person with ASMD, irrespective of the treatment used.

Carer disutility values

3.18 There was an absence of published literature for carer disutility values in ASMD. Instead, the company sourced disutility values from Pompe disease, a condition in which the body cannot break down glycogen for energy, resulting in glycogen accumulation in tissues. It then applied a

carer disutility of -0.15 for all health states. The EAG had clinical advice suggesting that Pompe disease would incur a higher carer burden and therefore a higher disutility than ASMD, so it preferred to source the values from different chronic conditions, including multiple sclerosis and meningitis. Also, the EAG provided different values for children and adults (arguing that children need more attention than adults), and higher utility decrements for severe disease (defined as spleen volume 15 times normal or greater). The EAG's carer disutility values ranged from -0.010 to -0.080. The committee agreed that it was reasonable that children and people with more severe health states would incur greater carer disutility, also noting that it preferred carer disutilities to be applied based on the person's health state irrespective of treatment (see section 3.17). The committee concluded that the EAG's approach of differentiating carers' disutilities by both the severity of health state, and whether the person treated is a child or an adult, was appropriate for decision making. After the first meeting the company revised its approach, so carers experienced differential disutility depending on whether the child was in a mild, moderate or severely impaired health state (determined by a combination of spleen volume and liver function), but the values were again derived from Pompe disease. The committee was concerned with sourcing disutility values from Pompe disease because it is likely that this would result in overestimating the disutility associated with caring for someone with ASMD, and so bias the analysis in favour of olipudase alfa. It concluded that the EAG's approach (which remained unchanged after the first meeting) was still preferable.

Number of carers

3.19 The company assumed that children would have an average of 2.6 carers (including siblings) whereas the EAG preferred an average of 1 carer per person. The EAG noted that there is little precedent for assuming more than 2 carers, even in evaluations for more severe lysosomal storage diseases, and that research into carer disutilities is limited, particularly in the context of sibling disutilities. The patient experts explained that there

is considerable strain on quality of life for the person with the disease, the impact it has on functioning in everyday life and the corresponding impact on carers and their wider social network. They also outlined the negative impact on siblings (see section 3.2). During its first meeting, the committee noted that the impact of the disease would be wider reaching than just the carer of the person with ASMD and would impact their wider social network. But it also considered that ASMD is not likely to produce such a profoundly large carer burden that 2 or more carers are needed to commit full-time efforts towards caring duties. In response to consultation, the company maintained that an average of 2.6 carers better reflected the caring needs for ASMD. The company also explored the scenario of an average of 1.5 carers, in line with suggestions from a patient group survey that suggested that 1.5 carers was the most appropriate assumption. The committee recognised the substantial impact ASMD has on both patients and carers, as outlined by the company in its submission and supported by the clinical and patient experts. But, considering the precedent in other highly specialised technology guidance for ultra-rare diseases, the committee did not agree that the evidence and information presented in this evaluation should be dealt with differently. It also noted that ASMD severity is on a spectrum, so caring needs would differ between the less and more severe health states and an average of 1 would be reasonable. The committee concluded that an average of 1 carer was appropriate for decision making.

Carer's disutility after bereavement

3.20 The company assumed a carer disutility of -0.50 if the person with ASMD died, and applied this disutility across the remainder of the time horizon used in the model. The EAG was concerned that there was no conclusive research into the application of carer disutilities after bereavement. Consequently, there is high uncertainty about whether disutilities should be applied after a patient dying, how big the disutility should be, and for how long. So, the EAG removed any disutility after death. The company explained that excluding carer's disutility for bereavement would be

counterintuitive, leading to a result in which carers are not affected by the death of their loved ones. The committee noted that there may be a carer's disutility associated with a patient dying, but that this would not be as high as -0.50 as assumed by the company. Also, it would not persist for the remainder of the time horizon of the model. The committee also noted that the EAG's approach may not capture the loss of utility associated with bereavement. Given the uncertainties and lack of research into the field, the committee concluded that it would be appropriate not to include carer's disutilities associated with bereavement numerically in the model, but it acknowledged the impact of a patient's death on carers and would qualitatively consider it in its decision making. In the second committee meeting, the company maintained its view that not including a disutility associated with the patient dying was counterintuitive and inappropriate, so did not change its base-case assumption. The patient experts stated that there would be a considerable disutility for the carer if a patient died, and that this would reduce somewhat over time. The committee noted this, but considered that the company's assumption that carers would live for 100 years and experience such a high disutility for this entire period of time inappropriate. The committee concluded that it would qualitatively consider the impact of a patient's death on carers in its decision making.

Recently diagnosed subgroup

3.21 After the first committee meeting, the company presented a new subgroup analysis of people newly diagnosed with ASMD. The company argued in its response that people who have had the disease for a longer period of time before treatment have a greater likelihood of having irreversible organ damage, which may limit the effects of treatment on key outcomes. The clinical experts explained that people with extensive lung fibrosis and liver cirrhosis may not return to full health after treatment because of the extent of the damage they have experienced. So, it is possible that people who have treatment immediately after diagnosis would experience greater benefits and be more likely to reach the least severe health state. The

clinical experts also explained that some people with the disease still only receive a diagnosis in adulthood, but noted that with increasing awareness of the disease the chances of this happening will decrease in the future and become rare. Regarding severity, the EAG noted that the subgroup analyses in the pivotal trial did not show variation in treatment effect according to baseline severity, although the analyses were limited because of small sample sizes. The committee recalled the challenges in diagnosing children and young people (section 3.5 and section 3.14). It recognised the difficulties in defining a 'recent' diagnosis in practice, and was concerned that some young patients may be missed. It recognised the appeal of starting treatment before organ damage occurs, but had not been provided with any direct evidence of greater effectiveness in newly diagnosed patients. There would also be ethical concerns if recommending the treatment only for people who have recently been diagnosed and excluding people with longer standing disease, given the unmet need. It concluded that the recently diagnosed subgroup proposed by the company was not appropriate for decision making.

QALY weighting

3.22 The committee understood that NICE health technology evaluations: the manual (2022) specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per quality-adjusted life year (QALY) gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. A weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. During its first meeting, the committee considered that some criteria for applying a QALY weighting were likely to be met, but there were uncertainties in the size of the QALY gain. The committee discussed the undiscounted QALY gains associated with

olipudase alfa during its second meeting. It noted this was 27.6 in the scenario considered the most plausible. In this scenario, the company assumed a 50% split between children and adults for the patient population. Considering the entirety of the evidence, the committee agreed that a full QALY weighting of 2.7 should be applied.

Cost-effectiveness estimates

The committee's preferred assumptions

3.23 The committee's preferred assumptions included the following:

- The EAG's approach to modelling long-term treatment effect of continuing the treatment effect for 9 years, then freezing it at year 10 (see section 3.9).
- Including disease-specific mortality for children in the model (see section 3.10).
- The company's parametric approach to modelling mortality (see section 3.11).
- A discount rate of 1.5% for the cost-effectiveness analysis (see sections 3.12 to 3.15).
- The EAG's approach to modelling body weight, with the starting weight at the lower end of the UK average (see section 3.16).
- Applying carer disutilities depending on the health state of the person with ASMD, regardless of which treatment they have (see section 3.17).
- Using carer disutilities that depend on disease severity and whether the person with ASMD is an adult or child (see section 3.18).
- Using an average of 1 carer per child with ASMD (see section 3.19).
- Not including carer disutilities associated with patient death in the model. The committee agreed to consider this qualitatively in its decision making instead (see section 3.20).

Both the company and EAG's base-case ICERs for olipudase alfa compared with standard care were over £300,000 per QALY gained (the

exact ICERs are confidential and cannot be reported here). The committee considered that it had not been presented with any ICERs that were likely to be within the range NICE normally considers an effective use of NHS resources for a highly specialised technology, even when taking into account the decision to apply a QALY weighting of 2.7, which meant that the committee were willing to accept a higher ICER than usual (see section 3.22).

Managed access

Recommendation with managed access

3.24 The committee considered whether a recommendation with managed access may address the uncertainty in the clinical evidence and assumptions. It noted that the company had submitted a managed access proposal. It proposed to address the uncertainties about the long-term treatment effect through data collection from the ongoing extension study of LTS13632 and the extension study of ASCEND, and an international Niemann-Pick disease registry. The company also planned qualitative studies to understand the quality of life of carers and the burden of the disease on patients and carers. The committee was aware that assumptions about long-term treatment effect and carer's disutilities, especially carer's disutilities associated with patient death, substantially affected the ICERs. It discussed whether further data collection from a managed access agreement could help resolve these and the surrounding uncertainties. It noted that both the ongoing studies are due to complete in 2024, which would not be long enough to resolve all of the uncertainties relating to long-term treatment effect. And data from the Niemann-Pick international registry could be retrieved outside a managed access agreement. For uncertainties relating to carer's disutilities, there was a lack of detail on the methods of the planned qualitative study, and the committee was concerned that the study may be subject to a small sample size and uncertainties related to this. The committee noted that some data may be collected from the ongoing or planned studies, but it

was unclear how much additional value they would bring to resolving the uncertainties in the model. Further, it would need to be shown that olipudase alfa was plausibly cost effective in the context of a highly specialised service. But the committee recognised that, at the price the company had chosen to charge, olipudase alfa was not plausibly cost effective. So, it concluded that a recommendation with managed access was not appropriate for addressing the uncertainties in this evaluation.

Other factors

Equalities

3.25 No equality issues were identified in the evaluation.

Innovation

3.26 The committee recognised that olipudase alfa is the first treatment addressing the underlying causes of ASMD. The evidence shows that it was associated with improvement in several clinical outcomes, and that the treatment effect may continue. During the first committee meeting, the clinical experts stated that symptoms that patients regard as normal (limited exercise capacity, pain, fatigue) may disappear with treatment and people develop a new understanding of what 'normal' life is. The general public's preference weighting in the company's vignette study may help to account for these symptoms, but it is unlikely that the QALY calculations fully captured them, and so the benefit of olipudase alfa may be underestimated. In response to the draft guidance consultation, the company listed a series of other benefits associated with the treatment that may not be fully captured in the model. But the EAG noted that although these benefits may not be fully captured in the model, several others were incorporated into the vignette study the company used to inform health state utilities. These included, for example, fatigue, ability to function, abdominal pain and discomfort, exercise tolerance, emotional impacts, hospitalisations, infections, bleeding events, ability to eat normally, reduced height, muscle strength and school attendance. The

company's model may have underestimated the benefits associated with the treatment because of how the health states were defined (see section 3.9). The committee considered that there were no other benefits that had not been captured in the model. It concluded that olipudase alfa is innovative in treating ASMD and took this into account in its decision making.

Conclusion

Recommendation

3.27 The committee was not presented with a plausibly cost-effective estimate after taking into account all of its preferred assumptions and other considerations (see section 3.23). So, it could not recommend olipudase alfa for routine commissioning to treat ASMD type AB or type B.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names o the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Peter Jackson

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Tom Jarratt
Technical lead

Yelan Guo
Technical adviser

Vonda Murray
Project manager

ISBN: [to be added at publication]

Redacted slides

NICE National Institute for Health and Care Excellence

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and A/B)

Chair's presentation

2nd evaluation committee meeting

Highly Specialised Technologies committee

Chair: Peter Jackson

ERG: Peninsula Technology Assessment Group (PenTAG)

NICE technical team: Tom Jarratt, Yelan Guo, Richard Diaz

Company: Sanofi

December 2023

Key issues

Long term treatment effect: Does the committee consider that interviews with clinicians conducted by the company substantiate olipudase alfa's treatment effect in the long term?

Discount rate: Does the committee consider 1.5% discounting to be suitable?

Carer's utilities: would the committee change its preferences on carer's utilities re:

- Differential utilities for carers; average 1 carer each child; and considering impact of patient's death on carers qualitatively

Modelling mortality: Does the committee consider the additional information provided by the company justifies its preferred parametric approach for modelling mortality?

Recently diagnosed subgroup: What is the committee's view on the incident patient subgroup proposed by the company? Is it plausible for consideration?

Uncaptured benefits associated with olipudase alfa: Does the committee agree that key factors that may influence cost effectiveness of olipudase alfa have been captured in analysis?

QALY weighting: Does quality-adjusted life year (QALY) weighting apply?

MAA: Is olipudase alfa suitable for managed access?

Abbreviations: MAA: managed access agreement

Olipudase alfa not recommended

Committee noted uncertainties and requested further analyses:

Key conclusions, clinical:

- **Population representativeness**: populations in trials may be representative of those in the NHS, but uncertainties in whether the range of people who would have olipudase alfa in clinical practice included in trials;
- **Long term treatment effect**: Olipudase Alfa improves clinical outcomes associated with ASMD, but uncertainties in its longer-term treatment effect;
- **Treatment effect on health-related quality of life (HRQoL)**: evidence mixed but noted limitations in evidence given different study designs, small sample sizes, and relatively short duration of follow up in trials.

Key conclusions, economic:

- **Discount rate**: 3.5%, criteria for non-reference discount rate of 1.5% not met because:
  - Risk of mortality unclear;
  - Uncertainty in whether extent of improvement full or near-full health; and
  - Uncertainty in how long treatment effect may maintain;

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Key conclusions:

Economic (continued):

Carer's disutilities: should be based on health state irrespective of treatment;

- **Differential carer's disutilities**: EAG's approach of differentiating by both severity of health state, and children versus adult preferred ;
- **Number of carers**: an average of 1
- **Carer's disutilities for mortality:** would consider qualitatively rather than numerically in model;
- **QALY weighting**: criteria may be met but uncertainty in size;
- **MAA**: not appropriate option for addressing uncertainties;

Further analyses requested:

- **Long term treatment effect**: explore scenario of a treatment effect that continues for 9 years and frozen from year 10;
- **Mortality**: EAG approach for modelling mortality preferred but requested company to present additional information and analysis for its revised approach post TE;

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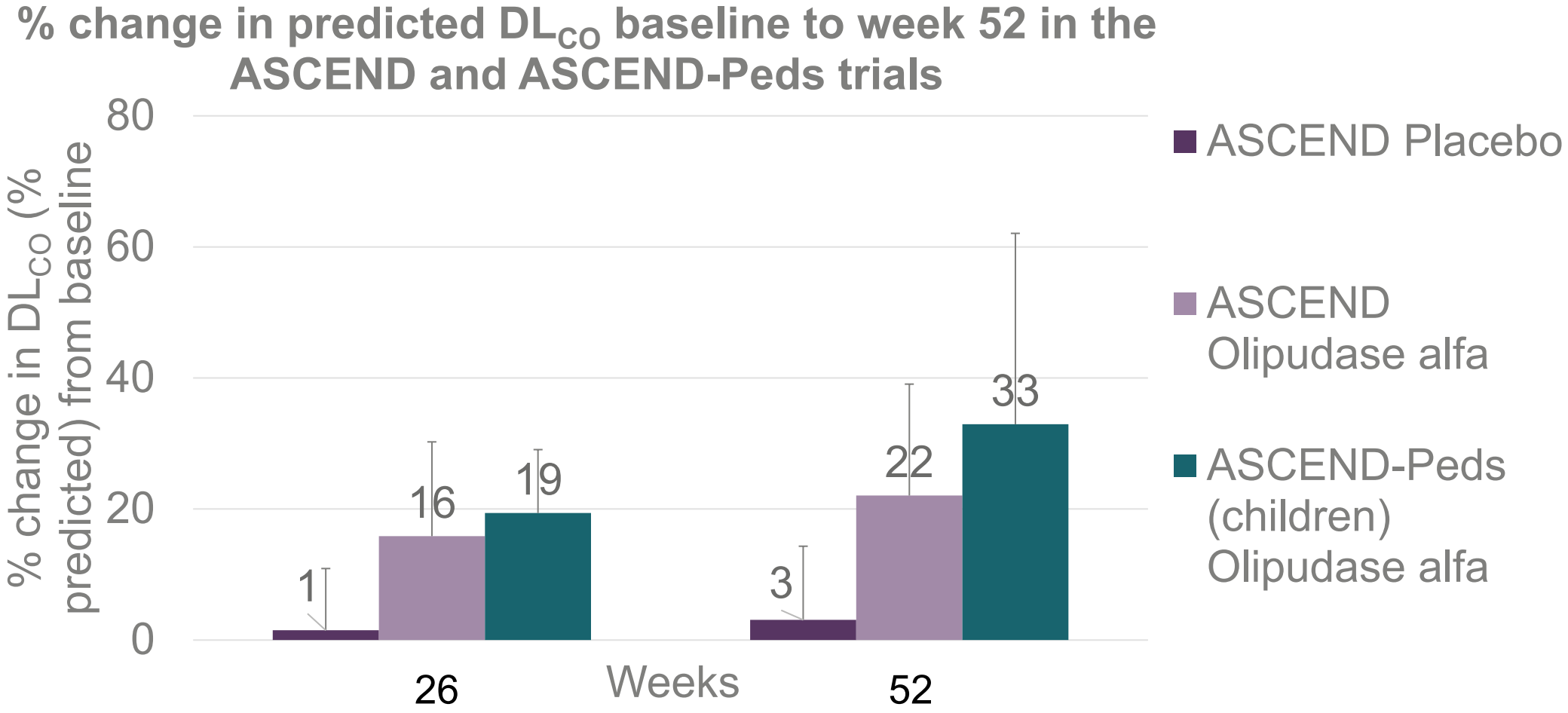
Abbreviations: MAA: managed access agreement; QALY: Quality-adjusted life years; TE, technical engagement

Recap: Clinical trial results, % change in predicted DL_{CO}

DG: evidence showed olipudase alfa was associated with a greater improvement from baseline in mean percentage predicted Dlco compared with placebo



DLCO results adjusted for haemoglobin concentration and ambient barometric pressure as anaemia common in ASMD. Error bars represent the standard error.

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Abbreviations: DG: draft guidance; Dlco: diffusing capacity of the lungs for carbon monoxide

Recap: Clinical trial results, change in Spleen volume

DG: Spleen volume still enlarged after taking olipudase alfa

Month 12 ASCEND:

- 94% were responders to olipudase alfa (defined by company as **change** ≥30%)
- No change for placebo arm

Overview of consultation responses

Company: in response to draft guidance,

- Obtained advice from 6 clinicians with experience of using olipudase alfa; response includes clinical opinion sought from interviews;
- As requested, revised its base with scenario analyses exploring:
  - Long-term treatment effect;
  - Approach to modelling overall survival;
  - Assumptions relating to patient weight;
- In addition, provided analysis not requested by committee, including:
  - Impact of ASMD on carers and number of carers;
  - Subgroup analysis for recently diagnosed patients;

Responses and comments from:

- **Patient experts:** impact on carers and uncaptured benefits of olipudase alfa;
- **Patient/professional group, NPUK:** unmet needs and other benefits not captured by outcomes in clinical trial;
- **Clinical experts**: long term treatment effect;
- ***NHSE*:** "With regard to the long term benefits of this drug, there would be some merit in pursuing a managed access agreement; the data collection would be supported by the NHS services which should improve compliance"

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Abbreviations: NPUK: Niemann-Pick UK

Key issue: Long-term treatment effect

ECM1 company approach (Post-TE)	Committee preference
Patients transition to least severe health state from year 10 and stay there for time horizon	Plausible to assume some long-term effect; explore freezing treatment effect at year 10

Company post ECM1 –Revised base-case: Smoothed acceleration in treatment effect from year 2 to 10, perfect effect from 10 year, then frozen

- Discussions with 6 clinicians (managing ASMD in 29 patients, 11 had olipudase alfa) indicate rapid improvement in first year which continues into long term
- Questions covered nature of ASMD, pooled survival analysis, and experience with olipudase alfa in the short and long term:
  - For most children, when treated early, normalisation between 1.5-10 years
  - For adults, between 2-10 years; those with high disease burden (extensive lung fibrosis and liver cirrhosis) would benefit, but not reach normal health
  - 3 clinicians felt unable to predict treatment waning, 3 estimated there would be none
- Base-case of reaching least severe state by year 10 is therefore conservative
- *Scenario analyses: transitions frozen at year 3, 6, and 10*

EAG: Company's approach incorrect interpretation of committee preference;

- Health-state frozen from year 10 but model assumes everyone had gradually reached best health-state by this point – more optimistic than original base-case as higher proportion now responded early;
- ***EAG scenario***: treatment effect continues by maintaining constant transition probabilities from year 2 onwards and freezes from year 10 (except for mortality)

Abbreviations: ECM1: Evaluation committee meeting 1; TE: technical engagement

Key issue: Long-term treatment effect

EAG – Long-term effect plausible but no data to substantiate it

- **No new data cut reported,** long term data in trials uncertain because of high attrition in outcome assessment

Interviews with clinicians - Questions appropriate and relevant, however uncertainties because of limitations in methods:

- Clinicians treated median of 2 patients (range 1-4), treatment duration not reported
- No transcripts or quotes from interviews, qualitative analysis methods unclear
- Unclear how much of clinicians' conclusions based on experience or on interpretation of data (including opinions on treatment effect wanning and timepoint for normalisation)

Clinical expert consultation comments:

- Rapid response in primary outcome measures in first 6-12 months of treatment, but clear ongoing improvement after that
- Clinical parameters improve for at least 6.5 years - No evidence of effect reversing
- Patients achieve near-normal QoL after 2-4 years of therapy, effect continues for 10 years
- Most lysosomal treatments only show improvement for 18-24 months

Does the committee consider interviews with clinicians substantiate company's assumption of long-term treatment effect?

Abbreviations: QoL: Quality of life

Key issue: Modelling mortality

Company original (pre-TE) / EAG approach: SMR	ECM1 company parametric approach (post-TE)	Committee preference
SPHINGO-100 provides SMRs vs. general population. Non-severe splenomegaly: 4.3 severe splenomegaly: 43.1	• BSC: pooled chart review data • Olipudase alfa: 0.1 hazard ratio applied to BSC mortality • include paediatric disease-specific mortality	Company's Pre-TE/EAG approach

What was said at ECM1

- Company's post-TE approach based on natural history study might better reflect hazard, however, severe limitation in reporting and lack of information

Company approach post ECM1 – used modified parametric approach

- BSC for children modelled using a prospective study (McGovern et al.)
- Company maintain that shape of survival curve using parametric approach more representative of natural history of ASMD
- 5/6 clinical experts agreed there were no concerns with generalisability
- Hazard ratio of 0.1 conservative given experts agree most people will return to normal or near-normal life

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Abbreviations: ASMD: acid sphingomyelinase deficiency; ECM1: Evaluation committee meeting 1; SMR: standardised mortality risk; TE: Technical engagement

Key issue: Modelling mortality

EAG – Company provided description of fit indices but SMR approach still preferred

Limitations with parametric approach still exist

- Use of fitted survival function to model BSC survival is unsuitable
- Insufficient justification for applying 0.1 hazard ratio to model olipudase survival

Issues with data in Chart review study

- Only 23.8% (10/42) paediatric deaths attributable to ASMD, rest were classified as unknown
- Low rates of mortality in adults (6 deaths, 2 related to ASMD)
- Childhood mortality rates in UK are lower (4.2 per 1000 live births) compared with other countries in the study (in particular, Brazil: 14.7 and USA: 6.3)

Does the committee consider the additional information provided by the company justifies its preferred parametric approach for mortality?

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Abbreviations: BSC: best supportive care; SMR: Standardized mortality ratio

Key issue: Discount rate

Was the biggest driver of cost-effectiveness at ECM1

ECM1 company approach	ECM1 committee preferences
1.5% for costs and benefits	3.5% for costs and benefits

What was said at ECM1, draft guidance

- **Would people with ASMD otherwise die or have a very severely impaired QoL?**
  Committee: ASMD likely severely impairs quality of life, but mortality risk is unclear.
- **Is it likely to restore them to full or near-full health?**
  Committee: Extent of improvement is uncertain (for example, spleen still enlarged)
- **Are the benefits likely to be sustained over very long time-period?**
  Committee: Treatment effect may maintain for some time but uncertainties

Company approach post ECM1 – 1.5% discount rate appropriate

- Clinical expert advice to company suggests people having olipudase would, over time, return to normal or very near normal health (including spleen and liver volume, liver and lung function, nutrition, daily functioning, hospitalisations, platelet count, and more) and this would be sustained into long-term.
- 2 exceptions: Patients with neurological symptoms (clinical experts estimate 20% of children, 10% of adults; severity varies); patients with irreversible organ damage but a few (20-25% of adults);
- Trial evidence and biologically plausibility supported by benefits of ERT in Gaucher disease

NICE

Does the committee consider 1.5% discounting to be suitable?

Abbreviations: ECM1: Evaluation committee meeting 1; ERT; enzyme replacement therapy

Consultation comments: treatment effect

Experts: too much focus by committee and model on spleen volume

Patient expert/professional group

- People who have had ASMD for extended period will have suffered irreversible damage **This would not be true for someone just diagnosed with disease**
- People experienced massive improvements in liver and spleen volume within 52 weeks, unrealistic to expect return to full health within this short period of time
- Although unlikely to return to 'Near normal or Full Health', burden of their disease will be massively reduced, especially in newly diagnosed patients;
- Concerned meaningful impact of a reduced spleen size for ASMD patients not fully recognised…whether or not it reaches 'normal', reduction is associated with significant clinical and psychological benefits, greatly improved QoL, and ability to participate in life

Clinical expert

- Unsurprising that spleen volumes do not normalise given degree of baseline splenomegaly. Phase 1b study shows generally continued benefit (stabilisation in normal range or continued improvement towards normal) over 6.5 years of published data.
- Dosing study suggests that costs could be saved by offering lower doses to patients

Abbreviations: QoL: Quality of life

Key issue: Discount rates

EAG – No new evidence, maintain that 3.5% is most suitable

- Olipudase provides meaningful benefit but no clear evidence olipudase alfa returns people to full or near-full health, at final follow-up spleen volume, liver volume and respiratory function meaningfully below norm.
- Additionally, company assumed below normal weight for patients, which impacts dosing and costs; suggests deviation from normal or near-normal health status
- Variation in response in those treated
- Plausible that irreversible organ damage would be lower if treated immediately following diagnosis but no data on actual numbers
- Estimates of % with neurological symptoms may be reasonable, some children with symptoms may represent other issues unrelated to ASMD that are resolved prior to adulthood

Key issue: Carer utilities

Disutility for mortality was a biggest ICER driver at ECM1

ECM1 company base-case	ECM1 committee preference	Updates post-ECM1
Disutility for BSC arm only	Disutility for both arms	Disutility for both arms
Value based on Pompe disease (-0.15)	EAG values, higher if patient is child or has severe disease	Based on Pompe disease with varying severity
2.6 carers per child	1 carer per child	Maintained base-case
-0.50 loss for remaining time horizon if patient dies	Consider qualitatively	Maintained base-case

Company response to consultation:

- EAG approach underestimates disutility, does not account for impact of impaired lung function (as recognised by all 6 experts consulted) - Pompe dataset differentiates mild, moderate and severe states, captures lung impairment.
- Parent/caregiver survey highlighted significant impact on carers; described having to share the burden with others (e.g. grandparents) to manage appointment schedule.
- 2.6 carers more reflective – *Scenario analysis with 1.5 carers*

New carer disutilities in company base-case

DLco	SV 1-6	SV 6-15	SV >15
100 - 80	-0.072	-0.162	-0.180
80 – 40	-0.162	-0.162	-0.180
<40	-0.180	-0.180	-0.180

EAG: Same value to children and adults, maintain view that Pompe is not suitable proxy for ASMD as it is more severe

Abbreviations: DLCO: Diffusing capacity of the lungs for carbon dioxide; ECM1: Evaluation committee meeting 1; ICER: incremental cost-effectiveness ratio

Key issue: Carer utilities

Patient experts:

- Preferred assumptions have higher disutility for children and severe spleen volume but spleen size alone not a good indicator and adults not necessarily better off due to progressive nature of disease
- Carer involvement can be all-consuming, frequent and multiple medical appointments, regular monitoring, and several clinical teams, often located in different locations plus challenges of coordinating appointments at any age / point of progression.
- Clinicians do not see the considerable preparation and days of recovery needed to visit hospital for clinic, number of carers should be higher
- Bereavement would have large impact for a significant period, reducing over time

EAG: Agree that ASMD and bereavement both have large impact on carer(s) but issue is a methodological one about applying carer disutility into HTA submissions, maintain:

- No precedent for >2 carers
- Normal STAs only include impact on single individual, suitable compromise in HST is to expand to include impact on a single carer
- Company approach to bereavement disutility assumed carer will live an additional 100 years and experience same loss for entire period, maintain that methodological uncertainties around applying this disutility means that considering it qualitatively is more appropriate

Would the committee like to change its preferences for carer's utilities?

Abbreviations: HST: Highly-specialised technology; HTA: Health technology appraisal; STA: Single technology appraisal

Uncaptured benefits

ECM1: there might be benefits not fully captured but uncertain

Company approach post ECM1 –

Other benefits not factored in cost-effectiveness estimate include improvement in:

- Fatigue, tiredness, low energy levels (not solely related to lung function or organomegaly) and exercise tolerance;
- Patient height, which can have a large impact on psychological wellbeing;
- Abdominal pain and discomfort;
- Bleeding complications, splenic crises requiring hospitalisations, frequent infections;
- Inability to eat normally and maintain a healthy weight;
- High cholesterol levels that often result in requirement for treatment;
- In infants and young children delayed growth and development (for example inability to sit due to poor muscle tone).

EAG – Some were not captured in model, but several others incorporated into vignettes company used to inform health state utilities, for example:

- Impact on fatigue, ability to function, abdominal pain and discomfort, exercise tolerance, emotional impacts, hospitalisation, infections, minor bleeding events, ability to eat normally, reduced height, muscle strength and school attendance;
- Company's pivotal trial assessed olipudase alfa's treatment effect on fatigue, pain, and functioning, no benefit showed after 1 year's use;

Abbreviations: ECM1: Evaluation committee meeting 1

Does the committee agree that key factors that may influence cost effectiveness of olipudase alfa have been captured in analysis?

Incident patient subgroup

Company submit subgroup evidence for patients recently diagnosed

- People with longer standing disease more likely to have permanent organ damage
- Company provides subgroup for people treated from diagnosis

Additional amendments for subgroup analysis

Parameter	ECM1 committee preferred base-case	New subgroup parameter
Starting age	-	Based on age at ASMD diagnosis in ASCEND or ASCEND-peds • Adults: 18 years; Children: 2.5 years
Long-term efficacy	Freeze from year 10	Move to least severe health state from year 5 and stay there for remaining time horizon

Patient expert

- People who have had ASMD for extended period will have had irreversible damage **This would not be true for someone just diagnosed with disease**

***EAG*:** Subgroup analysis based on pivotal trial did not show variation in treatment effect according to baseline severity, though analyses limited because of small sample size

Should a separate recommendation be considered for this subgroup?

Abbreviations: ECM1: Evaluation committee meeting 1

Company updated and EAG base case assumptions

Assumptions in updated company and EAG base cases

Model feature	Company	EAG	Agreement
Discount rate	1.5%	3.5%	✗
Long-term treatment effect	Freeze from year 10 but revised with an acceleration factor between year 2 to 10	Transition probabilities constant between year 2-9, frozen from year 10	✗
Carer disutility			
• Disutility for both arms?	Yes	Yes	✓
• Disutility based on health-state	Based on Pompe disease but different severities	Vary by: severe (vs. non severe) and children (vs. adults)	✗
• Number of carers	2.6	1	
• If patient dies	-0.50 for time horizon	None	✗
Mortality	Parametric approach (pooled chart review and McGovern)	SMR approach (SPHINGO-100 study)	✗
Child disease-specific mortality?	Yes	Yes	✓
Weight	HSE data with lower mean	Same (but different implementation)	✓

Abbreviations: ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate

Committee preferred assumptions from ECM1

Preferred assumptions

Preferred assumptions	DG section
3.5% for benefits and costs	3.12-3.15
Model health states recycle based on trial data for 9 years then freeze from year 10	3.9
Carer disutility based on patient health-state irrespective of treatment received, and use EAG source of values	3.17-3.18
1 carer per child and per adult patient	3.19
No carer disutility associated with patient dying (impact to be considered qualitatively)	3.20
EAG approach to modelling mortality but include disease-specific mortality for children	3.10
EAG approach to modelling patient weight, adjusted to use lower end of UK average	3.16

Committee conclusion on cost-effectiveness:

- ICER substantially above £100,000 per QALY gained
- Olipudase met the criteria for a QALY weighting **Unclear of what weight to use**
- Even when considering other factors such as impact of caregiver bereavement and QALY weighting, olipudase was not considered cost-effective

Abbreviations: DG: Draft guidance; ICER, incremental cost-effectiveness ratio; QALY: Quality-adjusted life year

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Abbreviations: QALY: Quality-adjusted life year; QoL: Quality of life

NICE National Institute for Health and Care Excellence

Thank you.

NICE National Institute for Health and Care Excellence

Back up information

Recap: Nature of condition

ASMD: One of inherited metabolic disorders caused by enzyme deficiencies within lysosome, known as lysosomal storage diseases (LSDs); progressive, debilitating and life-limiting

Diagnosis: ASM activity levels followed by molecular genetic testing to confirm ASMD

- Most diagnosed during childhood: diagnosis age varies but typically 2-6 years
- Currently subtypes determined by clinical presentation; no clear diagnostic test available to distinguish between type A, B, or AB

Incidence & prevalence:

- ~1 to 2 people diagnosed each year in England (type A, B or AB)
- ~40 to 50 people diagnosed in total but likely more given lack of newborn screening
- Most diagnosed patients in the UK have ASMD type B

Mortality: increased risk, respiratory or liver failure leading cause of death, neurodegenerative disease adds further risk to ASMD A/B; life expectancy: less than 60 years of age in the UK

Treatment: currently no treatment address underlying pathology of ASMD; only symptomatic, palliative or supportive care available, involving wide range of specialisations

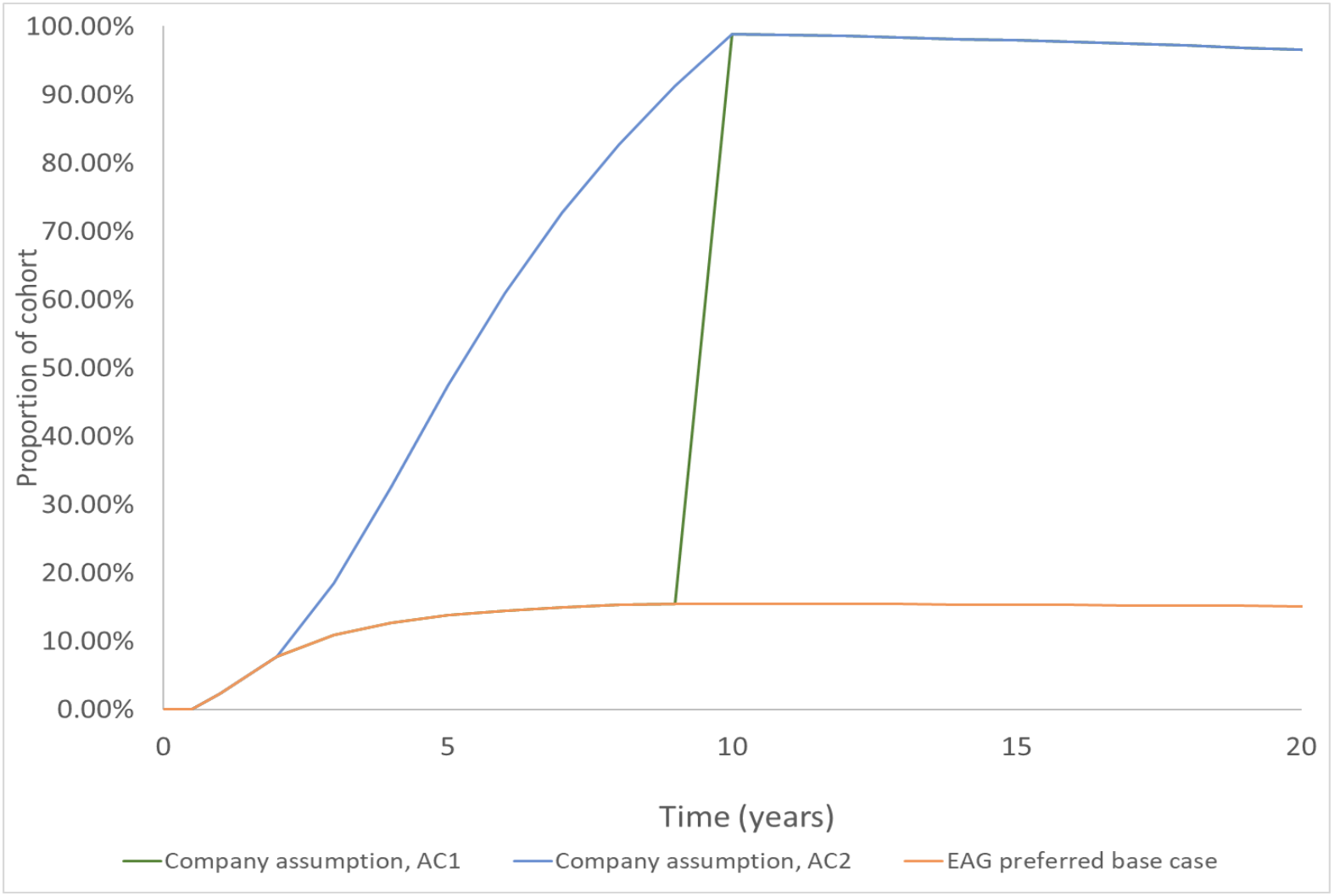
Consultation comments: Uncaptured benefits of treatment with Olipudase Alfa

Patient experts/professional group

- Olipudase Alfa stops deterioration and reverses huge amounts of damage in key areas
- No best supportive care for many elements of disease (fatigue, memory and developmental problems);
    - Fatigue can be significant, drain on energy can prevent normal development;
    - Treatment with Olipudase Alfa increases energy levels, could be life changing for patients;
- Trial and model focussed too heavily on spleen volume and lung function, benefit on other aspects of condition not captured:
    - **Malnutrition:** can be significant, olipudase alfa provides huge improvement very early in treatment process (including reducing nausea): This was not captured
    - **Bone thinning:** Bone and joint pain, significantly reduced mobility. Pain cannot be treated with Ibuprofen/anti-inflammatories because of liver involvement;
    - **Other:** Neutropenia, headaches, night sweats, palpitations, poor healing and skin problems);

Key issue: Long-term treatment effect

Proportion of adult cohort in best health state (DLCO>=80, SV<6)



EAG: company's assumptions not reasonable extrapolations of observed data;

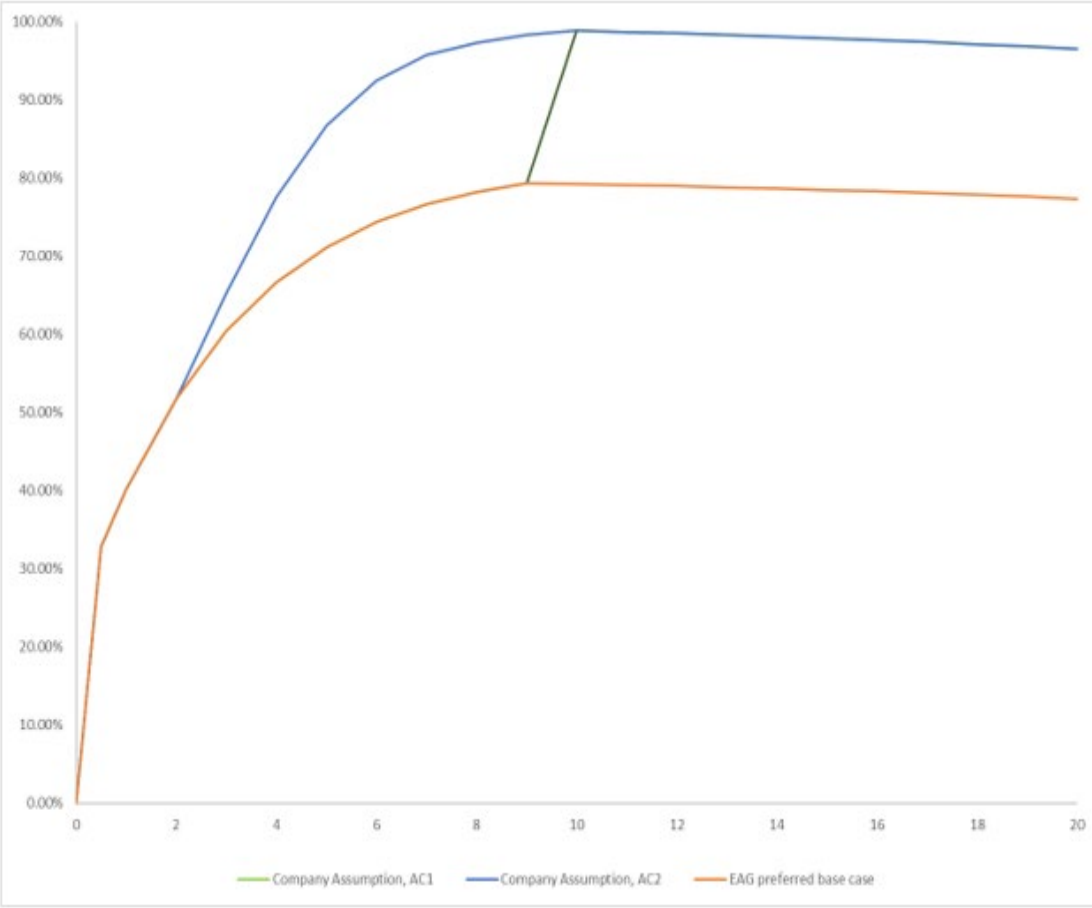
EAG's preferred scenario: implied a continued increase in effect with a declining rate from year 2; proportion in best health stabilises around year 5 or 6 (with a slight decline due to mortality effect)

Source: EAG response, figure 1: Markov trace for proportion of cohort in the best health state at each time point;

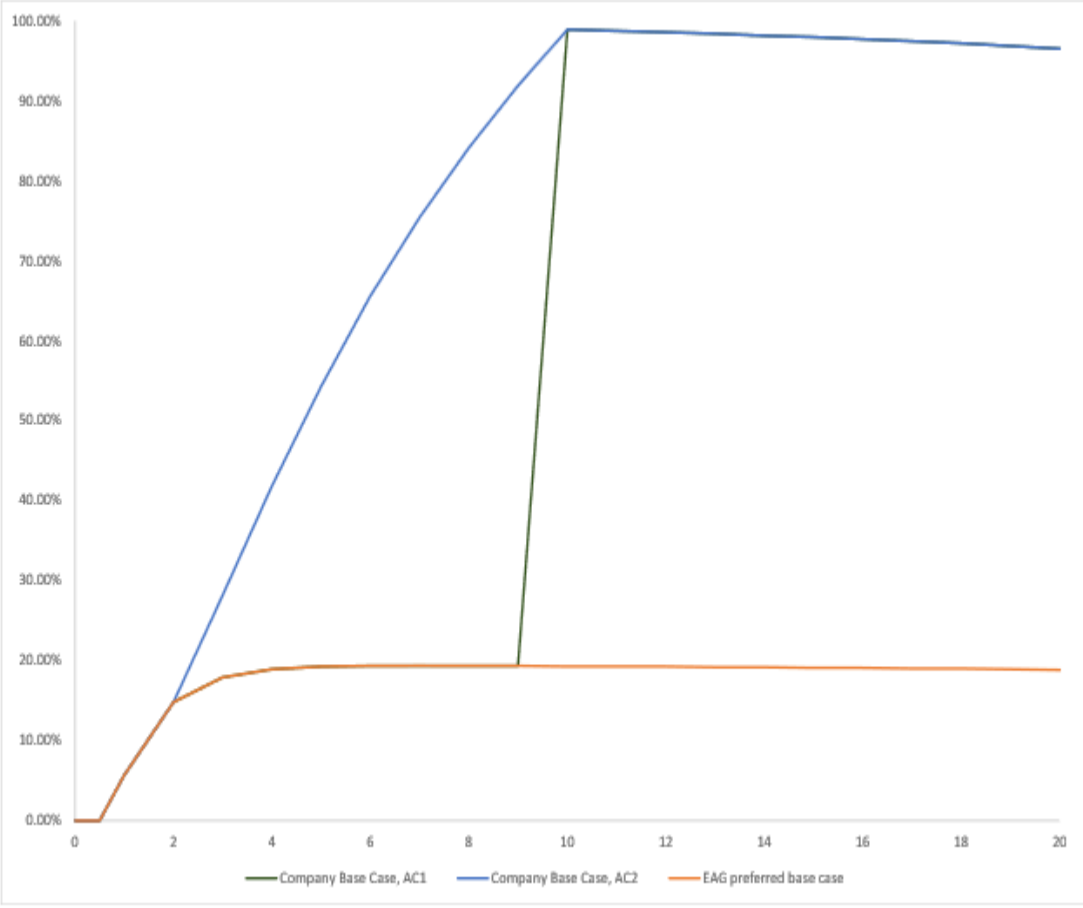
Abbreviations: DLco, diffusing capacity of the lungs for carbon monoxide SV: Spleen volume

Key issue: Long-term treatment effect

Proportion of adult cohort in best SV health state (SV<6)



Proportion of adult cohort in best DLCO health state (DLCO>=80)



Source: EAG response, figure 2 and 3

Abbreviations: DLco, diffusing capacity of the lungs for carbon monoxide SV: Spleen volume

EAG: Other comments

Trial generalisability

- EAG also noted uncertainties in the following areas:
  - Proportion of participants in the trials with ASMD type AB (not recorded in the trial)
  - the typical height and weight of people with ASMD
  - due to exclusion of people with the most severe and mild disease from the trials.

Exit interviews with trial participants

- Methods not presented, nor was a full discussion of the data from the interviews
- Clinical benefits likely improve but magnitude uncertain
- Measures used by the company to assess fatigue, pain and functioning did not capture any differences between participants receiving and not receiving olipudase alfa

QALY weighting

EAG: does not consider appropriate to apply QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Life incremental QALY gained	Weight
Less than or equal to 10	1
11 to 29	Between 1 to 3 (equal increments)
Greater than or equal to 30	3

EAG: may not be appropriate to apply QALY weight, because;

- Lack of robust clinical data informing company's economic model given rarity of condition;
- High degree of uncertainty in company's assumptions;
- Results sensitive to assumptions on long term treatment effect, carer's disutilities, patient weight and discount rate;

Abbreviations: QALY: Quality-adjusted life year

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Abbreviations: MAA: managed access agreement

Managed access

Considerations: how much uncertainties can be resolved by ongoing studies, and would further qualitative data for carer's disutilities useful for decision making

Company: Studies either ongoing or planned to address uncertainties in evidence

- **For long term treatment effect and understanding of ASMD patients in the UK, ongoing studies:**
  - ❑ Long-term extension study KTS13632 (n=25), up to 9-year follow up;
  - ❑ ASCEND (n=36), extension treatment period, open-label up to 4-year;
  - ❑ International Niemann-Pick Disease registry (INPDR);
- **For carer's QoL and burden of the illness, planned studies include:**
  - ❑ Qualitative interviews of ASMD caregivers;
  - ❑ A-third part study jointly sponsored by ASMD registries in different countries including US and UK;

Managed access team: potential candidate for MAA but uncertainties remain

- **Long term treatment effect and weight**:
  - ❑ 5-year time frame for MAA, both extension studies finishing in Q2 2024, may be not long enough to resolve all uncertainties relating to long-term treatment effect or weight;
- **Carer's QoL**:
  - ❑ qualitative data to be collected but value of resolving uncertainties (number of carers, carer's disutilities, carer's disutilities relating to patient death) in model unclear; may be subject to small sample size;
- **Disease specific mortality in paediatric patients**:
  - ❑ data may be available from INPDR during appraisal, could be retrieved outside of managed access;

Abbreviations: MAA: managed access agreement

NICE National Institute for Health and Care Excellence

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and A/B) [ID 3913]

Highly Specialized Technology Appraisal Committee

[December 2023]

Part 2 slides

Key issues

Long term treatment effect: Does the committee consider interviews with clinicians conducted by the company substantiate olipudase alfa's treatment effect in the long term as assumed?

Discount rate: Does the committee consider 1.5% discounting to be suitable?

Carer's utilities: would the committee change its preferences on carer's utilities re:

- Differential utilities for carers; average 1 carer each child; and considering impact of patient's death on carers qualitatively

Modelling mortality: Does the committee consider the additional information provided by the company justifies its preferred parametric approach for modelling mortality?

Recently diagnosed subgroup: what is the committee's view on the incident patient subgroup proposed by the company? Is it plausible for consideration?

Uncaptured benefits associated with Olipudase alfa: Does the committee agree that key factors that may influence cost effectiveness of olipudase alfa have been captured in analysis?

QALY weighting: Does quality-adjusted life year (QALY) weighting apply?

MAA: Is Olipudase alfa suitable for managed access?

Company updated and EAG base case assumptions

Assumptions in updated company and EAG-base cases

Model feature	Company	EAG	Agreement
Discount rate	1.5%	3.5%	✗
Long-term treatment effect	Freeze from year 10 but revised with an acceleration factor between year 2 to 10	Transition probabilities constant between year 2-9, frozen from year 10	✗
Carer disutility			
• Disutility for both arms?	Yes	Yes	✓
• Disutility based on health-state	Based on Pompe disease but different severities	Vary by: severe (vs. non severe) and children (vs. adults)	✗
• Number of carers	2.6	1	
• If patient dies	-0.50 for time horizon	None	✗
Mortality	Parametric approach (pooled chart review and McGovern)	SMR approach (SPHINGO-100 study)	✗
Child disease-specific mortality?	Yes	Yes	✓
Weight	HSE data with lower mean	Same	✓

Abbreviations: ICER, incremental cost-effectiveness ratio; SMR, standardised mortality rate

Company latest base-case

Company base-case (1.5% discount rate)

	Incremental (olipudase alfa vs BSC)				ICER (£/QALY)
	Costs (£)	Life years gained	QALYs	Undiscounted QALYs	
Children	[redacted]	22.05	34.87	61.09	[redacted]
Adult	[redacted]	9.08	19.78	31.99	[redacted]
Combined	[redacted]	15.57	27.32	46.54	[redacted]

Company base-case, incident patient subgroup (1.5% discount rate)

	Incremental (olipudase alfa vs BSC)				ICER (£/QALY)
	Costs (£)	Life years gained	QALYs	Undiscounted QALYs	
Children	[redacted]	21.41	36.18	65.17	[redacted]
Adult	[redacted]	10.07	24.00	42.28	[redacted]
Combined	[redacted]	19.71	30.09	53.72	[redacted]

Company base-case with committee preferences

Model results with committee preferences using the SMR approach to mortality (3.5 %discount rate)

	Incremental (olipudase alfa vs BSC)				ICER (£/QALY)
	Costs (£)	Life years gained	QALYs	Undiscounted QALYs	
Children	[redacted]	3.81	8.07	23.50	[redacted]
Adult	[redacted]	4.56	5.89	11.91	[redacted]
Combined	[redacted]	4.18	6.98	17.70	[redacted]

Model results with committee preferences using parametric approach to mortality (3.5% discount rate)

	Incremental (olipudase alfa vs BSC)				ICER (£/QALY)
	Costs (£)	Life years gained	QALYs	Undiscounted QALYs	
Children	[redacted]	10.80	11.66	36.85	[redacted]
Adult	[redacted]	4.18	7.04	18.96	[redacted]
Combined	[redacted]	7.49	9.35	27.91	[redacted]

EAG' preferred assumptions in its base case: Paediatric population

Deterministic exploratory analyses

Treatment	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company original base-case (EAG corrected)	[redacted]	34.87	[redacted]
EAG preferred assumptions			
Costs and benefits discounted at 3.5%	[redacted]	19.21	[redacted]
Mortality based on splenomegaly	[redacted]	22.44	[redacted]
Removed carer disutility associated with death of patient	[redacted]	23.15	[redacted]
Treatment effect continues to year 10, then frozen.	[redacted]	30.41	[redacted]
Patient weight: lower end of HSE2019 data	[redacted]	34.87	[redacted]
Magnitude of carer disutility	[redacted]	34.86	[redacted]
1 carer for children	[redacted]	33.69	[redacted]
EAG base-case	[redacted]	7.90	[redacted]

EAG' preferred assumptions in its base case: Adult population

Deterministic exploratory analyses

Treatment	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company original base-case (EAG corrected)	[redacted]	19.78	[redacted]
EAG preferred assumptions			
Costs and benefits discounted at 3.5%	[redacted]	11.48	[redacted]
Mortality based on splenomegaly	[redacted]	14.73	[redacted]
Removed carer disutility associated with death of patient	[redacted]	15.24	[redacted]
Treatment effect continues to year 10, then frozen	[redacted]	15.13	[redacted]
Patient weight: lower end of HSE2019 data	[redacted]	19.78	[redacted]
Magnitude of carer disutility	[redacted]	18.69	[redacted]
EAG base-case	[redacted]	5.81	[redacted]

EAG: base case and undiscounted incremental QALYs

	Incremental costs (£)	Incremental QALYs	Undiscounted Incremental QALYs		ICER
Population			Excluding caregivers	Including caregivers	
Children	[redacted]	7.90	22.44	23.05	[redacted]
Adult	[redacted]	5.81	11.65	11.74	[redacted]

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Back up information

Committee preferred assumptions from ECM1

Preferred assumptions

Preferred assumptions	ECD section
3.5% for benefits and costs	3.12-3.15
Model health states recycle based on trial data for 9 years then freeze from year 10	3.9
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Committee conclusion on cost-effectiveness:

- ICER substantially above £100,000 per QALY gained
- Olipudase met the criteria for a QALY weighting **Unclear of what weight to use**
- Even when considering other factors such as impact of caregiver bereavement and QALY weighting, olipudase was not considered cost-effective

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
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Managed access

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Managed access

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Managed access team: potential candidate for MAA but uncertainties remain

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- **Carer's QoL**:
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- **Disease specific mortality in paediatric patients**:
  - ❑ data may be available from INPDR during appraisal, could be retrieved outside of managed access;

Other considerations

Managed Access

Is the technology considered a potential candidate for managed access?	Yes	Treatment is a candidate for the IMF. Currently no treatments for this indication and it can provide large QALY gains for children and adults.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Uncertainties could be resolved with further data from ongoing trials but some uncertainty is likely to remain. Several uncertainties need committee input.
Can data collection be completed without undue burden on patients or the NHS system	Unclear	Some burden is likely to fall on clinicians.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	Yes - Minor	Agreeing a DCA that includes data collection from the registry may impact timelines. Unclear whether this treatment would be given a routine recommendation based on its clinical effectiveness data.

Is olipudase alfa suitable for managed access?

Vonda Murray

From: Richard Diaz
Sent: 07 December 2023 12:33
To: Mandy Tonkinson; Yelan Guo; Thomas Jarratt
Cc: Vonda Murray
Subject: RE: Splenectomy and Mortality

Thanks Mandy. I think the committee is aware of this. But I will mention it.

Richard Diaz (he, him)
Associate Director – Technology Appraisals and HST
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | M1 4BT | United Kingdom
Tel: 44(0)161 870 3274
Web: www.nice.org.uk

From: Mandy Tonkinson <Mandy.Tonkinson@nice.org.uk>
Sent: Thursday, December 7, 2023 12:32 PM
To: Richard Diaz <Richard.Diaz@nice.org.uk>; Yelan Guo <Yelan.Guo@nice.org.uk>; Thomas Jarratt <Thomas.Jarratt@nice.org.uk>
Cc: Vonda Murray <Vonda.Murray@nice.org.uk>
Subject: FW: Splenectomy and Mortality

Hi Rich, Yelan and Tom

I've received the email below from James one of our ID3913 PE's.

I don't know relevant this is in the decision making, can it be shared with Peter/committee?

Best wishes

Mandy Tonkinson
Public Involvement Adviser – Public Involvement Programme
National Institute of Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | Manchester | M1 4BT | United Kingdom
Tel: 44 (0) 161 413 4009
Web: http://nice.org.uk

From: James Dyson <jdautoengineering@outlook.com>
Sent: Thursday, December 7, 2023 12:13 PM
To: Mandy Tonkinson <Mandy.Tonkinson@nice.org.uk>
Subject: Splenectomy and Mortality

Hi Mandy,

Would you be as good as to help me raise this with the committee after they shut me down.

I feel strongly that the there is a direct correlation between patients who have had a splenectomy and their mortality.
The spleen is extremely good at holding storage and removing it only means the storage will accumulate everywhere else, it is this accumulation of storage in other areas that is causing increased lung and liver disease and ultimately death. It is not a coincidence!

Thank you so much!

--

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Sanofi**

Please return to: **NICE DOCS**

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Sanofi would like to thank the National Institute for Health and Care Excellence (NICE) and the committee for the opportunity to comment on the draft guidance. Sanofi are disappointed that the current draft guidance does not recommend olipudase alfa for the treatment of ASMD. This response provides further support for key assumptions in relation to the uncertainties identified in the draft guidance. Following the issue of the draft advice, Sanofi sought to obtain advice from all clinicians with experience of using olipudase alfa in the UK. The following response includes clinical opinion from 6 out of 7 treating UK clinicians. A full summary of the interviews is provided as an appendix. Further information on our approach to modelling mortality is also included, as was requested by the committee. In summary the available evidence supports the following conclusions: • In the vast majority of patients, olipudase alfa treatment is expected to result in normal health and life expectancy, • This benefit is likely to be maintained in the long term,

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	• The overall survival in untreated patients with ASMD is better represented by the parametric approach than the SMR approach to modelling ASMD mortality, • ASMD has a profound impact not only on patients, but on their caregivers as well, including all members of the family, • Bereavement should be included in the cost-effectiveness analysis, • A number of important benefits of olipudase alfa on aspects of the disease such as fatigue, pain, or child growth and development patients are not captured in the economic model. In addition, data did not allow modelling of the impacts of treatment on areas such as school and work attendance, or social functioning. In order to support committee decision making we have provided a revised base case analysis and further scenario analyses (including those requested by the committee) to further explore the uncertainty surrounding key assumptions. These include varying: • the assumptions on long-term benefits of olipudase alfa, • the approach to modelling overall survival, • the impact of ASMD on caregivers and the number of paediatric caregivers, • the assumptions regarding patient weight. Whilst we believe that olipudase alfa provides life-transforming benefits to all patients, we have also provided cost-effectiveness analyses for patients with recently diagnosed disease for the committee's consideration. These patients will benefit from normal quality and length of life with olipudase alfa treatment and are also more representative of the patient population going forward, when treatment with olipudase alfa becomes available. We maintain that our base case analyses reflect the clinically plausible and often conservative assumptions and that given the ultra-rare nature of ASMD it would be inappropriate to take a highly conservative and risk-averse approach to decision making that can be inferred by some of the preferred assumptions outlined in the draft guidance.

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	Based on the company base case, the weighted ICER in paediatric patients is [redacted]er QALY gained and in adult patients [redacted] QALY gained ([redacted]er QALY gained for the combined population). For recently diagnosed patients the weighted ICER in paediatric patients is [redacted]er QALY gained and in adult patients [redacted]er QALY gained ([redacted]er QALY gained for the combined population). We are committed to working with all stakeholders to ensure that UK patients can access this transformative medicine. We urge the committee to consider uncertainty in the context of the extreme rarity and severity of ASMD and the many likely benefits of treatment with olipudase that it is not possible to capture within the cost-effectiveness analysis.
1 Long-term treatment effect	**Existing evidence from long-term studies and clinical opinion both support that the benefits of olipudase alfa are maintained long-term.** The ongoing long-term treatment study (LTS13632) of olipudase alfa in paediatric and adult patients with ASMD who have previously received treatment in clinical studies DFI1342 and ASCEND-Peds provides the longest follow up. At the latest data cut (01 March 2021), a reduction of [redacted] ([redacted]and [redacted] ([redacted]spleen volume and liver volume, respectively, was observed in adult patients treated with olipudase alfa up to Month 78 compared with baseline levels. Additionally, a [redacted]improvement in platelet count from the pre-infusion baseline was observed by Month 78. An improvement of [redacted]in % predicted DL_{CO} was observed by Month 78 compared with the pre-infusion baseline. In paediatric patients in LTS13632, treatment with olipudase alfa resulted in a reduction in spleen volume and liver volume of [redacted]and [redacted]respectively, by Month 48 compared with baseline levels. Additionally, a mean improvement of [redacted]was observed in platelet count from pre-infusion baseline by Month 48. A [redacted]improvement in % predicted DL_{CO} was observed by Month 48 compared with the pre-infusion baseline. These results highlight the rapid and continued effect on reducing organomegaly and improving organ function seen in patients treated with olipudase alfa.

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	In discussions with six UK clinicians who, in total, are currently managing 29 ASMD type B and A/B patients and have treated 11 patients with olipudase alfa, it was highlighted that patients not only rapidly improve in the first year or two following the initiation of treatment, but also continue improving beyond that time, in the majority of cases reaching or approaching normal health. According to clinical opinion, the efficacy of the response to treatment with olipudase alfa would be maintained and would not decrease over time. When asked about the most plausible scenario in terms of effect of olipudase alfa beyond the clinical trial horizon, the responses were: • For the majority of paediatric patients, particularly when treated early, normalisation would be achieved. The suggested time to achieving this state would vary between patients and estimates between 1.5 and 10 years were provided. • For adult patients, it is expected that patients would improve before stabilising at 2-10 years; it is expected that patients with high disease burden at the start of treatment (extensive lung fibrosis and liver cirrhosis) would benefit substantially, but not reach normal health. Based on clinical opinion the company base case analysis in which patients reach the mildest health state (approximating normal health) in 9 years is a conservative approach for the vast majority of the patient population. This, in particular, applies to patients representative of the UK ASMD population going forward: with recently onset disease and without irreversible damage to their health caused by ASMD. Following the request from the committee, a scenario analysis was also carried out where the treatment effect continues for 9 years and is frozen at year 10. Additional scenario analyses were also carried out based on the clinical advice, with transitions frozen at year 3 and 6. However, based on the available evidence the company base case assumption where patients reach the mildest health state by year 10 can be considered conservative. The scenario analyses are reported in the accompanying documentation.
2 Modelling mortality	**The parametric approach to modelling mortality provides a closer representation of the natural history of ASMD** Within this appraisal two approaches to modelling mortality have been considered:

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- Standardised mortality risk (SMR)
- Parametric fits

SMR approach

In the original company base case, the SMR approach was used as mortality data was limited and did not allow fitting of a parametric model. Data from the SPHINGO-100 observational study of 58 people with ASMD type B was used to estimate SMRs of 4.3 and 43.1 for people with mild and severe splenomegaly (≥15 multiples of normal), respectively.

Parametric fit: adults

As further data was collected from an international chart review (n=270; submitted as an addendum in April 2023), a parametric approach became possible [2].

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]e demographic characteristics are consistent with the information obtained in discussions with clinical experts regarding the composition of the UK patient population.

Surgical splenectomy was documented in patient records at diagnosis for [redacted]tients. Although less commonly undertaken in recent clinical practice than in the past, clinical advice to Sanofi supports it is still considered as a management option for patients with very advanced spleen-related symptoms.

In this approach, overall survival was modelled using a single- and piecewise-parametric approach. Data from adult and paediatric patients was analysed together, as in a retrospective study there is high uncertainty

	regarding the age of onset of the disease in the included patients. Goodness of fit was assessed by Akaike information criterion (AIC) and Bayesian information criterion (BIC), as well as assessment of visual fit. This involved using different parametric models to assess the fit of the observed survival curves. Parametric approaches used in this testing included: • Exponential model • Weibull model • Gompertz model • Log-logistic model • Log-normal model • Generalised Gamma model Although only the optimal survival curves for the observed data were included in the addendum, multiple SPLINE and STREG analyses were conducted prior to selection of the curve with best fit. Further to the committee request for additional information relating to modelling mortality and goodness of fit, the comprehensive SPLINE and STREG analyses have been submitted along with this document (additional Microsoft® Excel files). These were not used for modelling, as they either did not provide a good fit to the observed data or required too high a number of degrees of freedom. As outlined in the Addendum (submitted in April 2023), the piecewise parametric approach was chosen as the most appropriate, since it provided a better fit to the observed Kaplan Meier data compared with a single fitted parametric survival curve. Gompertz distributions both before and after the splitting point of 40 years provided the lowest AIC/BIC statistics compared to other distributions. The first Gompertz distribution (i.e., before 40 years) provided a very close fit to the observed data. The second Gompertz distribution (i.e., after 40 years) provided both the best fit to the observed data but may be considered conservative as it predicted that all patients would be expected to die by age 80 (i.e., the earliest age predicted compared with all other distributions). However, given the heterogeneity of the patient population, this may not capture the entire spectrum of disease. The second-best fitting distribution in the second time-period (the Weibull distribution) was therefore chosen. Scenario analyses are provided with different parametric fits. In individual discussions five out of six clinical experts highlighted the shape of the survival curve obtained using the parametric approach was more representative of the natural history of the disease (high mortality in paediatric patients, followed by a plateau and another increase in mortality in

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	patients in their late 50s and beyond) than the curve obtained using the SMR approach. Clinical experts all believed there are no major concerns regarding the generalisability of the pooled analysis to the UK population. <u>Parametric fit: paediatric patients</u> A different approach was chosen for paediatric patients, as the study by McGovern et al (61 patients paediatric at entry – defined as age <21 years due to delayed puberty) provided a prospective analysis of paediatric patients [1]. A one-piece parametric fit was considered the most appropriate based on AIC, BIC and assessment of visual fit. Detailed analyses of different fits have been submitted along with this document (additional Microsoft® Excel files). The estimates obtained from this study were also consistent with the higher mortality observed in paediatric patients. <u>Effects of olipudase alfa in parametric fit approach</u> A hazard ratio of 0.1 based on the SPHINGO-100 study (mild vs severe splenomegaly) was used to approximate the effects of olipudase alfa compared to best supportive care. This was based on the effects of olipudase alfa on spleen volume and is a conservative assumption given clinical opinion agreed patients treated with olipudase alfa are expected to have a normal or very near to normal life span. In conclusion, the parametric approach provides a more clinically plausible estimate of overall survival in ASMD type B and A/B patients compared to the SMR approach, as it accounts for higher mortality in paediatric patients followed by a plateau representing the milder phenotype and increased probability of death starting from the late fifth decade of patients' lives. This conclusion was supported by clinical opinion. It is also based on larger datasets (n=270 for adults and n=61 for paediatric patients) than the SMR approach (n=59). The paediatric analysis is based on a prospective study and there is little reason to believe either dataset would not be generalisable to the UK, in particular given the unavailability of disease modifying treatment for ASMD.
3 Disease-specific	We are pleased that the Committee agree that disease-related mortality in children should be included in the economic model.

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mortality in children	
4 Discount rate	**Olipudase alfa meets the criteria for 1.5% discounting** We strongly believe that olipudase alfa meets all criteria for a 1.5% discount rate. Following the committee's uncertainty regarding olipudase alfa meeting all criteria for the 1.5% discount rate, further information is provided below. **Criterion 1: 'the technology is for people who would otherwise die or have a very severely impaired life'** In line with the draft guidance, this criterion is met. **Criterion 2: 'it is likely to restore them to full or near-full health'** Clinicians have indicated that the vast majority of patients treated with olipudase alfa are likely to achieve normal or near normal health. In clinical experience where follow-up has been sufficient to observe the majority of the benefits of olipudase alfa treatment, disease reversal and normalisation of all parameters have been observed. Clinical experts highlighted the following aspects of ASMD that have or were improving towards normal: • Spleen volume, • Liver volume, • Liver function, • Nutrition, • Need for hospitalisations, • Ability to carry out everyday activities, • Platelet count, • Lung function, • Chest infections, • Hypolipidaemia. All clinicians whose advice was sought highlighted the extremely rapid improvement with olipudase alfa over the first one to two years and continued improvement beyond that time. One clinical expert stated they have not seen a better response to treatment in their entire career. The only exceptions to this are likely to be patients with neurological manifestations and those with longer-standing disease where irreversible damage to affected organs already occurred due to unavailability of treatment.

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	Based on the clinician advice, neurological symptoms of varying severity were reported for approximately: • 10% of the adult population, • 20% of the paediatric population managed by the clinical experts. It was indicated that the severity of the neurological symptoms varies, and paediatric type B patients can be wrongly diagnosed as type A/B based on the presence of developmental delays. However, on treatment with olipudase alfa some of these patients catch up with normal development, indicating the underlying cause was not neurological, but likely related to factors such as problems feeding and fatigue. The other group of patients who may not reach normal health, those with irreversible damage to their organs, are considered very rare based on clinician advice: no current paediatric patients were reported and only one adult clinical expert estimated 20-25% of adult patients would fall in this category (the other two reported they did not have such patients in their current practice). These patients generally tend to be older with longer-standing disease resulting in irreversible damage to their health due to unavailability of disease modifying treatment. When treatment with olipudase alfa becomes available, these patients will become extremely rare in clinical practice. As there was uncertainty regarding the residual organomegaly and DL_{CO} levels achieved in the trials following olipudase alfa treatment, clinical opinion was also sought on the clinical relevance of organomegaly (separate from the organ function) and the range of DL_{CO} values indicative of lung impairment. Clinical experts highlighted that the size of the spleen and liver that would impact on patient's quality of life differed between patients. Some experts indicated that a spleen that is 2 to 6 MN may not be noticeable to a patient, whilst others focused on palpability or proximity to costal margins. Regarding DL_{CO} values indicating lung function impairment, again whether this is noticeable to patients may vary depending on their levels of activity. This measure is also not frequently used in very young patients. Four clinicians provided reference values in use that state DL_{CO} above 75% predicted is considered normal. This however needs to be interpreted in the context of between-patient variability. Overall, the available evidence highlights that olipudase alfa is likely to rapidly restore the vast majority of patients to normal or near normal health.

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	Criterion 3: 'the benefits are likely to be sustained over a very long period' Evidence from the clinical study LTS13632, clinical opinion, and proxy data relating to the use of enzyme replacement therapy in Gaucher disease support the benefits of olipudase alfa treatment being sustained in the long term. In the long-term study (LTS13632), adult and paediatric patients who received long-term treatment with olipudase alfa demonstrated sustained, durable benefit, with improvement in efficacy measures including: • Mean (SD) spleen volume o Decreased by 59.46% (4.67) at Month 78 in adult patients o Decreased by 69.07% (4.13) at Month 48 in paediatric patients • Mean percentage improvement in pre-infusion platelet count o Increased by 38.49% at Month 78 in adult patients o Increased by 35.83% at Month 48 in paediatric patients • Mean (SD) liver volume o Decreased by 43.75% (16.68) at Month 78 in adult patients o Decreased by 55.37% (11.05) at Month 48 in paediatric patients • % predicted DLCO o Improved by 55.29% by Month 78 in adult patients o Improved by 60.28% by Month 48 in paediatric patients • % change in ALT o Improved by 2.6% by Week 52 in adult patients o Improved by 61.1% by Week 52 in paediatric patients • % change in AST o Improved by 9.8% by Week 52 in adult patients o Improved by 65.0% by Week 52 in paediatric patients

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	In addition to these efficacy results, olipudase alfa showed a favourable long-term safety profile and infusions were well tolerated by both adult and paediatric patients. The biological plausibility of such long-term treatment benefit is supported by up to 30 years of data on the benefits of enzyme replacement therapy in Gaucher disease. Both diseases are sphingolipidoses where sphingolipids accumulate throughout the body, resulting in visceromegaly and hematologic and skeletal involvement. Gaucher disease has been successfully treated by enzyme replacement therapy which has been well tolerated [3, 4]. Clinical benefits included reduction in hepatosplenomegaly, correction of hematologic abnormalities[5, 6], and improvements in bone mineral density and quality of life [7, 8]. Gaucher disease can be considered an analogue to ASMD as both accumulate sphingolipid substrate and affected cell types and are amenable to enzyme replacement therapy. The experience with Gaucher disease as grounds for assuming long-term benefit was also mentioned in one of the discussions with clinical experts. As discussed above, clinicians indicated that the vast majority of patients continue to improve in clinical parameters during treatment and approach normal range over time in all measured disease parameters, including DL_{CO} and liver and spleen volume. There was agreement amongst all clinical experts whose advice was sought that patients would be expected to maintain efficacy and that no treatment effect waning is anticipated. All clinical experts agreed that, except for a very small group of patients with severe neurological manifestations and irreversible organ damage, patients treated with olipudase alfa can expect a quality of life and life expectancy comparable to that of the general population. Olipudase alfa is therefore expected to return the vast majority of patients to normal or near normal health and the benefit of treatment would be maintained in the long term.
5 Patient weight	**Patients with ASMD are often lighter and shorter than the general population.** Patients in the ASCEND trial had a mean weight of 64.5 kg compared with the mean male adult weight of 78.9–85.4 kg and mean female adult weight of 66.6–72.1 kg in the general population [9]. Patients in the ASCEND-Peds trial had a mean weight of 23.4 kg. Adolescent patients had a weight of 40.6 kg, child patients had a weight of 22.8 kg, and infants had a weight of 14.3 kg. In contrast, children's weight in the general population in the UK in 2019 was 9.5 kg for infants aged <2, 16.2 kg for children aged 2 to 4,

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	22.8 kg for those aged 5 to 7, 34.1 kg for ages 8 to 10, 47.0 kg for ages 11 to 12, and 59.7 kg for ages 13 to 15 [9]. Based on clinical advice, the height and weight of these patients was considered to be at the lower end of normal for adults (with the exception of one patient substantially below the normal range) and below normal for paediatric patients not treated with olipudase alfa. Following the committee meeting, the company base case has been updated with the EAG assumptions to provide a more conservative estimate of the weight of UK patients. Further scenario analyses have also been included.
6 Caregiver disutilities	**The impact of ASMD on caregivers is profound and Pompe disease provides a good approximation.** Following the committee recommendation that carer's disutility should be based on the health state of the person with ASMD. Our base case has been revised accordingly and it is proposed that the dataset from Pompe disease is used to inform these disutilities. As no data for ASMD currently exists, we believe this dataset provides a good approximation of the impact of ASMD on caregivers, in line with one of the patient expert responses to the Technical Engagement. Although Gaucher disease has been suggested as a potential proxy condition, no dataset was identified that could be used to inform the economic model. The values from Pompe disease, another rare condition, are a more appropriate reflection of the impact of caring for an ASMD patient than the values proposed by the EAG. The EAG approach assumes one disutility for caregivers of patients with spleen volume < 15 MN (-0.023 for paediatric and -0.01 for adult patients) and a different one for caregivers of patients with spleen volume ≥ 15 MN (-0.08 for paediatric and -0.045 for adult patients). These values grossly underestimate the caregivers disutility and do not account for the impact of impaired lung function on the need for care, recognised by all six clinical experts. In contrast, the Pompe dataset provides sufficient granularity to differentiate between mild, moderate and sever health states. It also allows to capture the impact of lung impairment (resulting in, for example, limited ability to walk about) on the caregiver. It is also more internally consistent, as it comes from one study and applies to a single rare disease. A caregiver expert statement described the impact of caring for a patient with ASMD on their life. This included having to stop work, withdrawing from

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	friends and family, and finding it difficult to function in everyday life. The caregiver described having difficulty coping with the emotional impact of not knowing how best to help their child, including feelings of guilt, panic attacks, and bouts of crying when alone. The quality of life of parents (in their capacity as primary caregivers) and siblings is substantially affected by the burden of caring for patients with ASMD compared with families that do not have a child with ASMD [10]. Caregivers highlight spinal pain due to lifting the child and from stress and physical exhaustion as impacts on their physical health. Additionally, caregivers have difficulty maintaining their emotional and mental state, along with preserving social activities and relationships. Anxiety, depression, stress, and fatigue are common, and feelings of guilt and responsibility associated with passing on the disease to their child further exacerbates these feelings. Caregivers face the grief associated with losing a loved one prematurely as the health of their child deteriorates which impacts their quality of life. The social life of the caregiver was affected by isolation (from family support due to caring for their child and because of keeping the diagnosis to themselves) and lack of independence due to concern about other people not being able to properly care for the patient. In addition, parents of children with ASMD must live with the emotions associated with neglecting other children due to the need to provide care for the child with ASMD. This can result in further feelings of guilt. Siblings who provide care for the child with ASMD must also face feelings of neglect, exclusion, resentment, anxiety, and embarrassment due to them receiving limited attention from their parents. It is therefore necessary to utilise a set of values for caregiver disutility to captures the profound impact of the entire spectrum of disease. As such, the Pompe dataset provides the most appropriate values.
7 Number of caregivers	**Caring for a patient with ASMD affects the entire family** Caring for a child with ASMD has a profound impact on the entire family and the average of 1.0 caregiver per child proposed in the draft guidance is a gross underestimate. As in the example provided in the caregiver expert statement, both her and her husband were required to participate in caregiving duties. These include frequent medical appointments and monitoring with multiple clinical teams across different locations, as well as daily assistance with self-care. In addition, the disutility of caring for a patient applies to the entire family, as

	the impact on aspects such as mental health, or social functioning is not solely related to the burden of providing care. A parent/caregiver survey highlighted that parents are unable to further their own career or attend education due to providing care for a patient with ASMD due to medical appointments for symptoms of ASMD. Caregivers described having to take time away from work do manage appointments or having to change their schedules due to treatment appointments. Some caregivers described having to share the burden with other caregivers (e.g. grandparents) to manage the treatment appointment schedule appropriately. As highlighted above, the impact on quality of life of caregivers is not solely related to the burden of providing physical care, but also to emotional stress and mental health. Therefore, assuming 2.6 caregivers per child is more representative of the actual impact of ASMD than the 1.0 value. A patient expert has also suggested that on average 1.5 caregivers would be appropriate for both children and adults. Both of these approaches are included as scenarios in the cost-effectiveness analyses.
8 Impact of bereavement	**Bereavement has a profound impact on caregivers' utility and therefore needs to be captured in the economic model** Bereavement, and the expectation of future bereavement, has a profound impact on caregivers. Caregiver quality of life is profoundly affected as the caregiver faces the grief of losing a loved one prematurely. Bereavement also affects the whole family unit and not just one family member. There are undeniable uncertainties and lack of methodological guidance on the best approach to including bereavement in economic models. However, excluding bereavement leads to a spurious result where the caregivers' utility improves on the death of their loved one (suggesting from their perspective this may be preferable). As 'NICE health technology evaluations: the manual' recommends that all relevant health effects – including those of caregivers – should be included in the perspective on outcomes, bereavement and the expectation of future bereavement should be included in evaluations as they directly impact the health (mental) and quality of life the of the caregiver. The company base case therefore includes the impact of the long-term bereavement. Analyses are also provided that include different scenarios to

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	explore the uncertainty related to methodological approaches to modelling bereavement.
9 Trial generalisability	**The effects seen in olipudase alfa trials are expected to be generalisable to the UK patient population** The inclusion criteria for the ASCEND and ASCEND-Peds were developed and approved by regulators in order to represent the disease spectrum as fully as possible and ensure that trial results would not be confounded by patient heterogeneity. UK clinical opinion was sought on the likelihood that effects of olipudase alfa will vary for patients who fall outside of the trial inclusion criteria. Advice was provided that patients whose disease is less severe than those included in the clinical would be expected to achieve normal health. It was also observed by one clinician that a patient who would have been too severe to meet the inclusion criteria for the clinical trial has now been treated with olipudase alfa based on an unsolicited compassionate use request and has shown a response at least comparable to clinical trial patients, if not more dramatic.
10 Patient quality of life	**Patients' quality of life improved following treatment with olipudase alfa** The committee discussed that there was some uncertainty regarding the quality of life improvement with olipudase alfa, as no statistically significant difference compared to placebo was seen in the ASCEND trial. However, the ASCEND trial was not powered on quality of life endpoints. Further, given the ultra-rare nature of the condition, none of the tools used to assess HRQoL (such as EQ-5D, SF-36, or BPI-SF) were validated for use in ASMD. In addition, it is likely that patient adaptation to their disease resulted in them not fully perceiving the impact of ASMD on their daily life. This would limit the possibility of improvement following treatment with olipudase alfa. Exit interviews with patients following the clinical trials indicated some had not realised the extent of their symptoms due to experiencing these from a young age. Only following treatment patients realised their condition had been impairing their quality of life. Following treatment with olipudase alfa, patients' feelings of self-worth and self-confidence increased, as they highlight that they feel better about themselves as their organomegaly dissipated and their worry about fatigue decreased. Additionally, patients reported having more energy, being able to exercise due to not being as breathless, and their capacity to work increased compared with prior to

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	treatment. Independence is another factor that increased following treatment.
11 Clinical impacts of olipudase alfa not captured in the economic model	**A number of important impacts of ASMD and benefits of olipudase alfa could not be captured in the economic model** As ASMD is an ultra-rare disease, inevitable there was limited evidence that could inform the economic model. Therefore, a number of important disease symptoms with a profound impact on daily activities could not be included. Based on the clinician advice these were: • Fatigue, tiredness, low energy levels (not solely related to lung function or organomegaly), • Exercise tolerance, • Patient height, which can have a large impact on psychological wellbeing, • Abdominal pain and discomfort, • Bleeding complications, • Splenic crises requiring hospitalisations, • Frequent infections, • Inability to eat normally and maintain a healthy weight, • High cholesterol levels that often result in requirement for treatment, • In infants and young children delayed growth and development (for example inability to sit due to poor muscle tone). All of these symptoms are improved and mostly brought within normal range with olipudase alfa and thus a number of benefits of treatment have not been captured in the economic model. In addition, it was not feasible, given the limited data in this ultra-rare disease to include the benefit of olipudase alfa on aspects such as school and work attendance. Such data limitations are inevitable, given the extreme rarity of ASMD. It is not possible to capture the full value of olipudase within a cost-effectiveness framework and therefore additional benefits such as those outlined above need to be factored into committee decision making.
12 Model changes	A document providing details of all the changes to the economic model following the additional analyses undertaken for the addendum and technical engagement has been submitted along with this document.
Factual Inaccuracies	
1	Economic Model: Company's modelling approach; page 12

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	In Section 3.8 of the Draft Guidance document, it is stated that 'the movement between the health states was determined by transition probabilities informed by data from the clinical trials (DFI13412, DFI13803, LTS13632, and DFI12712) along with additional data from the SPHINGO-100 trial and a pooled chart review analysis'. This is incorrect, as the pooled chart review analysis was not incorporated into the determination of the movement between health states. The pooled chart review analysis was incorporated into the addendum as it provided new survival estimates for adults and children with ASMD. Sanofi suggests amending the content to the following: 'The movement between the health states was determined by transition probabilities informed by data from the clinical trials (see section 3.5), along with additional data from the SPHINGO-100 study.'
2	Economic Model: Modelling long-term treatment effect; page 12 In Section 3.9 of the Draft Guidance document, it is stated that the company modelled health-state transitions for the best supportive care arm using data from the placebo arm of ASCEND. However, according to the original submission (Document B), transition probabilities for adults in the first year were calculated using ASCEND and SPHINGO-100 for the best supportive care arm. In contrast, for subsequent years, transition probabilities were calculated using only SPHINGO-100. For paediatric patients, the SPHINGO-100 study was used to determine the transition probabilities for the first year and subsequent years in the best supportive care arm.
Inconsistencies in content	
Page 12	In Section 3.9, trials is spelled incorrectly. Sanofi suggests amending the content to the following: It explained that the most robust data from the trials are up to 1 year, with 2-year data having limitations because of the high rates of missing outcome assessments at this time point (see section 3.6).
Page 14	In thedraft advice, the abbreviation AIC is associated with 'area under the curve' and BIC is associated with Bayesian information criteria. However, this is incorrect. The abbreviation AIC should be associated with Akaike information criterion and BIC should be associated with Bayesian information criterion. Sanofi suggests amending the content to the following:

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	Also, only the extrapolations for the overall survival in adults were presented, but the Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics were provided for the overall population including both adults and children, so it was not possible to select the best fitting curve (based on AIC and BIC statistics) for each.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted]d information that is [redacted]If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID 3913]

Company response to draft guidance – Additional model results

November 2023

Version 1.0

File name	Version	Contains confidential information	Date

1. Introduction

This document contains additional model analyses as requested by the committee and confirms the company base case following the draft guidance. In addition, a scenario analysis was included for an incident patient population. The document contains the following sections:

- Base case model description
- Company base case results
- Results with assumptions based on the committee preferences
- Incident patient population scenario
- Scenario analyses based on the company revised base case and draft guidance

2. Base case model description

The company base case model is utilising the same model as in the technical engagement response. The only exception is that it has been updated by the EAG to include the potential to incorporate corrections and to run additional scenario analyses.

The revised company base case utilises the survival data submitted in company addendum, together with adjustments, made to address comments in the draft guidance. The main assumptions together with the required settings in the model are:

1) 1.5% discount rate for costs and benefits

- Implemented using the ‘Settings’ page of the model, in cells E9 and E10

2) Assumption on long-term efficacy:

- patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which all patients transition to the SV <6 / DLCO >80 state from year 10 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients’ probability to transition to the ‘SV <6 / DLCO >80’ state from the other health states between year 2 and year 10
- this change in the model is made on the ‘Clinical Inputs’ sheet, cell J4 (TP smoothing). In addition, cell E19 on the ‘Settings’ page requires to be changed to 9 years, to ensure the full effect is captured in the model

3) Overall average of 2.6 carers per patient, updated in cell F68 on the ‘Settings’ page (=0.78+0.77)

4) Assume Pompe caregiver utility decrements, updated cell H72 on the 'Utilities' page (=1)

5) For the paediatric population, set average weight of adults based on Health Survey for England 2019 data; for the adult population, set the weight of adults based on Health Survey for England 2019 data assuming the same z-score as for

18 year-olds in the existing model and assuming a standard deviation the same proportion of the mean

In addition, the company have incorporated the EAG corrections (as described in the EAG report):

- general population utility was updated based on the latest NICE algorithm
- an inappropriate correction for cycle length for the two first cycles in AE calculations;
- an inappropriate use of probabilities rather than rates in calculation of complications;
- an inappropriate correction for cycle length for the first two cycles for liver, spleen and CV complications;
- an inappropriate formula to calculate complication QALYs for all types of complications;
- dosing escalation data for children for week 6, 10, 12 and 14 were incorrectly inputted in the model.

The EAG commented on the company response to technical engagement (ID3913 Olipudase EAG TE response [ACIC], that in addition to the revised mortality approach submitted in an addendum in April 2023, the EAG noted other changes to the revised model that were not documented to the EAG and caused additional uncertainty. As discussed during the committee meeting, this was an unintentional oversight. Details of the changes made to the model between the original submission and the addendum are included in Appendix A of this document for completeness.

An additional correction was made to the model to account for the incorrect trial baseline data pulling through on the ‘Clinical Inputs’ sheet (which was from the settings for the severe sub-group model submitted in August 2022).

Additional notes on model use

The table on the ‘Settings’ sheet (G87:O94) will give the user results for adult and paediatric patients using the settings that they have chosen from the model, once the ‘Run BC analysis’ button has been clicked. That is, the user should choose their preferred model settings, then click on the ‘Run BC analysis’ button, and the table will display the results from the scenario chosen.

The user may wish to note, that in order to ensure the correct results for the paediatric population are showing on the ‘Base Case Results’ sheet, the user needs to change cell E15 to Children (<18 years), then change cell E22 to ‘One-piece fit’ on the ‘Settings’ sheet.

3. Company base case

The deterministic model results for the company revised base case are provided in Table 1.

Table 1: Company revised base case results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	22.21	[redacted]	22.05	34.87	61.09	[redacted]	[redacted]
	BSC	[redacted]	16.83	−12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	19.29	[redacted]	15.57	27.32	46.54	[redacted]	[redacted]
	BSC	[redacted]	20.89	−8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

4. Model results with committee preferences

Model results with committee preferences are provided in Table 2.

The analysis requested by the Committee has been implemented as follows:

- Analysis exploring the scenario of continuing treatment effect then freezing it at year 10. The analysis includes freezing transition probabilities at 10 years.
- Modelling mortality: the EAG's approach to modelling mortality is preferred but the company should present additional information and analysis in its revised approach for decision making. The analysis presented below was therefore based on the SMR approach with the company original assumptions relating to SMRs.
- Disease-specific mortality for children is appropriate to include in the model.
- Discount rate: 3.5% for the cost-effectiveness analysis.
- Patient weight: the EAG's approach to modelling weight is preferred but the starting weight should be at the lower end of the UK average in the model.
- Carer disutilities should be applied depending on the health state of the person with ASMD, regardless of which treatment they have.
- The EAGs approach of differential carer disutilities depending on severity of disease and whether the person with ASMD is an adult or child is preferred.
- An average of 1 carer per child with ASMD is preferred.
- There may be carer disutilities associated with patient death but this should be considered qualitatively in decision making instead of numerically in the model.

Table 2: Model results with committee preferences using the SMR approach to mortality

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	24.53	20.08	[redacted]	3.81	8.07	23.50	[redacted]	[redacted]
	BSC	[redacted]	20.73	12.01						
Adult	Olipudase alfa	[redacted]	19.11	15.00	[redacted]	4.56	5.89	11.91	[redacted]	[redacted]
	BSC	[redacted]	14.55	9.11						
Combined	Olipudase alfa	[redacted]	21.82	17.54	[redacted]	4.18	6.98	17.70	[redacted]	[redacted]
	BSC	[redacted]	17.64	10.56	–	–	–			

Abbreviations: ASMD, acid sphingomyelinase deficiency; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Since the committee requested further information on the justification for the parametric approach to mortality, results of the model using the assumptions listed above, but with the parametric approach to mortality included as opposed to the SMR approach, are provided in Table 3

Table 3: Model results with committee preferences using the parametric approach to mortality

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	24.10	19.66	[redacted]	10.80	11.66	36.85	[redacted]	[redacted]
	BSC	[redacted]	13.29	8.01	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	22.97	17.69	[redacted]	4.18	7.04	18.96	[redacted]	[redacted]
	BSC	[redacted]	18.79	10.65						
Combined	Olipudase alfa	[redacted]	23.54	18.68	[redacted]	7.49	9.35	27.91	[redacted]	[redacted]
	BSC	[redacted]	16.04	9.33	–	–	–	–	–	–

Abbreviations: ASMD, acid sphingomyelinase deficiency; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

5. Incident patient subgroup

An exploratory analysis of cost-effectiveness in an incident subgroup was undertaken following consultancy meetings with clinical experts. The patients in this subgroup may have an increased potential to benefit from treatment with olipuduase alfa compared to patients with long standing disease, as it is unlikely any permanent organ damage has taken place.

The model inputs for the incident subgroup analysis are as in the company base case with the following adjustments:

1) Starting age of patients in the model
    a. The age of patients in the model is updated from the mean age to the age at ASMD diagnosis based on the ASCEND and ASCEND-Peds trials for adults and children respectively.
        i. Mean age at ASMD diagnosis for adults: 18 years
        ii. Mean age at ASMD diagnosis for paediatric patients: 2.5 years
2) Long-term efficacy assumption
    a. patients receiving olipudase alfa can transition to an alternative health state for up to 4 years, after which all patients transition to the SV <6 / DLCO >80 state from year 5 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients' probability to transition to the 'SV <6 / DLCO >80' state from the other health states between year 2 and year 5. This assumption was based on the advice received in clinician discussions.
3) Combined population
    a. In the company base case, the combined ICER is based on a 50%:50% proportion of child and adult patients. For this scenario analysis, in line with clinical advice received, we assume that the majority of patients (85%) are children

The results of the scenario analysis are presented in Table 4 below.

Table 4: Incident patient population scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	40.62	24.64	[redacted]	21.41	36.18	65.17	[redacted]	[redacted]
	BSC	[redacted]	19.21	-11.53	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	40.54	25.32	[redacted]	10.07	24.00	42.28	[redacted]	[redacted]
	BSC	[redacted]	30.47	1.32	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	40.61	24.98	[redacted]	19.71	30.09	53.72	[redacted]	[redacted]
	BSC	[redacted]	20.90	-5.11	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6. Scenario analyses

6.1 *Long-term treatment effect*

6.1.1 *Transition probabilities frozen at 10 years*

The model results for the long-term treatment effect scenario requested by the committee are provided in Table 5. The model included the assumption that patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which patients will remain in their health state.

Table 5: Long-term treatment effect scenario results – TPs frozen at 10 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	18.25	[redacted]	22.05	30.90	54.58	[redacted]	[redacted]
	BSC	[redacted]	16.83	−12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	11.91	[redacted]	9.08	15.33	25.33	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	15.08	[redacted]	15.57	23.12	39.96	[redacted]	[redacted]
	BSC	[redacted]	20.89	−8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.1.2 *Additional long-term treatment effect scenarios*

Several additional scenarios to demonstrate the long-term treatment effect assumptions on the model are provided below.

6.1.2.1 Transition probabilities frozen after 2 years

The model results for a scenario where patients receiving olipudase alfa can transition to an alternative health state for up to 2 years, after which patients will remain in their health state are provided in Table 6.

Table 6: Long-term treatment effect scenario results – frozen after 2 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	17.29	[redacted]	22.05	29.94	52.90	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	11.98	[redacted]	9.08	15.40	25.44	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42						
Combined	Olipudase alfa	[redacted]	36.46	14.63	[redacted]	15.57	22.67	39.17	[redacted]	[redacted]
	BSC	[redacted]	20.89	-8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.1.2.2 No further transitions after 2 years (observed benefit continued)

In this scenario analysis transition probabilities were replayed in the olipudase alfa arm at two years i.e. after year two patients moved through health states based on the transition probabilities observed in year two of the trials. This was a scenario presented by the EAG in their report. The model results are provided in Table 7.

Table 7: Long-term treatment effect scenario results – no further transitions after 2 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	16.20	[redacted]	22.05	28.85	51.26	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	10.97	[redacted]	9.08	14.39	23.95	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	13.59	[redacted]	15.57	21.62	37.60	[redacted]	[redacted]
	BSC	[redacted]	20.89	-8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.1.2.3 No further transitions after 5 years (observed benefit continued)

In this scenario analysis transition probabilities were replayed in the olipudase alfa arm at five years i.e. after year two patients moved through health states based on the transition probabilities observed in year two of the trials. The model results are provided in Table 8.

Table 8: Long-term treatment effect scenario results – no further transitions after 5 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	17.73	[redacted]	22.05	30.38	53.70	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	11.69	[redacted]	9.08	15.11	25.00	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	14.71	[redacted]	15.57	22.75	39.35	[redacted]	[redacted]
	BSC	[redacted]	20.89	-8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.2 *Modelling mortality*

The company revised base case incorporates additional data, and a parametric approach as submitted in the Company Addendum in April 2023. Best fits were chosen for the base case based on clinical opinion. Further details have now been provided per the committee request in the company response to the draft guidance. For completeness, the tables below (Table 9 to Table 15) show results for the other curves that were not best fits for both adult and paediatric patients.

Table 9: Modelling mortality using the parametric approach – Child: Gompertz-Gompertz and Adult: Gompertz-Gompertz

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	42.52	26.82	[redacted]	12.42	28.33	50.01	[redacted]	[redacted]
	BSC	[redacted]	30.10	-1.51	–	–	–	–	[redacted]	[redacted]
Adult	Olipudase alfa	[redacted]	32.60	14.75	[redacted]	7.57	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.36	–	–	–	–	[redacted]	[redacted]
Combined	Olipudase alfa	[redacted]	37.56	20.78	[redacted]	10.00	23.22	39.05	[redacted]	[redacted]
	BSC	[redacted]	27.56	-2.43	–	–	–	–	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 10: Modelling mortality using the parametric approach – Child: Gompertz-Weibull and Adult: Gompertz-Weibull

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	43.41	27.81	[redacted]	13.34	29.35	53.35	[redacted]	[redacted]
	BSC	[redacted]	30.07	-1.54	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	38.72	22.08	[redacted]	11.21	24.56	42.67	[redacted]	[redacted]
	BSC	[redacted]	27.51	-2.48	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 11: Modelling mortality using the parametric approach – Child: Gompertz (one-piece) and Adult: Gompertz-Gompertz

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	5.41	[redacted]	11.98	21.02	28.80	[redacted]	[redacted]
	BSC	[redacted]	13.32	-15.61	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	32.60	14.75	[redacted]	7.57	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.36	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	28.95	10.08	[redacted]	9.78	19.56	28.44	[redacted]	[redacted]
	BSC	[redacted]	19.17	-9.48	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 12: Modelling mortality using the parametric approach – Child: Gompertz (one-piece) and Adult: Gompertz-Weibull

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	5.41	[redacted]	11.98	21.02	28.80	[redacted]	[redacted]
	BSC	[redacted]	13.32	-15.61	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	29.67	10.88	[redacted]	10.53	20.40	30.39	[redacted]	[redacted]
	BSC	[redacted]	19.14	-9.52	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 13: Modelling mortality using the parametric approach – Child: Weibull (one-piece) and Adult: Gompertz-Gompertz

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	22.21	[redacted]	22.05	34.87	61.09	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	32.60	14.75	[redacted]	7.57	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.36	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	35.74	18.48	[redacted]	14.81	26.49	44.59	[redacted]	[redacted]
	BSC	[redacted]	20.93	-8.00	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 14: Modelling mortality using the parametric approach – Child: Gompertz-Gompertz and Adult: Gompertz-Weibull

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	42.52	26.82	[redacted]	12.42	28.33	50.01	[redacted]	[redacted]
	BSC	[redacted]	30.10	-1.51	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	14.75	[redacted]	9.08	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.36	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	38.28	20.78	[redacted]	10.75	23.22	39.05	[redacted]	[redacted]
	BSC	[redacted]	27.53	-2.43	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 15: Modelling mortality using the parametric approach – Child: Gompertz-Weibull and Adult: Gompertz-Gompertz

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	43.41	27.81	[redacted]	13.34	29.35	53.35	[redacted]	[redacted]
	BSC	[redacted]	30.07	-1.54	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	32.60	16.36	[redacted]	7.57	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	38.00	22.08	[redacted]	10.46	24.56	42.67	[redacted]	[redacted]
	BSC	[redacted]	27.55	-2.48	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 16 below shows the results using the EAG's approach to modelling mortality (that is, standard mortality ratios (SMRs) related to spleen volume) including the use of disease-specific mortality for children.

Table 16: Modelling mortality using the SMR approach scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.37	21.92	[redacted]	5.83	20.24	33.86	[redacted]	[redacted]
	BSC	[redacted]	32.53	1.68	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	25.89	6.63	[redacted]	5.36	13.21	18.52	[redacted]	[redacted]
	BSC	[redacted]	20.54	-6.57	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	32.13	14.27	[redacted]	5.59	16.72	26.19	[redacted]	[redacted]
	BSC	[redacted]	26.53	-2.45	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.3 *Discount rate*

The model results for a discount rate scenario using 3.5% for both costs and benefits are provided in Table 17.

Table 17: Discount rate of 3.5% scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	24.10	15.56	[redacted]	10.80	19.21	61.09	[redacted]	[redacted]
	BSC	[redacted]	13.29	-3.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	22.97	14.70	[redacted]	4.18	11.48	31.99	[redacted]	[redacted]
	BSC	[redacted]	18.79	3.21	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	23.54	15.13	[redacted]	7.49	15.35	46.54	[redacted]	[redacted]
	BSC	[redacted]	16.04	-0.22	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

The model results for a discount rate scenario using 0% for both costs and benefits are provided in Table 17.

Table 18: Discount rate of 0% scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	62.68	27.75	[redacted]	41.89	61.09	61.09	[redacted]	[redacted]
	BSC	[redacted]	20.79	-33.34	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	48.95	10.49	[redacted]	17.07	31.99	31.99	[redacted]	[redacted]
	BSC	[redacted]	31.88	-21.50	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	55.81	19.12	[redacted]	29.48	46.54	46.54	[redacted]	[redacted]
	BSC	[redacted]	26.34	-27.42	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.4 *Patient weight*

The model results for the patient weight scenario are provided in Table 19. The model used the assumption that weight was on the lower end of the UK average for both children and adults.

Table 19: Patient weight scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	22.21	[redacted]	22.05	34.87	61.09	[redacted]	[redacted]
	BSC	[redacted]	16.83	−12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	19.29	[redacted]	15.57	27.32	46.54	[redacted]	[redacted]
	BSC	[redacted]	20.89	−8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.5 *Carer disutilities*

The model results for the carer disutilities scenario are provided in Table 20. This scenario demonstrates results using the EAG preferred utility values that were applied depending on the health state of the person with ASMD, regardless of treatment. This scenario also accounts for the EAG's preference to have utility values based depend on severity of disease and whether the person with ASMD is an adult or child.

Table 20: Carer disutility scenario results – EAG preferences

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	25.78	[redacted]	22.05	34.86	61.77	[redacted]	[redacted]
	BSC	[redacted]	16.83	−9.09	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	18.93	[redacted]	9.08	18.69	30.84	[redacted]	[redacted]
	BSC	[redacted]	24.95	0.24	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	22.35	[redacted]	15.57	26.78	46.30	[redacted]	[redacted]
	BSC	[redacted]	20.89	−4.42	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.6 *Number of carers (one carer per child with ASMD)*

The model results for the number of carers (one carer per child with ASMD) scenario are provided in Table 21.

Table 21: Number of carers (one carer per child with ASMD) scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	7.09	[redacted]	11.98	19.89	27.55	[redacted]	[redacted]
	BSC	[redacted]	13.32	-12.80	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	29.67	11.72	[redacted]	10.53	19.83	29.77	[redacted]	[redacted]
	BSC	[redacted]	19.14	-8.11	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

An additional scenario is provided for 1.5 carers per child with ASMD, as the patient experts stated that may be a close approximation for the number of carers (page 539 of 609 of the committee papers accessed here: https://www.nice.org.uk/guidance/gid-ta10788/documents/committee-papers). Results of this scenario are provided in Table 21.

Table 22: Number of carers (1.5 carers per child with ASMD) scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	6.55	[redacted]	11.98	20.25	27.96	[redacted]	[redacted]
	BSC	[redacted]	13.32	−13.71	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	29.67	11.45	[redacted]	10.53	20.02	29.97	[redacted]	[redacted]
	BSC	[redacted]	19.14	−8.56	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.7 *Carer disutilities associated with death*

The model results for the carer disutilities associated with death scenario are provided in Table 23. The model included the assumption that carer disutilities associated with death only extend for five years after death.

Table 23: Carer disutilities associated with death (bereavement) scenario results – disutilities extend for 5 years only

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	27.79	[redacted]	22.05	24.50	40.03	[redacted]	[redacted]
	BSC	[redacted]	16.83	3.29	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	24.16	[redacted]	9.08	15.57	23.46	[redacted]	[redacted]
	BSC	[redacted]	24.95	8.59	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	25.98	[redacted]	15.57	20.03	31.75	[redacted]	[redacted]
	BSC	[redacted]	20.89	5.94	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

The model results for a scenario where no carer disutilities associated with death are included in the model are provided in Table 24.

Table 24: Carer disutilities associated with death (bereavement) scenario results - no disutility associated with death

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	28.86	[redacted]	22.05	23.15	39.39	[redacted]	[redacted]
	BSC	[redacted]	16.83	5.71	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	25.35	[redacted]	9.08	15.24	23.45	[redacted]	[redacted]
	BSC	[redacted]	24.95	10.11	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	27.10	[redacted]	15.57	19.20	31.42	[redacted]	[redacted]
	BSC	[redacted]	20.89	7.91	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Appendix A

Five changes to the model submitted in the company addendum were made in addition to the implementation of the updated mortality approach.

Change 1

Description:	The mortality implementation for the McGovern study was slightly updated to account for it being a cumulative from baseline and not per cycle.
Sheet and cell number(s):	Model Calculations: N122:223; O122:223
Old formula:	Col N: 1-(EXP(-(EXP(-(m.childMortalityWei.param1*m.childMortalityWei.param2))*(C122^m.childMortalityWei.param2)))). Col O: 1-(EXP((EXP(-(m.childMortalityGom.param1))/m.childMortalityGom.param2)*(1 - EXP(m.childMortalityGom.param2*C122)))).
Revised formula:	Col N: (EXP(-(EXP(-(m.childMortalityWei.param1*m.childMortalityWei.param2))*(E123^m.childMortalityWei.param2))))/$N$118. Col P: selects the corrected mortality: IFERROR(MAX(J123,1-N123/N122),1) Col O: (EXP((EXP(-(m.childMortalityGom.param1))/m.childMortalityGom.param2)*(1 - EXP(m.childMortalityGom.param2*E123))))/$O$118. Col Q: selects the corrected mortality: IFERROR(MAX(J123,1-O123/O122),1)
Rationale:	Survival is cumulative from baseline and the proportional difference is now used to estimate mortality.

Change 2

Description:	Fixed a bug in the dose escalation calculation for children where only one mean dose of 0.3 mg/kg was accounted for in the schedule when there should be two (also described in the EAG response to the company response to TE).
Sheet and cell number(s):	Mean Dose Calculation: F5:O30
Old formula:	Dose #4 was originally not escalated to 0.6 mg/kg
Revised formula:	Updated to escalate dose #4 to a second step of 0.3 mg/kg
Rationale:	Corrected dosing to align with correct regimen

Change 3

Description:	Fixed a rounding error in the transition probabilities that caused a small difference in the incremental LYs between both arms when the HR was set to 1. LYs are expected to be the same when using a HR of 1.
Sheet and cell number(s):	Clinical Inputs J157, J301
Old formula:	14.2%; 2.042%
Revised formula:	14.22%; 2.041%
Rationale:	Total summation of transition probabilities were calculated to total 100%

Change 4

Description:	Updates the formula for weighted QALYs
Sheet and cell number(s):	Base Case Results: F74
Old formula:	'Model Calculations'!$HW$45*IF('Model Calculations'!$HW$45<=10,m.QALYWeight1,IF('Model Calculations'!$HW$45>=30,m.QALYWeight3,'Model Calculations'!$HW$45/10))
Revised formula:	IncQALYs*IF('Model Calculations'!HW45<=10,m.QALYWeight1,IF('Model Calculations'!HW45>=30,m.QALYWeight3,'Model Calculations'!HW45/10))
Rationale:	The actual final QALY gain is weighted according to the UNDISCOUNTED incremental results. The weight choice is based on the undiscounted incremental QALY, whereas this applies to the final Incremental QALY that is presented in the results.

Change 5

Description:	Updated the list of list of distributions on the “Lists and Constants” tab to delete un-used distributions.
Sheet and cell number(s):	Lists&Constants: D67:D73
Old formula:	Weibull; Log-normal; Generalized gamma; Log-logistic; Exponential; Gompertz
Revised formula:	Weibull; Gompertz
Rationale:	Removed unused distributions as part of model clean up.

NICE National Institute for Health and Care Excellence

Olipudase alfa for treating Niemann-Pick disease types A and B [3913]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 16/11/23. Please submit via NICE Docs.

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Olipudase alfa for treating Niemann-Pick disease types A and B [3913]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to declare
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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The guidance states "Best supportive care aims to manage the symptoms, such as improving nutrition and breathing, and treating infection." I am very concerned that this statement and the symptom summaries in the extended slides do not give a clear, accurate picture of the number or severity of the other symptoms and it is not made clear that "best supportive care" does very little to improve them and in consequence, the poor QoL experienced by the patient and carers. I am concerned that the following key symptoms, not related to the spleen, were omitted or not given emphasis in the extended slides and guidance. (This is relevant to the model, where other symptoms add more cost in Best Supportive Care - see details in my point 2): a. Bone thinning is mentioned in the slides. However, I would like to emphasis the bone disease which develops causes bone and joint pain and significantly reduces mobility. Sphingomyelin also builds up in the bones and patient have poor absorption of vitamin D (even with supplements). This pain cannot be treated with Ibuprofen/anti-inflammatories due to the liver involvement. Bone pain would stop my son walking even before breathlessness. He would bend down clutching his shins even as a 6yr old before the disease had progressed. Shin and arm fractures are common in NP type B children just from everyday activity. Yesterday he showed an Orthopaedic surgeon in clinic how his shins were no longer hurting following 7 months of treatment and he has asked if he can start to carry his own bag. b. In section 3.3 some best supportive care attempts are described. I would like to add that there is no best supportive care for fatigue, memory and developmental problems. I would like to give fatigue more emphasis than is mentioned in the guidance or extended slides as it has a major impact on QoL and requires a lot of 'caring'. In the slides "tiredness" has been attributed to Anaemia. It is in part; however, the fatigue is caused by a drain on energy. The cells are working

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	hard (but unable to) to remove the sphingomyelin. This state of continual draining of energy, especially when eating is prevented by nausea, results in a state of constant calorie deficiency and therefore, exhaustion. This not only effects daily activity (needing carers to help feed, move and facilitate ability to attend appointments, manage health care, and the necessities of daily life) but to attend education or work. The fact that my son was bright and motivated to study, yet so restricted by his energy levels and the resulting memory difficulties from fatigue, was a great source of mental stress for him. Treating with Olipudase Alfa has dramatically increased his energy levels, this has been life changing for him. The drain on the body's energy resources also prevents normal growth, puberty and muscle development. c. Bowel problems are not mentioned. Storage in the bowel prevents effective absorption, coupled with another symptom of daily and frequent diarrhoea, leading to a malnourished state. Food is needed frequently, at least every 2 hours (but only small amounts are tolerated due to the large liver and spleen reducing stomach capacity) and the food passing through ineffectively, means that nutritional health is very poor, as well as not consuming enough calories to support the calorific need (see my point 1b above). Treatment with Olipudase Alfa so far in 7 months has stopped the nausea (allowing my son to leave the house in the morning when well people can). He is eating bigger main meals, not needing to snack, and functioning on that chosen reduced food intake better and much longer (does not need as many calories to do more). As a carer, life no longer revolves around constant food preparation and managing his intake of food, to enable him to function. d. I would like to emphasise that Interstitial Lung Disease is a key measurable symptom which Olipudase Alfa treats and impressively reverses. To clarify, the build-up of Sphingomyelin in the lungs causes poor lung function, reducing the available area for gaseous exchange. Therefore, treatment with Olipudase Alfa is drastically improving quality of life by reducing storage in the lungs, and as a result improving lung function (reducing breathlessness and dizziness, increasing endurance). My son was breathless when walking and talking. After 7 months of treatment, he is not. Incredibly, he is playing badminton again – having had to give that up years ago when his lung function (DLCO) progressively declined to under 50%. e. Other symptoms not mentioned in the extended slides or the above list, include neutropenia, headaches, night sweats, palpitations, poor healing and skin problems. I hope I have managed to help clarify for the committee that the storage of sphingomyelin is everywhere – not simply where measured, and causes progressive deterioration on health and QoL. These are all in addition to symptoms caused by the spleen, including; abdominal pain, sleeplessness (made worse by oxygen at night), fear of rupture, low platelets (bruising, lack of clotting and healing, risk of internal bleeding) low neutrophils (frequent infection and resulting hospitalisation), and simple daily difficulties like inability to bend to put socks on, wash, wear normal clothes.

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	Storage all over the body is broken down by Olipudase Alfa effectively treating all of the disease at source, instead of fire-fighting *only a few* of the many complex symptoms, under several NHS departments. I would like to ensure the committee understand the considerable number of symptoms which it successfully treats, to fully appreciate the benefit of Olipudase Alfa. I ask the committee, does any of this information effect quality of life years?
2	In the model, I am concerned that Best Supportive Care costs have been underestimated. For example, in 'Routine Care' costs they focus only on the spleen, liver and lungs, whereas my son would also regularly see a Haematologist, Dermatologist, Gastroenterologist and Orthopaedics (Physiotherapist too, which is mentioned). His clinic appointments and tests caused 8-12 days lost per year. A greater cost is the frequent hospitalisations. As I described in my evidence, he was hospitalised for 3-14 days sometimes 4 times a year on Tazocin IV antibiotics as per febrile neutropenia protocol (neutropenic due to his Niemann-Pick type B disease). He was also hospitalised for a bleed on his liver. Therefore, for various symptoms of Niemann-Pick disease, he had over 25 emergency admissions by age 15yrs. I know of other patients who were continually hospitalised for nosebleeds and infections. This information also effects 'Indirect Costs' of 'School Days Lost' which would have been higher for my son (also affects 'workdays lost' for carers) than currently in the model. Since treatment with Olipudase Alfa his platelets and neutrophils are the highest they have ever been, therefore if treated from diagnosis at 3yrs I believe this cost and huge effect on our QoL would have been prevented. May I ask the committee to check the 'Complications' costs are realistic comparisons between Olipudase Alfa and Best Supportive Care with the clinicians.
3	Number of carers needed. I am concerned about the following assumption in the guidance, "the EAG provided different values for children and adults, arguing that children need more attention than adults, and higher values for severe disease (defined as spleen volume 15 multiples of normal or greater). The carer disutility values used by the EAG range from -0.010 to -0.080. The committee agreed that it was more logical that children and people with more severe health states would incur greater carer disutility,". In this disease it is not correct to assume that children are more unwell than adults nor that adult severity of disease can be indicated by spleen size alone. It is a progressive disease, and liver fibrosis, interstitial lung disease, fatigue, bone disease, all decline over time as storage (everywhere) increases, meaning that mobility and the ability to selfcare also decline. In addition, there are mental difficulties, isolation, dependency, depression and anxiety from coping with deteriorating health in the long term. Basing the assumption on the spleen only, is not realistic as symptoms vary person to person. Regarding carer numbers, I would like the committee to consider the amount of effort that is required on the art of the carer to allow the NHS to deliver best supportive care for both children and adults. Clinicians do not see the considerable preparation and days of recovery needed to visit hospital for clinic. To enable patient's education or work requires so much effort on the part of the carer – which is given without consideration for QoL as the carer is nearly

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	always a parent. There is no time for career, other children's care, or self. Therefore, I disagree with the committee's value of 1 carer – even on varied states of health for child or adult. In the disease community I know families with a relative less effected and in better states of heath than my son, where helping the patient battle their fatigue, malnutrition, daily limitations and mental health as well as appointments and liaison with education, work (if possible) and disability benefits is all encompassing for the families. In this disease, caring is not only providing medical practical tasks, like tube feeding. A big challenge is that the patient is cognitively aware of their decline. I agree with the company that significant care is no longer needed (and so societal benefit achieved) when the patient becomes self-sufficient on treatment.
4	I am concerned about the focus on "the Spleen remaining 6 times the size following treatment" regarding the modelling assumptions and discussion around the Near Normal Health state (criteria 2), for 2 reasons: a. When my son was under 8 years, his spleen was 12 times normal, despite some fatigue, he functioned well. As it progressed and sphingomyelin storage increased everywhere not just the spleen, he became more unwell and less able to take part in full time education or take an easy summer job. Therefore, my concern is – if when the spleen has reduced to 6 times normal after treatment with Olipudase Alfa, the patient is able to; absorb nutrition, selfcare, exercise, work, learn, fight infection, clot their blood, have the energy to be out of the house and work as a normal healthy person and be self-sufficient without supportive medical and carer care, why is that not considered a near normal health state. Why are we not measuring this on patient outcomes. If a treated patient (able to do these things) filled in a DWP PIP form they would be considered normal enough to self-care and be fully mobile so why not in this model? b. In practice this treatment would be prescribed on diagnosis – earlier than given in the trials. Therefore, the prevention of disease progression must be considered. Most children I know were diagnosed at 3yrs when the liver and spleen are first noticeably enlarged or in adults when that or other symptoms first show. At this stage the disease has not progressed so much (deterioration is slow and constant). Therefore, treating at this stage will prevent progression to the more severe health states eg liver cirrhosis. Treatment before long term progression, reverses the disease and allows the patient to have near normal health (and QoL). Clinicians frequently cite of all the enzyme replacements developed, this has been the most effective in halting and reversing symptoms.
5	I would like the committee to clarify the incidence of AB in the population with NPUK, as they appreciated in the guidance that it is lower than in the trials. The paediatric clinician explained that the effect of having B (fatigue, memory problems and slow development) can appear in young children like they could have neurological symptoms but in fact as they grow it becomes apparent by around age 7-10yrs that they have B (not got AB) and that there is no neurological involvement. It concerns me greatly that treatment guidelines could be affected by consultants (quite rightly) considering both diagnosis possibilities. The reality is that by treating A or AB on diagnosis with Olipudase Alfa, the storage in the whole body (except the brain) will be treated.

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	By successfully treating those symptoms, near normal health would be achieved for Bs and a far better state of health for ABs – so better able to cope with their neurological symptoms.
6	The statement in the guidance, "Clinical trial evidence shows that Olipudase Alfa improves lung function and reduces the size of the spleen in both adults and children with ASMD at 1 year follow up. The treatment effect may continue in the longer term, but this is uncertain" concerns me. Trials have shown significant benefit past one year but with fewer participants but surely this is understandable in a rare disease. If larger numbers are needed, can we look to the wider world patient community as long-term benefit is seen in other countries successfully treating this disease with Olipudase Alfa. In addition, the discussion around long term modelling scenarios and the phrase 'falling-off of effectiveness' also concerns me. The treatment is working just as effectively at 10yrs, but at that time the treatment is breaking down the sphingomyelin as the body is produces it. At this time, it would still be unable to break it down without Olipudase Alfa. Therefore, the treatment is effective in all ongoing years, as without it, storage would accumulate, and health would decline. In the first couple of years, it is breaking down accumulated storage so shows more dramatic results in comparative measurement. I apologise if this is stating the obvious, but I just wanted to be sure all the committee understood this, as the phrasing used in discussing the modelling sometimes sounds like the Olipudase Alfa has stopped working after so many years and this is not the case.
7	I do not agree that the recommendations are sound and a suitable basis for guidance to the NHS. Without this treatment this painful disease will progress to death or a severely debilitated QoL, whilst the burden of evermore challenging and expensive best supportive care from the NHS and carers continues. I do not feel that the patients' symptoms, severely compromised QoL, the poor QoL and demand on the carers, and just how successfully Olipudase Alfa treats this disease, has been fully appreciated by EAG, the committee's extended slides and even by the company. Treated patients are self-sufficient, contribute to society like those in normal health, and not in need of the NHS's often unsuccessful attempts at alleviating worsening symptoms. Olipudase Alfa's effectiveness is greater than clinicians, families and the company expected. Therefore, the data chosen to be collected on the trials (though clearly showing success) does not show the even greater real evidence seen by clinicians, patients and families. In this case, the clinical and patient experts are key, and I hope they have more time to contribute in the coming meeting than the first, where a new shorter format enforced time pressure on the Chair.

Insert extra rows as needed

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Example 1	We are concerned that this recommendation may imply that ……..
1	I am extremely concerned that the committee are reviewing the treatment effect on HRQoL purely based on the data collected from a series of generic general health questionnaires, that were provided by the pharmaceutical company for the participants on the trials to complete. These questionnaires target very specific areas, for example, pain, fatigue and shortness of breath and although clinically relevant, lack the ability to track real world improvement. In the first 12 months these record the clinical effectiveness of this treatment but then as patients transition away from very poor health to better health states, the questionnaires become ineffective and fails to capture this improvement. This is most likely why the trial data shows a reduction in effectiveness after the first two years because the right questions weren't asked. An example of this would be, How often has your fatigue affected you doing things with your friends and family? Prior to treatment this was very high on the scale with most, if not all patients really struggling with fatigue, however after several months of treatment with Olipudase Alpha this returns to 'Not at all'. If these questionnaires had been created with clear disease specific metrics, then there would be little to no dispute about how much improvement this treatment has on HRQoL.

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2	I am concerned that the committee are not taking into consideration the other significant debilitating symptoms of this disease. In the development stages of the trial, emphasis was placed on areas the company and clinicians knew were likely to respond well to this enzyme replacement therapy. The key clinical symptoms, splenic volume, liver and lung function and lipid profiles became areas of focus, however there was little or no assessment of the other many burdens of the disease. Nutrition is a huge factor in maintaining health. Malnourishment in a typical individual with no co-morbidities will suffer from a raft of symptoms for example, tiredness, lack of interest in food / drink, frequent infections, poor recovery time, low mood, depression and poor concentration. All the symptoms that are also present in ASMD for various other reasons. Health Care Excellence can only be achieved with good nutrition and this is a founding principle of health. Olipudase Alpha, improves nutritional value, by removing the accumulation of storage from the bowel in weeks! Patients on Olipudase Alpha experience huge improvements to their symptoms of malnutrition very early on in the treatment process but this was neglected to be captured by the company through the lack of analysis in this area. The symptoms that are listed in the slides as burdens of the disease are limited to the headlining clinical complications that define this condition. If you were to ask the general population to define 'Parkinsons Disease' many would say 'a tremor and the shuffling of their feet' however there are hundreds of symptoms that these patients can suffer from and many are individually specific. The treatment for Parkinsons improves some of their condition but the side effects create new problems. Comparably the defining characteristics of ASMD are enlarged Liver and Spleen and poor Lung Function, however there are hundreds of symptoms specific to ASMD, many of which as patient experts we have raised through supporting evidence. In comparison between Parkinsons and ASMD, Olipudase Alpha, not only stops the deterioration of the disease but reverses huge amounts of damage to the individual. It affects nearly all the symptoms of the disease and has no significant side effects. If a treatment like that of Parkinsons is deemed clinically effective by suspending the progression of a disease as it is with many existing licenced medications, then Olipudase Alpha is in excess of 100% effective as it reverses huge amounts of damage to the individuals body.
3	I strongly disagree that this treatment as unsuitable for a review in the discount rate section 3.14 *'The committee considered that the persistence of a significantly enlarged spleen can not be considered as near normal or full health'.*

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	Splenic volume is one facet of this disease and volume alone cannot differentiate between near normal or full health. As patients, the severity of the disease can vary significantly, this may be attributed to the amount of Acid Sphingomyelinase the individual naturally produces, which in turn, governs the rate at which they deteriorate. This may also be attributed to their age and the length of time they have had to manage without successful treatment. If a patient had suffered from this disease for 30-40 years of their life, their organs would be more significantly affected compared to that of a newly diagnosed three year old. This huge amount of storage will have changed the patients body in many cases beyond repair. For example if you inflate a new balloon with air or water and then let it back out, it no longer behaves like a new balloon. It's change of state however, doesn't make it any less effective in it's intended purpose. A 35 year old patient with a disease affected splenic volume of 27 multiple of normal, that reduces in size to 6 multiples of normal with treatment, cannot be a defining characteristic of near normal health. Pregnant female bodies often change completely during child birth and never completely return to their pre-pregnancy state but we don't define these individuals as not returning to full health. As an affective, licenced treatment of ASMD, Olipudase Alpha will be specific to patients with this condition, their response would be proportionate to the level of severity of the disease that they are suffering from. If given to a newly diagnosed paediatric patient, their health will transition to '*Full Health'* very quickly and maintain that throughout their life if the treatment is continued. Realistically more affected individuals will hugely benefit from the reduction of years of accumulated storage and will experience marked improvement in many, if not all of their symptoms but it is unrealistic to expect their anatomy to return to that of a typical unaffected individual, especially not in 52 weeks.
4	I am concerned that the committee think Olipudase Alpha will be ineffective in the treatment of ASMD types AB and A based on the fact that it is unable to reverse the neurological involvement that these patient suffer. Although individuals affected by ASMD type AB and A are unlikely to return to 'Near normal or Full Health', the burden of their disease will be massively reduced, especially in newly diagnosed patients. The neurological element of this disease with type AB and A is without doubt a defining characteristic but if the wider systemic health is improved, then it would

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	be fair to say, so would their quality of life. Additionally, as in affected Type B patients, early treatment will hugely reduce the disease progression making effective treatment of their other comorbidities much easier to manage.
5	I am extremely frustrated that the committee have concerns over the long term effectiveness of this treatment and whether Olipudase Alpha meets the 3 criteria to be eligible for a 1.5% discount rate. Evidence through extensive testing in key areas shows rapid and significant improvement to all the patients who participated in the trial. As this is a storage disorder, there will always be a finite amount of improvement depending on the level of storage that has accumulated per individual. The huge & immediate response to this treatment where the liver size and function significantly improves and 94% of patients experienced a greater than or equal to 30% reduction in splenic volume in 12 months, unequivocally proves the effectiveness of this treatment. It is only fair to say that as the storage is broken down and discarded from the body there could be a slower rate of improvement because on some level this will rely on the body's own healing process to repair the residual injury. Needless to say that this healing process to 'near normal health', is entirely based on a maintenance dose of Olipudase Alpha to keep the Sphingomyelinase from accumulating in the future. The fact that patients who have been medicated with Olipudase Alpha for nearly 10 years are still continuing to improve and in some cases have better health than equivalent typical individuals of comparable age and weight within the population, only re-enforces it's need for long term use.

Insert extra rows as needed

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1	I am concerned that the committee has underestimated the degree of clinical response to olipudase alfa. It is striking that every parameter measured improved significantly in almost every patient treated. ASMD is a progressive disease and a successful treatment might have been expected to reduce the rate of progression or stabilise disease: olipudase alfa reverses disease. This is a remarkable result. There is complete clearance of sphingomyelin from the liver (as demonstrated by histology) and from the alveoli (as demonstrated by imaging). There is improvement of liver function (as demonstrated by lipid profiles) and lung function (as demonstrated by gas exchange). Liver and lung disease are the major causes of mortality in ASMD (the committee note that respiratory deaths are due to pneumonia, but this is secondary to the infiltration of the lung by lipid-laden macrophages and, at least in part, will have been due to lipoid pneumonia rather than infectious pneumonia).
2	I am concerned that the committee (and the disease modelling) are overly focused on the outcome of spleen volume, perhaps because it is easy to measure and the reduction in size is so striking. Spleen volumes do not normalise, but this is not surprising given the degree of splenomegaly at baseline. The histology of the spleen in ASMD is not well described, but the enlargement is not solely due to sphingomyelin or infiltration with storage cells. There is also a considerable degree of hypertrophy of the spleen and it is not

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	surprising that this persists to a degree and it is likely to explain much of the residual splenomegaly observed after 2 years treatment. In data from the phase 1b study it is striking that there is an ongoing reduction in spleen size over at least 6.5 years of treatment.
3	I am concerned that the committee has underestimated the longevity of the response to treatment. There is a remarkably rapid response in the primary outcome measures in the first 6 to 12 months of treatment, but there is also a clear ongoing improvement after that. For lung parameters it is true that, due to Covid precautions, there are fewer data available on lung function, but the data there is remarkably consistent, showing ongoing improvements in gas exchange. A manuscript describing the 2 year data from the Ascend trial is in the process of being accepted for publication and it should be possible for the sponsor to make that available to the committee. Again, in the phase 1b data, improvements in clinical parameters continue for at least 6.5 years. Once any of these parameters have normalised, it is not possible for them to improve further, but this does not mean there is not ongoing efficacy: there is no evidence that any of the beneficial effects of olipudase alfa are reversed in patients receiving long-term treatment.
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Insert extra rows as needed

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Olipudase alfa for treating Niemann-Pick disease types A and B [3913]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Nominated clinical expert by Sanofi. [redacted]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Co-Investigator on Sanofi sponsored clinical trials: A randomised, double blind, placebo controlled, repeat dose, dose comparison study to evaluate the efficacy, safety and pharmacokinetics of olupidase alfa in patients with acid sphingomyelinase (DFI 12712). A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency (LTS 13632). No funding ever received from the tobacco industry.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	I believe the clinical benefit and long-term response to olipudase alfa has been underestimated by the committee. This is a treatment that works and it continues to work long-term. My personal experience of 4 adult patients receiving olipudase alfa, either through clinical trials, or post-trial access, is of continued benefit. Our adult patients have been receiving treatment for 9 years, 7 years, 6 years, and 5 years now. They show sustained benefits, with continued improvements in clinical outcomes over time, consistent with the papers of Lachmann *et al*, Orphanet J Rare Dis. 2023 Apr 25;18(1):94. doi: 10.1186/s13023-023-02700-x and Thurberg *et al*, Mol Genet Metab. 2020 Sep-Oct;131(1-2):245-252. doi: 10.1016/j.ymgme.2020.06.010. These improvements occur even in older adults with what might be considered ‘established’ disease. The treatment is well tolerated, there is no evidence of treatment ‘resistance’ developing with time and the outcomes assessed continue to move / stabilise in the correct direction (towards health).

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	I believe that appropriate treatment will significantly reduce the long-term risks of cirrhosis, disabling interstitial lung disease and cardiovascular disease.
2	Dose escalation studies of olipudase alfa in adults (Wasserstein et al, Mol Genet Metab. 2015 Sep-Oct;116(1-2):88-97. doi: 10.1016/j.ymgme.2015.05.013.0) show that even before the full (currently licensed) dose of olipudase alfa (3mg/kg alternate weeks) was reached lipid profile, plasma ceremide and chitotriosidase were falling. This, and our experience with ERT for other conditions such as Gaucher disease, suggests that once significant sphingomyelin clearance is achieved then it may be possible to maintain (some) patients on a lower dose – hence reducing costs to the NHS. This could be carefully monitored using available imaging and biomarkers.
3	Once patients are stable, then aside from their own substantial health improvements, the need for significant input and resource use across NHS services (hepatology, respiratory, gastroenterology, nutrition support, haematology, cardiology etc) will also reduce. It is not clear how this has been considered in the economic model.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted]

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are very concerned that the magnitude of the response to Olipudase has been underestimated by both the company (Sanofi) and NICE. Every, measurable manifestation (and many less easily measurable) show benefit following treatment and generally continued benefit (stabilisation in the normal range or continued improvement towards normal) over the 6.5 years of published data. Experience from patients and treating investigators (including here in the UK and at our site) has been that benefit continues for over 10 years of therapy. This is different to what we see for most lysosomal treatments (and almost every other enzyme replacement therapy) in which improvement (if seen at all) is measurable for 18-24 months then there is either stabilisation or decline at a slower rate than natural history. The outcomes seen with Olipudase are vastly superior to many of the other lysosomal storage disorder treatments approved by NICE over the last 5- 10 years. The draft guidance does not reflect the significant and dramatic benefit seen by patients, clinicians or patient organisations nor our interpretation of the data.
2	We would continue to affirm that treated patients achieve a very near normal quality of life after 2-4 years of therapy. This from direct observation and assessment of treated patients
3	The clinical case for Olipudase seems very clear and straightforward to me, the only issue there can be resulting in the current draft guidance is the cost of the drug. As clinicians involved with this drug for many years I think we could agree ways to reduce the dose used as we frequently do in Gaucher disease, an analogous LSD. While this would be veering from the dose on the label we know from the long dose escalation periods that children and adults with ASMD show dramatic clinical and biomarker responses to lower doses than 3mg/kg alternate

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	weekly. A long term maintenance dose of 1mg/kg alternate weekly may be feasible for many patients and give similar results. There are adequate clinical, radiological and biochemical markers which could be used to dose titrate safely and with efficacy.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Niemann-Pick UK

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that in not recommending Olipudase alfa for the treatment acid sphingomyelinase deficiency (ASMD; Niemann-Pick disease) type AB or type B, that the Committee has not fully understood or taken into account the high physical and psychological burden for patients (their carers and siblings) and the high level of unmet medical need that significantly impacts their quality of life. Olipudase alfa has shown significant clinical benefit and long-term impact on the quality of life and psychosocial status for patients, and their families, as detailed in evidence provided by patients and family members, who have taken time to share their lived experience, the everyday challenges they face in living with ASMD and the significant, and meaningful way in which olipudase alfa has improved their health and quality of life.
2	We are concerned that the Committee has not recognised the meaningful impact of a reduced spleen size for ASMD patients. The severity of symptoms often prevents ASMD patients from fully participating in daily activities. Spleen size in particular affects their ability to eat usual sized meals, requiring patients to eat small meals and snacks many times a day – and usually requiring the support of carers to achieve this - without ever achieving

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	necessary nutritional levels. It causes severe fatigue, affecting their energy levels and pressing on their lungs and other organs, making it hard to walk any distance, to use stairs, to attend school or work or take part in social activities. It results in bullying at school, prevents patients from buying clothes 'off the rack' and makes them feel 'different', resulting in psychological and mental health issues. An enlarged spleen also brings many clinical issues, including bruising, uncontrollable nose bleeds, slow healing, and low platelets, plus the hospital visits and interventions required to treat them, all due to this one symptom alone. Therefore, we would like to stress that a reduction in spleen size is meaningful, whether it reaches 'normal' or not, it brings significant clinical and psychological benefits, that greatly improve quality, and ability to participate, in life.
3	We are concerned about the carer disutility assumption as stated in the guidance. ASMD patients experience different symptoms and challenges, and rates of progression, with patients having variable abilities and disabilities, some requiring constant support into adulthood with significant carer burden. Therefore age / and or spleen size cannot be used to accurately predict or measure carer involvement. As symptoms are variable and severe, and dependent on disease progression, carer involvement is necessary and can be all-consuming, considering the frequent and multiple medical appointments, regular monitoring, and several different clinical teams, often located in different locations plus the challenges of coordinating appointments at any age / point of progression.
4	Whilst we agree in part with the EAG view on carer disutility associated with patient death, we are concerned that the Committee has not fully recognised the impact of bereavement on parents, carers, and siblings, who report feelings of anxiety, stress and depression, linked to their thoughts about the patient's death. Anxieties are exacerbated by constant fatigue brought by caring duties and the extreme stress in knowing the outcome of ASMD, without treatment, is death. The profound effects of bereavement and feelings of guilt, for passing on a genetic disease, or in the case of siblings, for being unaffected, can result in long-term issues, including mental health issues, that can affect ability to participate in normal life, to work, undertake social activities and to maintain family relationships for many years following bereavement. Therefore, we believe that the death of a patient has an impact for a significant period, with carer disutility reducing over time.

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5	We are concerned that the Committee has underestimated the clinical benefits of treatment and the evidence that it can overcome disease severity and reverse disease impact. Clinical data is very strong and shows clearance of storage and reversal of disease. In particular evidence shows improvements to lung function and that this improvement continues in the longer term.
6	We are concerned by the EAG's assumption that the target population for olipudase alfa would be clearly recognisable to clinicians, and we feel that the issues in accurately identifying where a patient sits on the spectrum of ASMD disease have not been fully considered. It is difficult even for leading experts, to determine the clinical distinctions of disease type A/B / disease type B early in the disease course. This results in a diagnosis of "A/B" being stated on documents and as the distinction between A/B and B often can't be determined for years, treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment. Evidence supports the benefits of treating those with a confirmed A/B diagnosis, showing that treated patients experiencing increased physical and mental health benefits.
7	We are concerned about the effect of a negative decision on the patient community, who have closely followed (and participated in) the development of Olipudase Alfa since 1999. Patients and families have contributed in many ways, not just through their participation in the clinical trial. They have completed long and numerous qualitative and quantitative surveys, shared their experience by acting as a 'patient voice' at conferences and events, and given their time to support health technology assessment and regulatory processes. This small, and very well-informed patient community is well aware that Olipudase Alfa has shown significant clinical benefit, halting progression, reversing the debilitating symptoms of the disease, and extending life to the extent that the remaining health years have a significantly higher (near normal health) quality of life. They are also aware that this technology has received an interim approval in Scotland and that their peers across the border will have access under a data collection agreement, not to mention their friends in France, Germany, Brazil, Japan, and the USA. They are also aware of patients who have passed away, patients whose lives could have been saved and improved by earlier access to this treatment – and those who are awaiting a decision that will impact their future and that of their families.

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	This progressive disease has been shown to have a negative effect on the mental health of patients and families. The knowledge that there is a treatment – a treatment that works – but they can't access it, will cause significant long-term stress and anxiety for patients and their families, as well as those providing clinical care, who will not be able to provide care standards achieved in other countries.

Insert extra rows as needed

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Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID3913]

A Highly Specialised Technology Appraisal

Additional Analyses requested by the committee post-AC2

December 2023

Produced by

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Declared competing interests of the authors

D Hughes has received funding from Sanofi within the past 5-years for topics not related to olipudase alfa. No other competing interests.

Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This addendum is linked to EAG report

O'Toole, B.; Farmer, C.; Nikram, E.; Coelho, H.; Shaw, N.; Gissen, P.; Hughes, D.; Platt, F.; Whiteley, R.; Lee, D.; Melendez-Torres, G.J; Wilson, E.C.F..0BOlipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID3913]. Peninsula Technology Assessment Group (PenTAG), 2022.

1. INTRODUCTION

Following AC2, the committee requested additional analyses incorporating its preferred assumptions. This addendum presents those analyses, along with a threshold analysis stating the required PAS required to achieve an unweighted ICER of £300,000/QALY.

Specifically the committee's preferred assumptions were:

- Long-term treatment effect – Uncertainty in long term treatment effect, EAG's approach preferred for base case;
- Discount rate – 1.5% for both costs and benefits
- Carer's disutility:
    - Disutility for both arms;
    - Differential disutility: EAG approach preferred, by severity (vs. non-severe) and children (vs. adults);
    - Number of carers: 1 carer;
    - Carer's disutility associated with patient death: considered qualitatively rather than numerically;
- Mortality – company's parametric approach preferred
- Weight: EAG's approach preferred (HSE data with lower mean but different implementation from company's)
- Uncaptured benefit: understand improvement/benefits associated with treatment may be not fully captured by health-states defined by spleen volume and lung capacity; no other uncaptured benefits;
- QALY weighting: some QALY weighting may be applied but uncertainty in magnitude;
- Recently diagnosed subgroup: challenges in defining "recently" in this case and proposed subgroup not appropriate for consideration;

The EAG therefore modified its previous base case by the following:

- 1.5% discount rate for both costs and benefits
- Company's parametric approach to mortality (Weibull for paediatric, Gompertz and Weibull piecewise for adults)

2. RESULTS

Under the committee's preferred base case post AC2, the unadjusted ICER is [redacted] per QALY gained in the paediatric population and [redacted] in the adult (Table 1 and Table 3). Treatment is associated with an undiscounted incremental QALYs of 36.37 in the paediatric population and 18.72 in the adult. The discount on the list price required to reduce the ICER to £300,000 in the paediatric population is [redacted], and in the adult, [redacted] (Table 2 and Table 4).

Assuming 50% of patients are adult and 50% are children, the ICER is [redacted]. Due to the structure of the model calculating the discount required to achieve an ICER of £300,000/QALY is not straightforward, but a reasonable approximation would be midway between the adult and paediatric populations, namely [redacted].

Table 1: Committee preferred scenario results (paediatric population)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	Cost per QALY gained
Committee preferred deterministic base case						
Olipudase alfa	[redacted]	30.70	[redacted]	36.374	20.84	[redacted]
BSC	[redacted]	9.86				

Abbreviations: QALYs, quality adjusted life years; BSC, best supportive care

Table 2: Price discount required to achieve ICER of £300,000/QALY (paediatric)

£/20mg vial	% vs list price	Incremental Cost	Incremental QALYs	Cost per QALY gained
[redacted]	[redacted]	[redacted]	20.84	[redacted]
[redacted]	[redacted]	[redacted]	20.84	[redacted]

Table 3: Company base case results (adult population)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	Cost per QALY gained
Committee preferred deterministic base case						

	Total costs	Total QALYs	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	Cost per QALY gained
Olipudase alfa	[redacted]	25.5	[redacted]	18.72	11.73	[redacted]
BSC	[redacted]	13.77				

Abbreviations: QALYs, quality adjusted life years; BSC, best supportive care

Table 4: Price discount required to achieve ICER of £300,000/QALY (adult)

£/20mg vial	% vs list price	Incremental Cost	Incremental QALYs	Cost per QALY gained
[redacted]	[redacted]	[redacted]	11.73	[redacted]
[redacted]	[redacted]	[redacted]	11.73	[redacted]

Table 5: Committee preferred scenario results (50/50 paediatric/adult population)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	Cost per QALY gained
Committee preferred deterministic base case						
Olipudase alfa	[redacted]	28.1	[redacted]	27.55	16.29	[redacted]
BSC	[redacted]	11.82	[redacted]			

Abbreviations: QALYs, quality adjusted life years; BSC, best supportive care

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and A/B) [ID 3913]

For committee – contains ACIC information

Highly Specialized Technology Appraisal Committee [05 October 2023]

Chair: Peter Jackson

Lead team: Shehla Mohammed, Stuart Mealing, Jonathan Ives

External assessment group: Peninsula Technology Assessment Group (PenTAG)

Technical team: Tom Jarratt, Yelan Guo, Richard Diaz

Company: Sanofi

Key issues, clinical

Population representativeness:

- Does the committee consider that the population in trials represent those seen in the UK in terms of ASMD type, severity, and baseline characteristics including age and weight?

Long term treatment effect:

- What is the committee's view of olipudase alfa's treatment effect on clinical outcomes in the long term?
- What is the committee's view of olipudase alfa's treatment effect on quality of life (QoL) for people with type B or A/B? Does it agree that improvement in clinical outcomes may lead to improvement in children's QoL and functioning?

Key issues: economic

Discount rate: does the committee consider the criteria for non-reference-case of 1.5% discount rate met?

Long-term treatment effect: which assumption on the long-term treatment effect of olipudase alfa does the committee consider more appropriate?

Mortality: which approach is best for modelling mortality? Does the committee consider there is disease-specific mortality in paediatric patients with acid sphingomyelinase deficiency (ASMD)?

Carer's disutilities:

- Apply to Best supportive care (BSC) arm only or to health states regardless of treatment?
- -0.15 for carer's disutility or, differential disutilities for carers by severity of health states and adult/children?
- 2.6 or 1 on average per child?
- -0.5 carer's disutilities associated with patient death and for the remaining time horizon of the model or not?

Weight: which method, company vs. EAG's, of modelling patient weight does the committee prefer?

QALY weighting: Does quality-adjusted life year (QALY) weighting apply?

Others:

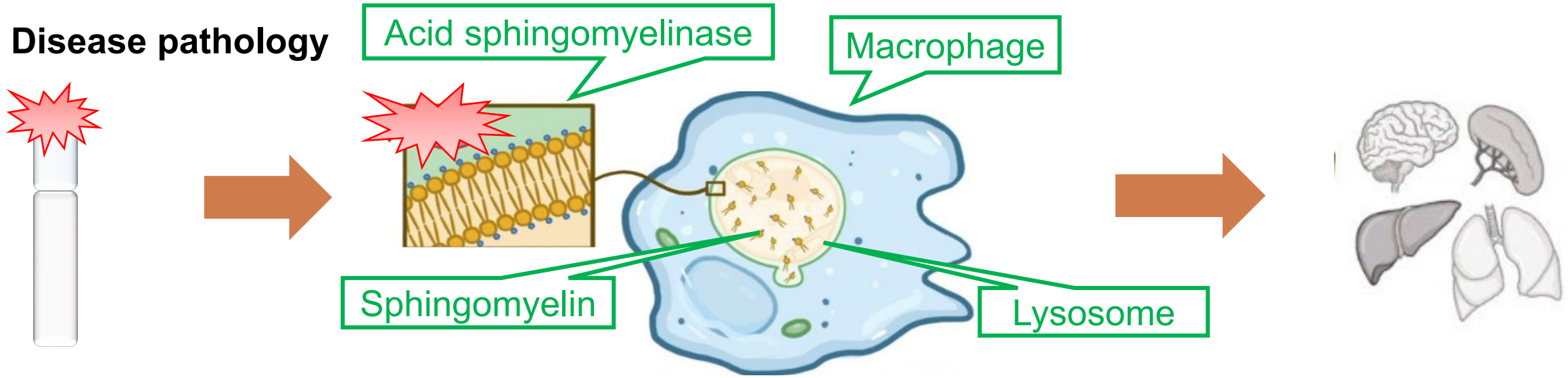
- Are there any equality issues that require additional consideration? If so, what are they?
- Are there any benefits not fully captured by the model?

3

Background: Niemann-Pick (NP) types B and A/B

Niemann-Pick disease: type B, AB, and A* also known collectively as acid sphingomyelinase deficiency (ASMD), caused by SMPD1 gene mutation; and characterised by build-up of sphingomyelin causing multi-organ damage;

Disease pathology



Mutation in SMPD1 gene

- Acid sphingomyelinase breaks down sphingomyelin
- Mutation causes ASMD, leading to sphingomyelin build-up in lysosomes

Build-up in other cells throughout body, causing damage

*company's MA wording does not cover ASMD type A; Type C and D also exist but not classed as ASMD as mutations are in NPC1 or NPC2 genes involved in cholesterol cellular trafficking
Source: adapted from National Organization for Rare Disorders, Acid Sphingomyelinase Deficiency

Background:

ASMD: One of inherited metabolic disorders caused by enzyme deficiencies within lysosome, known as lysosomal storage diseases (LSDs); progressive, debilitating and life-limiting

Diagnosis: ASM activity levels followed by molecular genetic testing to confirm ASMD

- Most diagnosed during childhood: diagnosis age varies but typically 2-6 years
- Currently subtypes determined by clinical presentation; no clear diagnostic test available to distinguish between type A, B, or AB

Incidence & prevalence:

- ~1 to 2 people diagnosed each year in England (type A, B or AB)
- ~40 to 50 people diagnosed in total but likely more given lack of newborn screening
- Most diagnosed patients in the UK have ASMD type B

Mortality: increased risk, respiratory or liver failure leading cause of death, neurodegenerative disease adds further risk to ASMD A/B; life expectancy: less than 60 years of age in the UK

Treatment: currently no treatment address underlying pathology of ASMD; only symptomatic, palliative or supportive care available, involving wide range of specialisations

Abbreviations: ASMD, acid sphingomyelinase deficiency

Signs and symptoms

ASMD A/B and B characterised by severe and multi-systemic clinical manifestations

	ASMD type-A/B	ASMD type-B
Description	Chronic neurovisceral	Chronic visceral
Age of onset	Varies, usually children	Varies, children or adults
Natural history	Variable manifestations, severity, and rates of disease progression, type A/B more severe than type B	
Age of death	Childhood to adulthood	Common to survive to adulthood
Symptoms		
Enlarged spleen/liver	+	+
Proatherogenic lipid profile	+	+
Delayed growth + puberty	+	+
Low platelets	+	+
Interstitial lung disease	+	+
Skeletal involvement	+	+
Liver disease	+	+
Cherry red macula	Some patients	Some patients
Low muscle tone	Some patients	Absent
Neurodegeneration	Slowly progressive	Absent

Olipudase alfa will not impact on neurological manifesta-tions

Abbreviations: ASMD, acid sphingomyelinase deficiency

Patient perspectives:

Debilitating disease with multiple complex healthcare needs; physical and psychological impacts on patients

Submissions from Niemann-Pick UK (NPUK)

- Symptoms affect ability to complete daily activities
  - ❖ Enlarged organs restrict lung capacity and can affect ability to exercise and eat usual sized meals, causing nausea and vomiting
  - ❖ Tiredness and fatigue common: enlarged spleen causes anaemia
  - ❖ Bone thinning can lead to increased risk of fracture and pain
  - ❖ Frequent nosebleeds from low platelets challenging to manage
  - ❖ Slow growth and puberty cause "*significant anxiety and distress*
- Life shortening disease without treatment, large psychological impact
  - ❖ Lack of understanding of disease leading to isolation and confusion
  - ❖ psychosocial impact of delayed growth/puberty and abdominal swelling from enlarged organs (especially large from ages 10-16)
  - ❖ Social isolation common with children commonly bullied at school

He is still a very happy boy, but no child wants to be throwing up five times a day.

We have been told he may not reach puberty until his late twenties

Patient perspectives: pathway and intervention

Current management of the condition complex and challenging for patients and carers

- Can take many years for diagnosis: currently no routine screening for ASMD in newborns
- Difficulties travelling to specialist centres, especially if person needs high burden of care
- Best supportive care complex: frequent hospital visits, clinical teams throughout country
- Lack of understanding from local healthcare (GP and hospital) given rarity of disease

Benefit of olipudase alfa:

- Only disease modifying treatment option for ASDM: halts progression and reverses many aspects of debilitating disease
- 'Life-changing' outcomes, side effects minor compared to ASMD
- 2 weekly infusions: patients may miss school/work
- Home treatment option preferred
- Early treatment will prevent significant and irreversible burden of disease, reduce comorbidity and mortality
- Wider societal impact outside of direct costs and benefits e.g. maintenance of earning potential for carers.

The drug has drastically improved our son's life. He looks and acts like any other kid his age. He is much more confident now that his belly is small, and he is similar in size to his peers. […] You would never know that he has ASMD

NICE

Abbreviations: ASMD, acid sphingomyelinase deficiency

Patient perspectives: Impact on carers and families

Impact on carers

- Psychological: anxiety, stress, depression and feelings of guilt (for passing on genetic disease, child's QoL etc.)
- Constant fatigue because of level of care and child's poor sleep
- Potential relationship breakdown, loss of earnings, genetic implications for family planning

Impact on siblings:

- Children with affected sibling: lack of attention from busy parents leading to feelings of exclusion, resentment, embarrassment and anxiety
- Children caring for affected adults: practical, emotional and psychological issues, which can lead to problems at school, social isolation, feeling neglected and being bullied

Abbreviations: ASMD, acid sphingomyelinase deficiency; QoL, quality of life

Clinical perspectives

Submissions from British Inherited Metabolic Disease Group

Aims of treatment:

1. Improve hepatosplenomegaly, respiratory / interstitial lung, haematological and bone disease
2. Prevent significant morbidity and premature death from pulmonary and liver disease

Diagnosis and management

- Diagnosis and initial treatment at lysosomal storage disorder specialist services:
    - ❖ expected all diagnosed patients known to a specialist centre.
- Once biochemical and clinical parameters improved / normalised, supportive treatment measures could be reduced: ongoing treatment & surveillance could be moved to homecare

Experience with olipudase alfa:

- Not expected to directly impact neurological disease in patients with neurovisceral disease (will still improve the visceral component)

Technology (Olipudase alfa, Xenpozyme)

Company: Olipudase alfa targets underlying pathology of ASMD, first and only disease-modifying treatment for ASMD, reversing the accumulation of sphingomyelin

Marketing authorisation	MHRA approval received 1st August 2022, *"as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B."* Olipudase alfa does not have a marketing authorisation for any other indication.
Mechanism of action	Recombinant human acid sphingomyelinase that reduces sphingomyelin (SM) accumulation in organs of patients with Acid Sphingomyelinase Deficiency (ASMD)
Administration	IV infusion every 2 weeks. Adult and paediatric patients will receive olipudase alfa at 3 mg/kg following a dose escalation regimen
Price	• List price per 20mg vial: £3,612 • List price for 12 months of treatment: Year 1 [redacted], years 2+ [redacted] • A simple patient access scheme has been approved for this technology

Decision problem

Company's decision problem generally consistent with scope

Population, intervention, comparators and outcomes from the scope

	Company final scope (as per NICE scope)	EAG comments
Population	People with ASMD (type B or A/B)	Consistent with scope but unclear how many had type A/B (HRQoL and functioning may differ to type B, and neurological symptoms may not be improved)
Intervention	Olipudase alfa	-
Comparator	Best supportive care	Appropriate but company did not include purely non-pharmacological interventions
Subgroups	None	Small numbers but subgroups for genetic markers, age of onset, or baseline severity would be useful
Outcomes	- Mortality - Adverse effects, fatigue and exercise - HRQoL (patient and carer) - Changes in spleen, lung and liver function/volume - Physical / neurological observations - Biomarker changes - Weight, height and onset of puberty in children and young people	Trial did not cover evidence for change in neurological symptoms, physical observations, onset of puberty or carer functioning. However, advice to EAG suggests key outcomes were measured (change in organomegaly, pulmonary function, liver function, HRQoL and functioning, and adverse events).

Abbreviations: ASMD, acid sphingomyelinase deficiency; HRQoL, health-related quality of life

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Baseline population characteristics in trials

EAG: population with more severe disease may have been excluded because of trials' in/exclusion criteria

	ASCEND		ASCEND-Peds	DFI13412
	Olipudase alfa N=18	Placebo N=18	N=20	N=5
Age, mean years (SD), range	36.2 (12.7), 18.8 – 59.9	33.5 (17.1), 18.6 – 65.9	8.2 (4.4), 1.5 – 17.5	32.6 (9.4), 23 - 48
Weight (kg), mean (SD)	67.4 (14.1)	61.6 (13.4)	23.4 (10.8)	[redacted]

EAG:

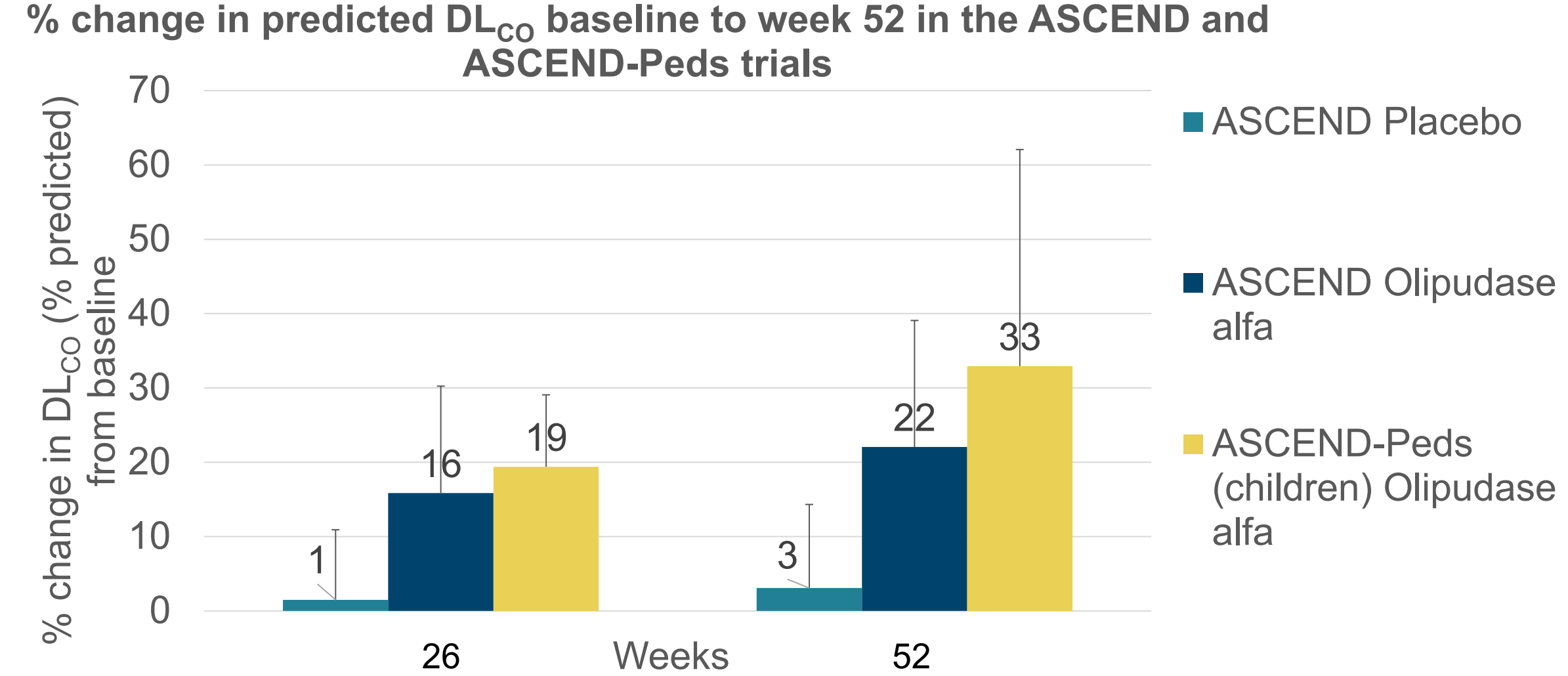
Weight: Baseline weight lower than expected in UK. Expert advice: some people may be smaller with ASMD but unlikely to see difference across population.

Disease severity: People excluded may be more likely to experience adverse events and have differential treatment effect, although ASCEND subgroup analyses did not find differences by severity; unclear subtype proportions (A/B or B) in trials, may be differences in cost/clinical effectiveness;

Does the committee consider the population in trials represent those seen in the UK in terms of ASMD type, severity, and baseline characteristics including age and weight?

Results, primary outcome: % change in predicted DL_{CO}

EAG: Olipudase alfa improved overall lung diffusion capacity compared with placebo, and trend continues over time



DLCO results adjusted for haemoglobin concentration and ambient barometric pressure as anaemia common in ASMD. Error bars represent the standard error.

Clinical trial results: % change in predicted DLco

EAG: while mean improvement in DLco continues over trial's follow up time, uncertainty in whether treatment effect may vary across the population

Company: Clinically significant improvement in DLco defined as improvement ≥15%

- Conducted responder analyses, response defined as % predicted DLco ≥15% at Week 52
- Responders at week 52: 27.8% (5/18) olipudase alfa vs 0% placebo

EAG

- High rate of attrition in DLco **outcome assessment** at 2-year follow up: 50%
- Further improvements in DLco beyond week 52, but unclear on the extent and number of responders as no further responder analyses conducted.
- Effect of treatment may vary across the population, by baseline symptom severity or time since diagnosis (as this may affect the extent to which organs have experienced irreversible change).

Clinical expert: "*The patients in the phase 1b study have now been treated for almost 10 years and there is no evidence of any decline in treatment effect.*"

What is the committee's view of olipudase alfa's treatment effect on overall lung diffusion capacity at 52 weeks and in the long term?

Abbreviations: DLco, diffusing capacity of the lungs for carbon monoxide

Results, primary outcome: % change in Spleen volume

EAG: Absolute spleen volume at the longest follow-up stabilised for both adult and children at 6 multiples of normal

[redacted]

Month 12 ASCEND:

- 94% were responders to olipudase alfa (defined by company as **change** ≥30%)
- No change for placebo arm

Expert advice to EAG: Level of reduction offers clinically meaningful benefit to functioning and mental wellbeing

What is the committee's view of olipudase alfa's treatment effect on spleen volume?

Results: HRQoL

EAG: likely measure of QoL and functioning may not be sensitive to improvement in clinical outcomes, magnitude of benefits may vary across ASMD type B and A/B

ASCEND

- HRQoL at baseline (for both arms) lower than general population norms for all subscales
- At 6- and 12-months: No difference between arms in HRQoL measured by EQ-5D or SF-36

Company and EAG agree findings inconsistent with key outcome data and patient testimony

ASCEND-Peds

- 5-7 years old: No effect until after year 1 of treatment, improvement (over baseline on PedsQL generic measure) near threshold for minimally important differences (MIDs)
- 8-18 years old: Mean improvements above MID by 6-months, further increase by 12-months

EAG: No comparator arm and open label trial, risk of bias and limits interpretation. Notes that other studies (not part of submission) do show benefit so effect (over baseline) may be genuine, particularly for over 5 years of age – Expert advice to EAG reiterates this

NICE What is the committee's view of olipudase alfa's effect on QoL for people with type B or A/B? Does it agree that improving clinical outcomes will improve children's QoL and functioning?

Abbreviations: ASMD, acid sphingomyelinase deficiency; HRQoL, health-related quality of life

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key issues identified by EAG

Key issues all have large impact on ICER

Issue	Resolved?	ICER impact
Discount rate: Should a rate of 1.5% or 3.5% be applied (to costs and benefits)?	No	Large
Long-term treatment effect: How long will benefit of treatment last?	No	Large
Carer's utilities: Treatment-dependant carer disutility, or same disutility for all? Is there carer disutility associated with patient dying? How many carers are there for children with ASMD?	No	Large
Mortality: Will children experience disease-related mortality?	No	Minor
Modelling patient weight: How should patient weight be modelled?	No	Moderate
Severe disease subgroup: Uncertainty around modelling for those with severe disease due to limited data	Unresolvable	Uncertain

Abbreviations: ASMD, acid sphingomyelinase deficiency; HRQoL, health-related quality of life

Modelling long-term treatment effect

EAG: uncertainty in treatment effect in long term given lack of evidence

Background

- In company's model, from year 3 onwards, people on olipudase alfa transition to least severe health states (Spleen volume <6 / DLco >80) and remain in this state for rest of time horizon
  - ASCEND main trial provides data up to 2 years in adults
  - Extension trial provide data up to 4 (children) and 6.5 years (adults)

Company after TE

- Changed base-case so that people transition to least severe state from year 10 onwards
- Longer term follow-up suggests patients restored to full or near-full health;

EAG

- Long-term data subject to high attrition and small sample (data on 5 adults and 7/20 children); Double-blind period of ASCEND, up to 1-year, most useful for decision making
- No evidence for company's assumption of everyone returning to full health at some point in time if taking olipudase alfa, trials show symptoms still occurring outside normal range
- Prefer health-state frozen after 2 years given uncertainty beyond this point

Experts

- Clinical expert: Patients in phase 1b study have been treated for almost 10 years without evidence of decline in treatment effect.

NICE Which assumption on the long-term treatment effect of olipudase alfa is more appropriate?

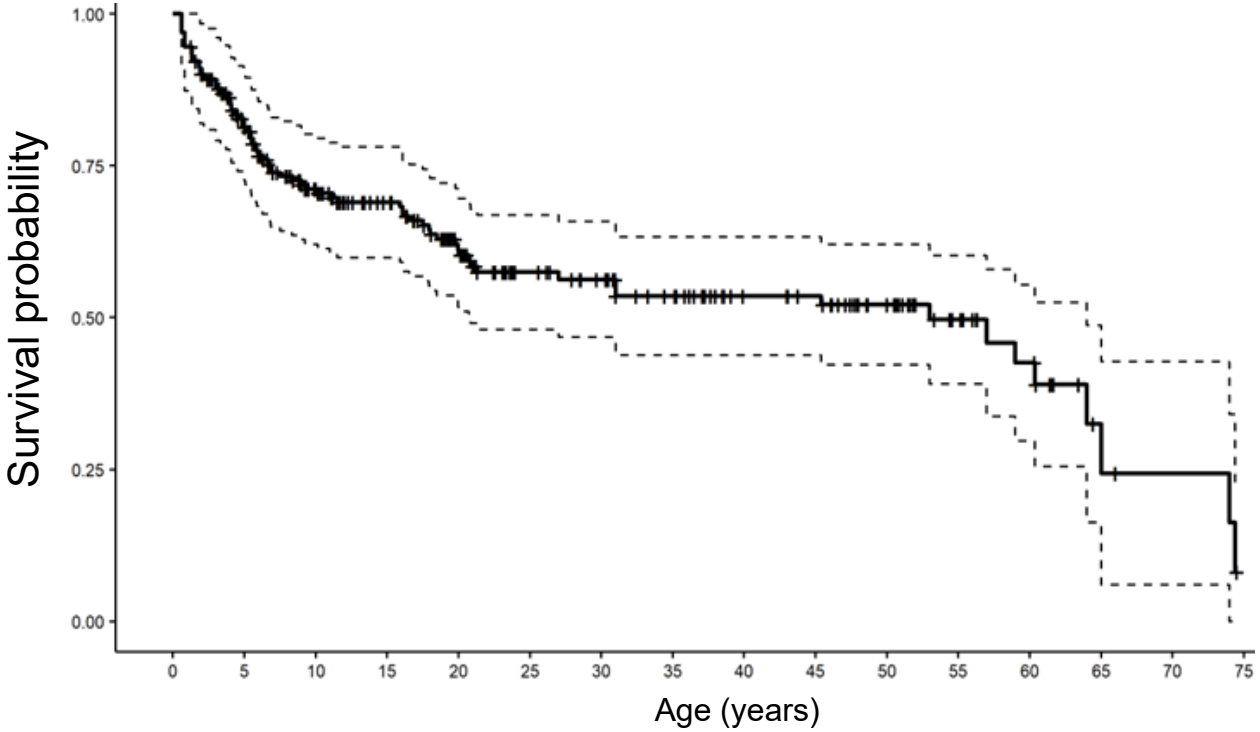
Modelling mortality:

Company and EAG had different approaches to modelling mortality

Company post TE:

- **BSC:** used chart review and pooled data analysis of ASMD patients (N=270, centres in Germany, France, US and Brazil) estimating mortality in BSC
- **Olipudase alfa** mortality: modelled by applying a hazard ratio (HR) of 0.1 to BSC mortality; Included paediatric disease-specific mortality

Kaplan-Meier survival curve for chart review, with risk adjustment (overall population, n=270)



EAG: uncertainty because details on methods of chart review not reported; no explanation of adjustment performed;

- Chart review study baseline characteristics may not be representative to the UK:
- lower proportion of type A/B disease (11.1% type A/B, 77% type B, 11.9% unspecified) and high prior splenectomy (7.04%) compared to key trials;
- Extensive missing data: ~80% for key baseline parameters (SV, Dlco and liver volume).
- HR of 0.1 for olipudase alfa sourced from poster, limited reporting of methods, subject to uncertainty and high imprecision

Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; SV, spleen volume

Modelling mortality:

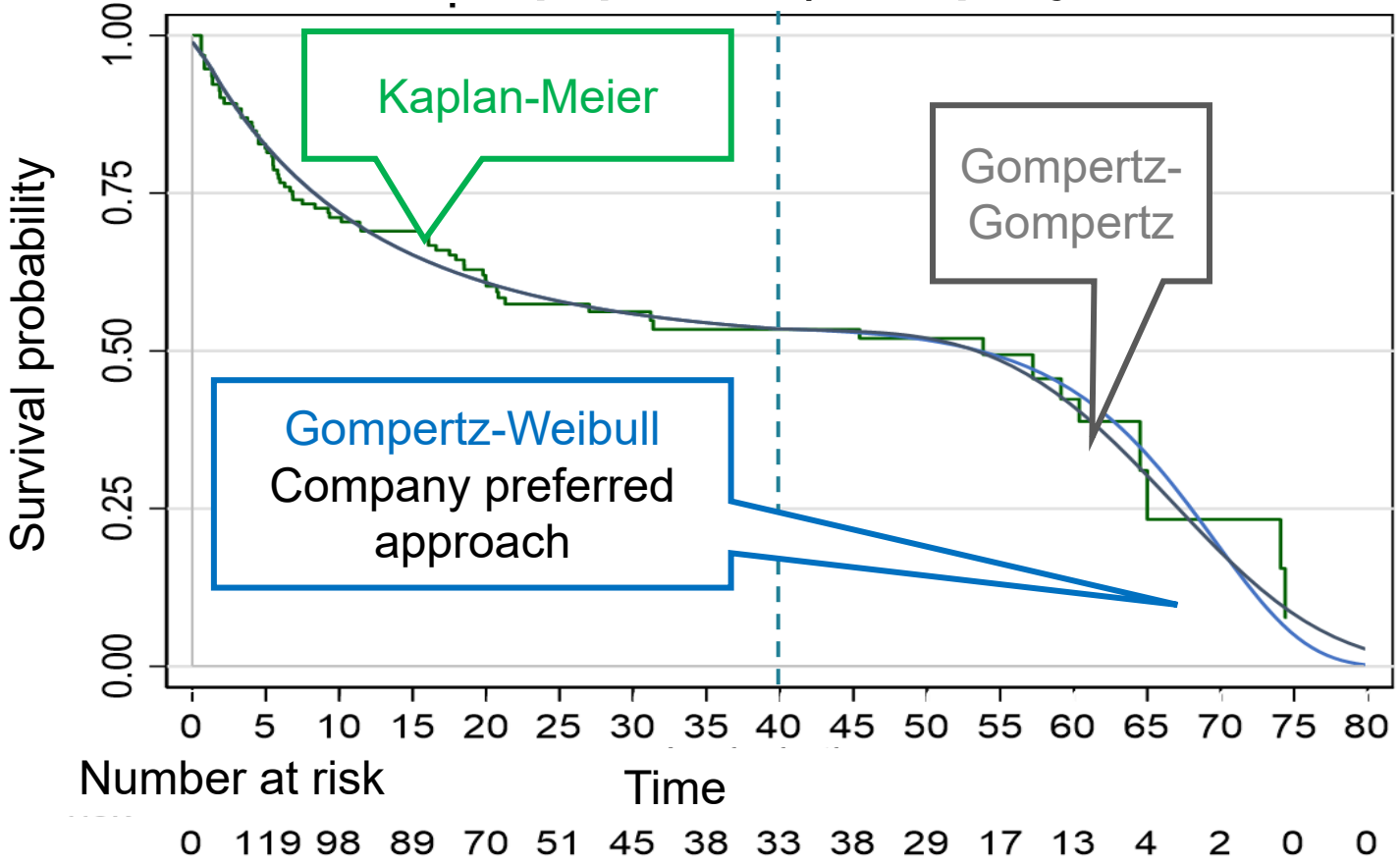
EAG: maintained its original approach as severe limitations in company's revised analysis post-TE;

EAG: company provided a single graph for KM curve for overall population and extrapolations in adults; other figures for extrapolation not provided (e.g., by subgroup) so cannot accurately assess new extrapolation; rationale for other changes in model not documented;

EAG final base-case:

- Used original company base-case: SPHINGO-100 data to estimate mortality risk and applying it to UK general population risk (10x risk to those with severe splenomegaly versus without)
- SPHINGO- 100: Conducted in North America | N=58 (type B), only 8 deaths over 11-year period
- Excluded disease-specific mortality in paediatric population in model

BSC: extrapolating long-term survival in adults (*with KM curve for overall population*), *company*



Which approach is best for modelling mortality? Will children die from ASMD?

Abbreviations: ASMD, acid sphingomyelinase deficiency; TE, technical engagement

Key issue: Discounting rates 1.5% vs 3.5% (1)

Company presents case for discounting rate of 1.5%: EAG preferred 3.5% for both

NICE criteria for non-reference-case discount rate of 1.5%:

May be considered if	Company	EAG
1) For people who would otherwise die or have a very severely impaired QoL	ASMD has severe implications on quality of life, functioning and mortality	Uncertainty as to extent of mortality risk and how it differs between type A/B and B
2) It is likely to restore them to full or near-full health **Clinical expert:** Olipudase alfa is capable of reversing effects of ASMD	Interviews of 10 paediatric patients / carers before and after olipudase alfa showed improvement in all non-neurological manifestations	• Evidence shows organs still enlarged, mean Dlco at 52 weeks ~60% predicted • Clinical advice suggests benefit will vary • Survey shows important improvement but small sample, unclear methodology
3) Benefits likely sustained over very long time-period **Clinical experts:** Patients in phase 1b study have had almost 10 years treatment with no evidence of decline in treatment effect	Extension study provides long-term follow-up	• Relatively short-term trial data in ASCEND and ASCEND-Peds compared to length of extrapolation in model • High attrition in long-term

Does the committee consider the criteria for non-reference-case of 1.5% discount rate met?

Abbreviations: ASMD, acid sphingomyelinase deficiency; Dlco; diffusing capacity of lungs for carbon monoxide; QoL, quality of life

Key issue: Carer disutilities (1)

EAG: uncertainty surrounding several assumptions on carer's disutilities

Overview: Company and EAG differ in 4 key areas, key drivers of cost-effectiveness.
Limited published evidence on ASMD carer disutility so EAG prefer more conservative assumptions

Company and EAG base-case assumptions

Company final base-case	EAG final base-case
No carer disutility for olipudase arm (only applied to BSC)	Disutility applied to both arms, should be based on patient's health state
Same carer disutility for all health states (-0.15, sourced from Pompe disease)	Higher disutility for severe health state, and different between adults and children
2.6 carers for children (to account for siblings)	1 carer for both
Carer disutility (-0.5) throughout modelled time horizon if patient dies	No carer's disutility associated with patient death

Patient expert: olipudase alfa led to child regaining ability to complete many everyday life functions → Large impact on carer QoL

EAG: Pompe would have greater carer burden than ASMD; sourced values from various chronic diseases

EAG: no precedent for >2 carers, including siblings is very uncertain

No established practice for death disutility: Unclear value and duration (company applied large disutility for duration of model)

Which assumptions for carer disutility do the committee think are most appropriate?

Abbreviations: ASMD, acid sphingomyelinase deficiency; QoL, Quality of life

Additional issues: Patient weight and severe subgroup

EAG assumes higher patient weight than company

Company and EAG base-case approaches to modelling weight

	Paediatrics	Adults
Company	Starting weight 20.53 kg → fluctuates over time according to z-score estimated from SPHINGO-100 (applied to UK growth chart weights)	Starting weight 64.52 kg → weight constant over time
EAG	Prefer 2019 Health Survey for England report data	Prefer UK average weight, changing over-time according to SPHONGO-100 (68.5kg)

Patient and clinical experts: Agree it is normal for children's weight and height to be lower than peers but growth can catch up – adults have similar weight distribution to UK average

Severe subgroup: Company provided subgroup analysis in people with severe disease (people in model start in most severe health-state); for illustrative purposes, limited data to inform analysis
Clinical expert: Trials excluded most ill patients but compassionate use in more severe disease suggests even greater response to treatment

EAG

- Transitions from most severe health-state based on overall trial populations data rather than specific clinical evidence → Expert advice suggests this may not be appropriate

Which method of modelling patient weight does the committee prefer?

Other considerations

Equality issues

- Company: no significantly equality issues but note that:
  - ❑ Significant inequity in terms of patients' socioeconomic outlook.
  - ❑ Inability to work and attend school has a negative financial impact (now or in the future) which is often worsened by need to travel to numerous medical appointments. Carer givers way also have difficulty maintaining full-time work due to caregiving commitments
  - ❑ Introduction of olipudase alfa would help alleviate these problems

Benefits not fully captured:

- Clinical expert: symptoms which patients regarded as normal (limited exercise capacity, pain, fatigue) disappear with treatment and they develop a new understanding of what 'normal' life is. QALY calculations cannot fully capture this.

Managed access

- Company proposed managed access

Are there any equality issues that require additional consideration?
Are there any benefits not fully captured by the model?

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

NICE

Abbreviations: QALY, quality adjusted life years; QoL, Quality of life

QALY weighting

EAG: does not consider appropriate to apply QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Life incremental QALY gained	Weight
Less than or equal to 10	1
11 to 29	Between 1 to 3 (equal increments)
Greater than or equal to 30	3

EAG: May not be appropriate to apply QALY weight, because;

- Lack of robust clinical data informing company's economic model given rarity of condition;
- High degree of uncertainty in company's assumptions;
- Results sensitive to assumptions on long term treatment effect, carer's disutilities, patient weight and discount rate;

NICE

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years

Company and EAG base case assumptions

Assumptions in company and EAG base case

Model feature	Company final base-case	EAG final base-case
Discount rate	1.5% (costs and benefits)	3.5% (costs and benefits)
Long-term treatment effect	Least severe health-state from year 10	Treatment effect frozen from year 3
Carer disutility		
• Disutility for both arms?	BSC arm only	Both arms
• Disutility based on health-state	-0.15, based on Pompe disease	Differential, based on various diseases
• Number of carers	2.6	1
• If patient dies	-0.50 across remaining time horizon	No disutility
Mortality & Disease-related mortality for paediatric	Based on chart review pooled data analysis; disease-related paediatric death included	Based on company's original approach; excluded disease-related paediatric death
Weight (paediatric)?	z-score applied to UK growth charts	Reflects UK mean (using Health Survey for England) at different ages
Weight (adults)	Based on ASCEND mean, remains constant	z-score for 18-year olds applied to UK mean

EAG: company's revised base case not appropriate for decision making given uncertainties and assumptions deemed inappropriate by EAG

Company base case and EAG's exploratory analysis

EAG conducted following exploratory analyses (in addition to those comprising EAG base-case):

Long term treatment effect:

- Continues for olipudase alfa from year 3
- Follows BSC transitions from year 2 (treatment effect waning scenario)

Mortality: SMR for severe splenomegaly reduced by 50% (to 21.5)

Adult weight: UK mean weight (77.3kg; gender split based on ASCEND trial and no weight fluctuation)

Compliance rate: 100% (up from 90% in base-case)

Age starting treatment (adults): 28 years (down from 34 years in base-case)

Age starting treatment (children): 2 years (down from 8 years in base-case)

Liver complication rates: 3.4% both arms (0.3% for olipudase and 3.4% for BSC in base-case, based on SPHINGO-302)

What are committee's preferred assumptions?

Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; SMR, standardised mortality rate

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

Key issues: economic

Discount rate: does the committee consider the criteria for non-reference-case of 1.5% discount rate met?

Long-term treatment effect: which assumption on the long-term treatment effect of olipudase alfa does the committee consider more appropriate?

Mortality: which approach is best for modelling mortality? Does the committee consider there is disease-specific mortality in paediatric patients with ASMD?

Carer's disutilities:

- apply to BSC arm only or to health states regardless of treatment?
- -0.15 for carer's disutility or, differential disutilities for carers by severity of health states and adult/children?
- 2.6 or 1 on average per child?
- -0.5 carer's disutilities associated with patient death and for the remaining time horizon of model or not?

Weight: which method, company vs. EAG's, of modelling patient weight does the committee prefer?

QALY weighting: Does QALY weighting apply?

Others:

- Are there any equality issues that require additional consideration? If so, what are they?
- Are there any benefits not fully captured by the model?

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Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; QALY, quality-adjusted life year

NICE National Institute for Health and Care Excellence

Thank you.

NICE National Institute for Health and Care Excellence

Back-up slides

Treatment pathway

No NICE or NHS guidelines for diagnosis and management of ASMD. Best supportive care = symptomatic/ palliative care for clinical manifestations

Olipudase alfa likely used as first line treatment alongside existing supportive interventions

Clinical manifestation	Management
Valvular insufficiency	Repair/ replace defective heart valves‡, stenting/ CABG for CVD‡
Lung involvement	• Avoid smoking, influenza & pneumonia vaccinations • Bronchodilators, pulmonary infection drugs • Lung transplant, allogeneic bone marrow transplant & HSCT* • Therapeutic bronchopulmonary lavage, supplemental O2/NPPV
Liver & spleen	• Nutritional support, ammonia reduction, hep A and B vaccinations • Non-selective beta blockers, antibiotics • Liver transplant†, partial splenectomy/ splenic arterial embolism
Dyslipidaemia	• Diet management • Statins (post-puberty)
Bleeding	Nasal packing & cauterisation for nosebleeds, transfusion (rare)
Other	Dietary & lifestyle changes to prevent bone loss, osteopenia & support growth; physical therapy; education

† Patients often too unwell due to comorbidity to receive liver transplant; ‡ Surgical intervention based on potential risks of bleeding issues or other contraindications. Abbreviations: CABG, coronary artery bypass grafting; CVD, cardiovascular disease; HSCT, hematopoietic stem cell transplantation

Clinical trials and studies

Clinical effectiveness mainly informed by 4 clinical trials
(1 RCT and 2 single-arm trials, all with extension studies)

Key: Ongoing trial; Completed trial; Additional data

Olipudase alfa

ASCEND Peds
Open label, single arm
52 week follow up in **children** (N=20)

DFI13412
Open label, single arm
26 week follow up in adults (N=5)

ASCEND
RCT + single arm extension study
2 year follow up in **adults** (N=36)

LTS13632
Open-label extension study
4 years (pediatric) and 6.5-years (adult) follow up (N=25)

Sanofi chart review
Chart review of people (n=270) treated in Brazil, US, Germany and France

Informs mortality in main analysis post TE

SPHINGO-100
Survey study of 30 children and 29 adults

Informs transition probabilities in BSC arm and informs weight in paediatric patients

McGovern 2013
Natural history study of adults (N=42) and children (N=61)

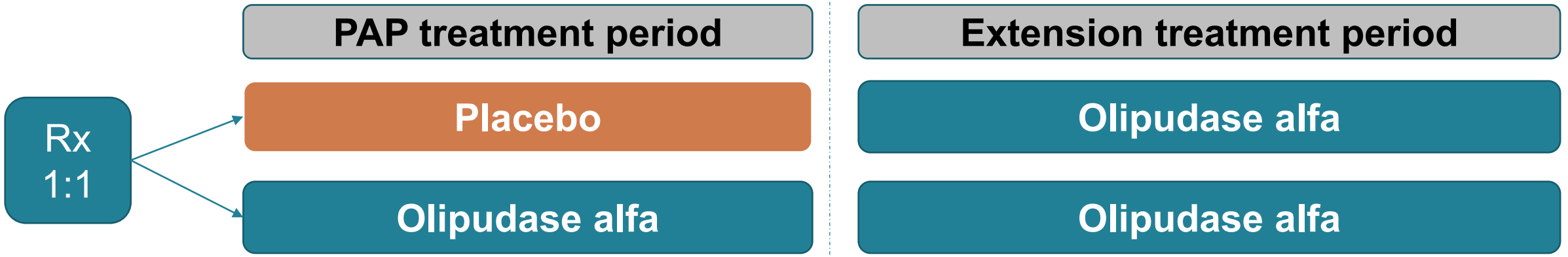
Informs mortality in scenario analysis for severe subgroup

Abbreviations: BSC, best supportive care

ASCEND clinical trial study design

Up to 3mg/kg for 3 months, then 3mg/kg every 2 weeks

True treatment crossover for placebo, mock crossover for active arm



Week	0	2	6	10	12	14 - 52	54	56	60	64	66	68 - EoT
Dose mg/kg (placebo arm)	N/A						0.1	0.3	0.6	1.0	2.0	3.0
Dose mg/kg (olipudase alfa arm)	0.1	0.3	0.6	1.0	2.0	3.0	3.0					

Key clinical trial designs and populations

Key: Ongoing | Completed

	ASCEND	ASCEND-Peds	DFI13412	LTS13632
Design	Double-blind RCT then extension study	Open-label single-arm	Open-label, single arm	Open-label extension to ASCEND-Peds & DFI13412
Population	36 adults with ASMD type B	20 children with non-type A ASMD	5 adults with ASMD	Completed treatment in ASCEND-Peds & DFI13412 (N=25) with acceptable safety profile
Comparator	Placebo	N/A	N/A	N/A
Follow-up	52 weeks, then 1-year extension	52 weeks	26 weeks	• 4 years (children, n=7) • 6.5 years (adults, n=5)
Countries	17 (North & South America, Asia Australasia, UK, Europe)	6 (Brazil, France, Germany, Italy, UK, US)	UK and US	7 (Brazil, Belgium, France, Germany, Italy, UK, US)

- **EAG**: Unclear subtype (A/B or B) in all studies, may be differences in cost/clinical effectiveness
- Type A/B presents with neurological symptoms unaffected by olipudase (25% of ASCEND, 40% of ASCEND-Peds had neurological symptoms consistent with A/B)
- Best quality evidence is at 1-year (adults and children)

EAG: Small number reaching 4/6.5 year follow up and high level of missing data (data available for 7/20 in paediatric population)

Abbreviations: ASMD, acid sphingomyelinase deficiency; RCT, randomised controlled trial

Key clinical trials: designs and outcomes

Key: Ongoing | Completed

EAG: stringent in/exclusion criteria may have excluded patients with higher disease severity

	ASCEND	ASCEND-Peds	DFI13412	LTS13632
1° outcome	• % predicted Hb and Altitude-Adjusted DLco • spleen volume and SRS	• safety • physical & neurological examination • abnormalities in ECG, vital signs & liver ultrasound	AEs	• Safety; DLCo • spleen & liver volume • neurological and physical observations; Immune response
Key 2° outcome	liver volume, platelet count, pain severity*, dyspnea severity†	PK, % Δ in DLco, spleen & liver volume, neurological and physical observations and imaging, pediatric physical outcomes, HRQoL	PK	Spleen & liver volume, lung function, hematology and lipids, HRQoL, growth‡, bone age & maturation‡
Inclusion criteria	DLco ≤70% of predicted normal; Spleen volume ≥6 x normal; SRS ≥5; Platelet count ≥ 60 x 103 /μL; INR ≤ 1.5	No acute/ rapidly progressive neurological abnormalities; Spleen volume ≥5 x normal; Platelet count ≥ 60 x 103 /μL; INR ≤1.5; Height of ≤-1 z score; ALT or AST ≤250 IU/L or total bilirubin ≤1.5 mg/dL	non-neuronopathic ASMD; DLco >20% & ≤80% of predicted normal value; Spleen volume ≥6 x normal; stable on lipid-lowering therapy; ALT or AST ≤250 IU/L or total bilirubin ≤1.5 mg/dL	Completed ASCEND-Peds or DFI13412 treatment with acceptable safety profile
Exclusion criteria	Requires ventilation; prior transplant; surgery scheduled during trial; requires medications that decrease olipudase alfa activity; unwilling to abstain from alcohol around treatment administration			

- As measured by Brief Pain Inventory-Short Form (BPI-SF)-Item 3 Scale Score, † As Measured by Functional Assessment of Chronic Illness Therapy (FACIT) Dyspnea Scale, ‡children only DLco, Diffusing Capacity of the Lung for Carbon Monoxide; SRS, Splenomegaly-Related Score

Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; DLco, diffusing capacity of lungs for carbon monoxide; HRQoL, health-related quality of life *for full list of abbreviations please see company submission

Key clinical trial baseline characteristics

	ASCEND Olipudase alfa N=18	ASCEND Placebo N=18	ASCEND-Peds N=20	DFI13412 N=5
Age, mean years (SD), range	36.2 (12.7), 18.8 – 59.9	33.5 (17.1), 18.6 – 65.9	8.2 (4.4), 1.5 – 17.5	32.6 (9.4), 23 - 48
Weight (kg), mean (SD)	67.4 (14.1)	61.6 (13.4)	23.4 (10.8)	[redacted]
Female, n (%)	9 (50%)	13 (72%)	10 (50%)	2 (40.0%)
Race, n (%)				
White	16 (89%)	16 (89%)	17 (85%)	5 (100%)
Asian	1 (6%)	1 (6%)	2 (10%)	0 (0%)
Other	1 (6%)	1 (6%)	1 (5%)	0 (0%)

Baseline characteristics for LTS13631 as per ASCEND-Peds (children, N=20) and DFI13412 (adults, N=5) except mean age at baseline: [redacted] for children, [redacted] for adults. Source: EAR, table 14

EAG: baseline weight lower than expected in UK. Expert advice: some people may be smaller with ASMD but unlikely to see difference across population.

Key clinical trial baseline characteristics

	ASCEND		ASCEND-Peds	DFI13412
	Olipudase alfa N=18	Placebo N=18	N=20	N=5
Age at diagnosis, mean years (SD), range	21.4 (20.3), [redacted]	14.6 (16.1), [redacted]	2.5 (2.5), [redacted]	7.2 (5.0), [redacted]
Severe splenomegaly (>15 MN), n (%)	5 (27.8%)	3 (16.7%)	12 (60%)	[redacted]
Severely reduced DLco (<40%), n (%)	3 (16.7%)	4 (22.2%)	1 (11.1%)	[redacted]

Baseline characteristics for LTS13631 (OLE) as per ASCEND-Peds (children, N=20) and DFI13412 (adults, N=5). Source: EAR, table 14

EAG comment

Age at diagnosis higher in ASCEND than DFI13412. Expert advice: lower age of diagnosis likely in future: improved understanding of condition and sibling testing

More severe splenomegaly at baseline in olipudase alfa arm but small numbers of people

Does the committee consider the population in trials represent those seen in the UK in terms of ASMD type, severity, and baseline characteristics including age and weight?

Abbreviations: Dlco, diffusing capacity of the lungs for carbon monoxide; MN, multiples of normal; SD, standard deviation

EAG comments

Population with more severe disease may have been excluded because of trials' in/exclusion criteria

Population
Disease severity: Clinical trials may have excluded people with mild and higher severity • People excluded may be more likely to experience adverse events and have differential treatment effect, although ASCEND subgroup analyses did not find differences by severity • Unclear subtype proportions (A/B or B)
Subgroups • no universally accepted measure of severity; • Outcomes for those with severe DLco and spleen volume at baseline limited because of small numbers in ASCEND considered to have severe symptoms (DLco: 3 participants in olipudase alfa and 4 in placebo arms; spleen volume: 5 in olipudase alfa arm and 3 in placebo arm)

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity of lungs for carbon monoxide

Results, secondary outcome: % change in Liver volume

- Participants having olipudase alfa showed mean reduction in liver volume in all trials
- Mean reductions >20% following 6-months treatment
- No change seen in placebo

No responder analyses done: unclear how many people had clinically meaningful response

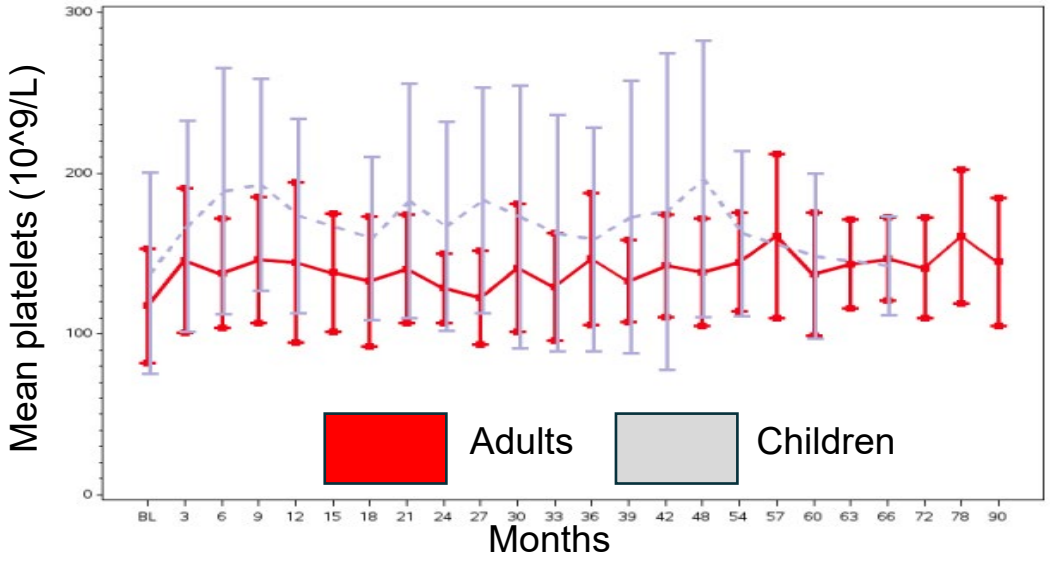
Results: Other efficacy outcomes

Improvement largely seen in other efficacy outcomes

Platelet counts

- Mean counts increased in adults receiving olipudase alfa, no change for placebo (ASCEND)

Platelet counts in LTS13632



- No data for children in ASCEND-Peds, but increase shown in LTS13632 (N=5)
- Figure shows adult counts remained fairly stable whereas counts in children had high variance and appears to reduce back towards baseline after 4 years
- EAG hesitant to conclude effect of olipudase alfa in children reduces after 4 years due to small sample size and stability seen in adults. Further data needed

Additional outcomes: improved liver function (ALT and AST), reduced cholesterol and triglyceride, and improved pulmonary function (forced vital capacity and O^2 uptake during exercise) in those having olipudase alfa in ASCEND. These outcomes also improved in ASCEND-Peds but no comparator arm. No deaths occurred in any of the trials.

- **EAG**: unclear if change in children clinically meaningful, expert advice to the EAG was effect may lead to overall improved QoL and functioning, which would have benefits for children's school life and wellbeing.

Abbreviations: ALT, Alanine aminotransferase; AST, andaspartate aminotransferase; QoL, quality of life

Adverse events

EAG: treatment related adverse event more common in olipudase alfa arm but appeared acceptable

	ASCEND N (%)		ASCEND-Peds N (%)
	Placebo (N=18)	Olipudase (N=18)	Olipudase alfa (N=20)
Pyrexia	--	--	15 (75%)
Contusion	--	--	6 (30%)
Infections and infestations	15 (83%)	15 (83%)	--
Nasopharyngitis	6 (33%)	8 (44%)	11 (55%)
Upper RTI	4 (22%)	6 (33%)	8 (40%)
Nervous system disorders	9 (50%)	13 (72%)	--
Headache	8 (44%)	12 (67%)	8 (40%)
Musculoskeletal & connective tissue	11 (61%)	12 (67%)	--
Respiratory, thoracic, mediastinal	5 (28%)	9 (50%)	--
Cough	2 (11%)	5 (28%)	14 (70%)
Nasal congestion	--	--	6 (30%)
Rash	--	--	3 (30%)
Vomiting	--	--	12 (60%)
Diarrhea	--	--	11 (55%)
Stomach pain	--	--	6 (30%)

Key issues, clinical

Population representativeness:

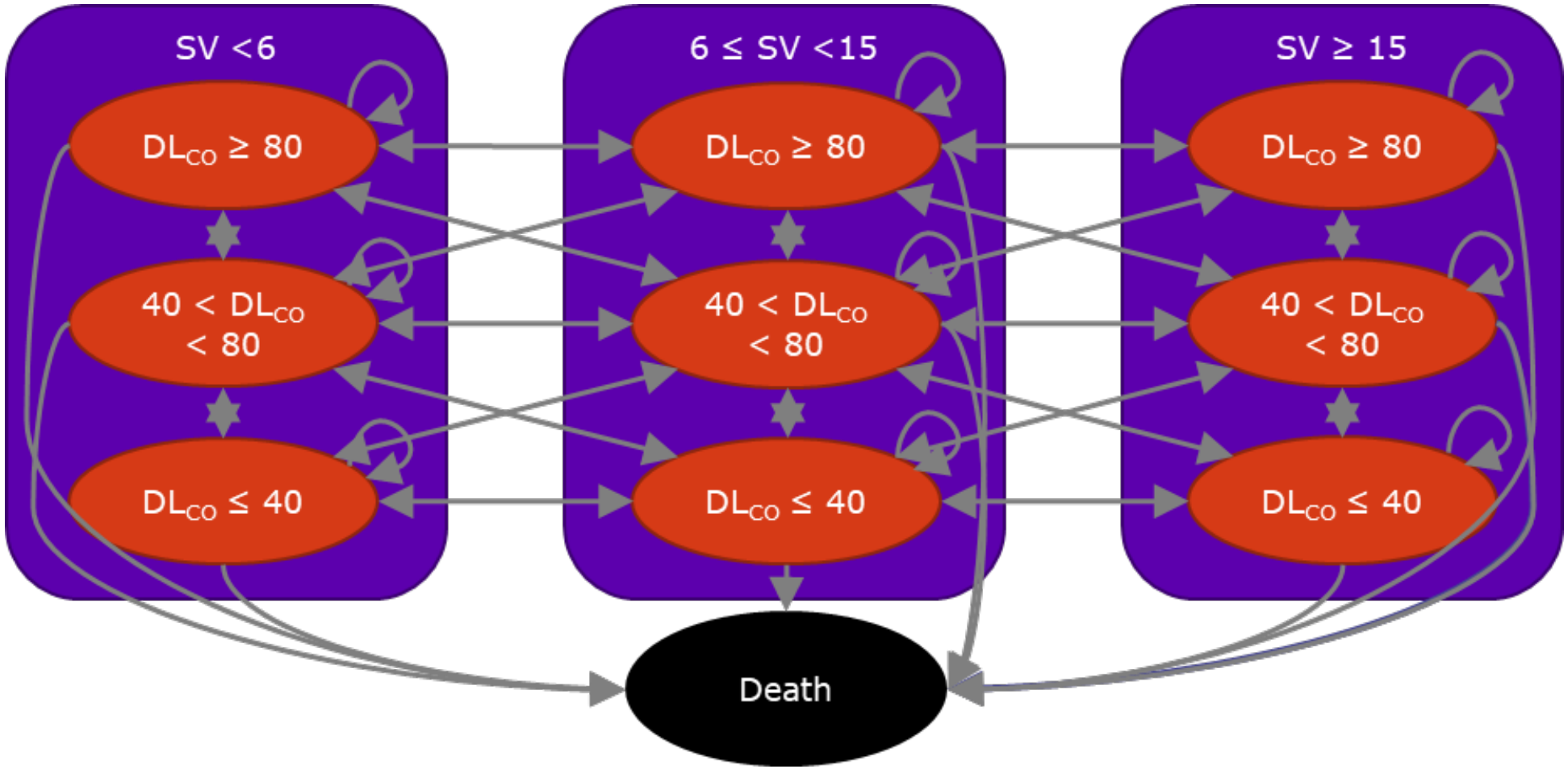
- Does the committee consider that the population in trials represent those seen in the UK in terms of ASMD type, severity, and baseline characteristics including age and weight?

Long term treatment effect:

- What is the committee's view of olipusedase alfa's treatment effect on clinical outcomes in the long term?
- What is the committee's view of olipudase alfa's treatment effect on QoL for people with type B or A/B? Does it agree that improvement in clinical outcomes may lead to improvement in children QoL and functioning?

Company's model overview

Cohort Markov model: 9 health states defined by levels of spleen volume (SV) and DL_{CO}



Disutilities by damage of:

- Liver
- Spleen
- Respiratory
- Cardiovascular
- Major bleeding

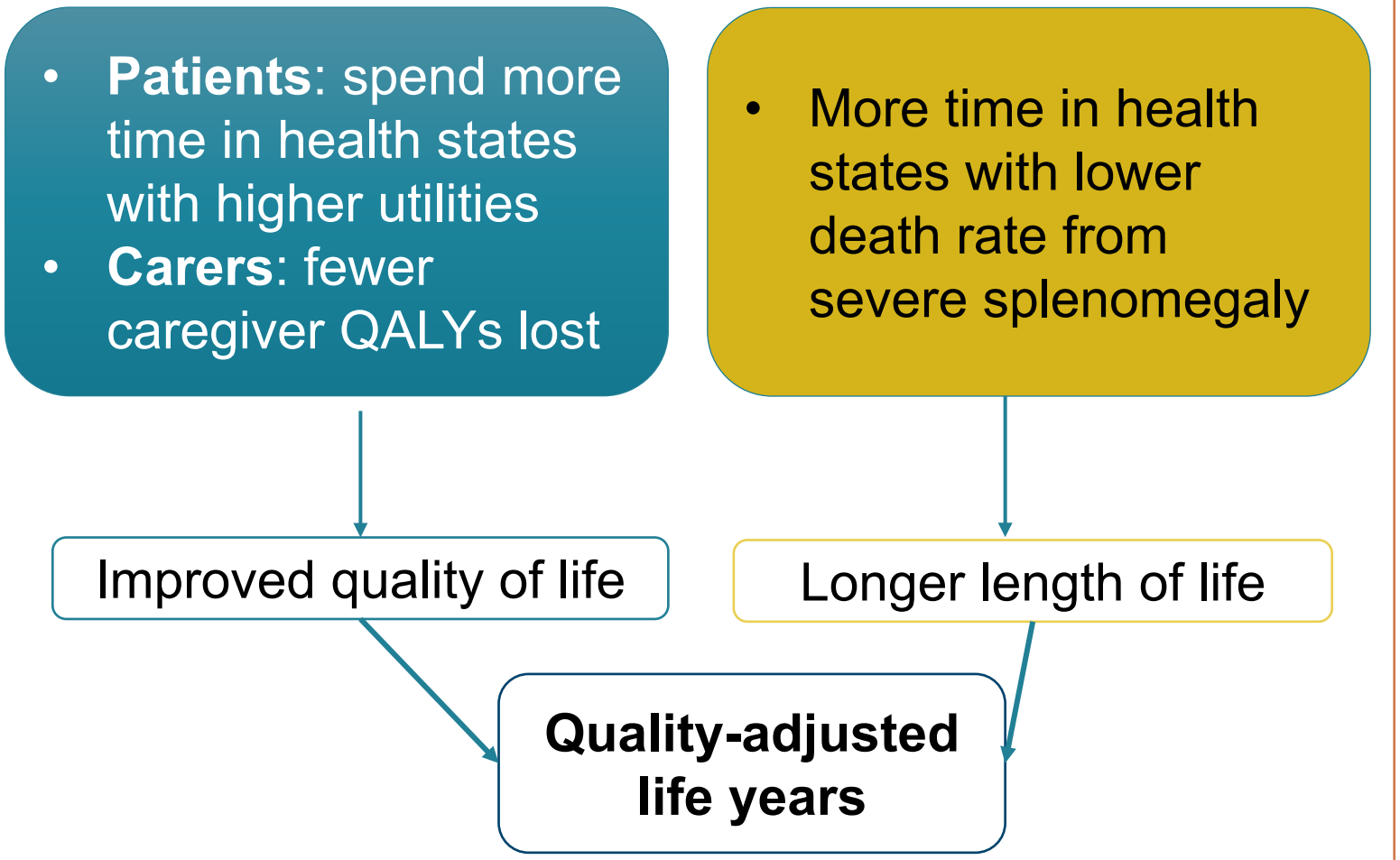
Utility decrement for caregivers determined by treatment

EAG: Company's approach likely appropriate, but lack of consensus on important outcomes amongst clinicians (liver function may also be important indicator of health)

Note. Decreased DLco and reduced spleen volume (SV) denote an improvement
Abbreviations: DLco, diffusing capacity of the lungs for carbon monoxide

Overview: how quality-adjusted life years (QALYs) accrue for olipudase alfa versus best supportive care

In the olipudase alfa arm (vs. BSC):



Technology affects costs by:

- ↑ treatment related costs
- ↓ clinical manifestations of disease and associated costs

Assumptions with greatest ICER effect in company's model:

- patient weight
- drug unit costs
- Compliance rate
- starting age
- Alternative discount rates
- Long-term treatment effect
- Carer disutility assumptions

Abbreviations: BSC, best supportive care; QALY, quality adjusted life years

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Derived from ASCEND and ASCEND -Peds
Age and weight	**Paediatric:** ASCEND-Peds (weight changes over time, rate of change informed by SPHINGO-100); **Adults**: ASCEND (weight does not change over time)
Intervention/comparator	**Olipudase alfa:** 0.3mg/kg every 2 weeks after dose escalation; **BSC**: routine care
Treatment effect	Olipudase alfa and BSC transition probabilities informed by: • ASCEND and ASCEND-Peds; DF131412; LTS13632 • SPHINGO-100; • Sanofi chart review;
Long term treatment effect extrapolation	**Olipudase alfa**: all patients transition to least severe health state from year-10 and stay there until death **BSC**: transition in every cycle
Mortality	Informed by *Sanofi Chart Review pooled data analysis* Additional scenario analysis for severe subgroup using McGovern 2013 study
Utilities	**Patient**: vignette study based on general population; **Carer:** utility decrement treatment-dependent**,** sourced from Pompe disease
Costs and resource use	**Olipudase alfa**: administration costs of infusion; adverse events related costs; costs varied by health-state; **BSC**: no treatment costs;
Cycle length	6-month for first year then 12-month afterwards, reflecting UK monitoring practice
Time horizon	100 years
Discounting	1.5% for costs and benefits

Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; DLco, diffusing capacity of lungs for carbon monoxide

Modelling mortality:

Company and EAG had different approaches to modelling mortality

Background

- **Company original base-case:** based on SPHINGO-100 study conducted in North America | N=58 patients with ASMD type B, only 8 deaths over 11-year period | Modelled mortality by standard mortality ratio (SMR) applying 10x increased risk with severe splenomegaly versus without; SMR then applied to mortality rates of general UK population as multiplier in model;
- Company: clinical advice suggested paediatric patients with ASMD type B die sooner than general population, incidence likely underreported as transition to adult services at 16 years;

EAG:

- Splenomegaly as key determinant/proxy of mortality appeared to be reasonable;
- Concerns about company's assumption on paediatric death from ASMD;
- Small sample size of SPHINGO-100 may lead to unreliable risk estimate;
- Conducted 2 scenario analyses:
  - reducing SMR for severe splenomegaly by 50%;
  - Based on clinical opinion, removed disease-related mortality in paediatric patients (EAG's based case)

Clinical expert: ASMD causes death in children and adults, as reported by Cassiman et al. 2016

Abbreviations: ASMD, acid sphingomyelinase deficiency; SMR, standardised mortality rate

Key issue: Discounting rates 1.5% vs 3.5% (1)

Company presents case for discounting rate of 1.5%: EAG preferred 3.5% for both;

Background: company makes case for 1.5% discount (applied to both costs and benefits) post TE; also provided sensitivity analysis using differential discount rate (3.5% costs and 1.5% benefits);

NICE 2022 Methods: non-reference-case discount rate of 1.5% may be considered, if
1) Technology is for people who would otherwise die or have a very severely impaired quality of life
2) It is likely restore them to full or near-full health
3) Benefits likely sustained over very long period of time

Clinical expert: ASMD causes severe impairment. Olipudase alfa is transformative, capable of reversing effects of ASMD, continues into long-term

EAG: Criteria not met; increased mortality risk for ASMD but uncertainty as to extent of risk or how this differs between type A/B and B;
Prefer 3.5% discount rate for both

Abbreviations: ASMD, acid sphingomyelinase deficiency; TE, technical engagement

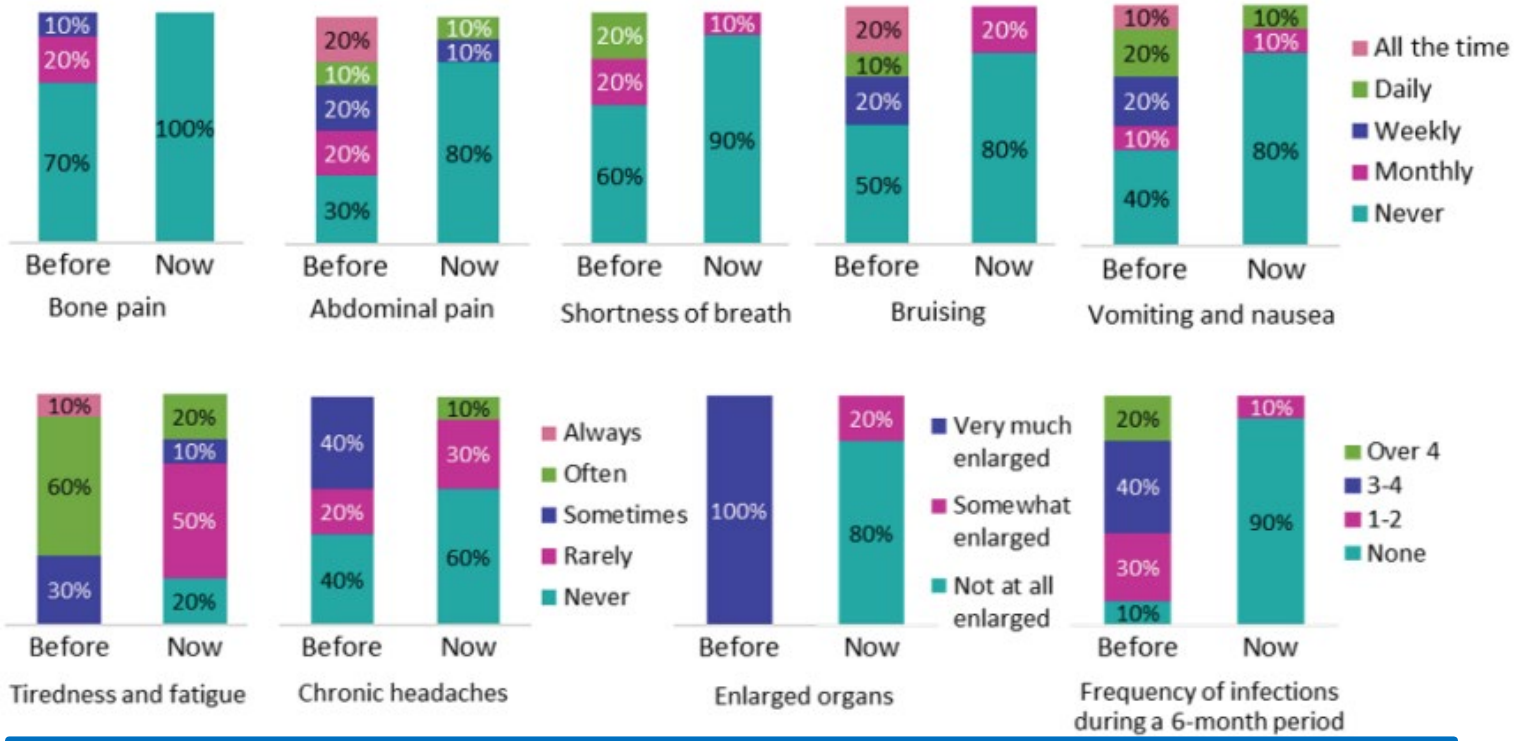
Key issue: Discounting rates 1.5% vs 3.5% (2)

EAG: olipudase alfa associated with improved clinical outcomes, but uncertain whether improvements could be considered the equivalent of returning people to full of near-full health.

Company: Presents online survey and semi-structured interviews of 10 paediatric patients or their caregivers before and after treatment with olipudase alfa

- Believe this plus evidence from clinical trials shows olipudase meets this criteria

Results of survey of 10 paediatric patients or carer



EAG: lack of robust evidence:

- Clinical evidence shows organs still enlarged, mean DLco at 52 weeks ~60% of predicted (severe end of threshold for mildly reduced respiratory function)
- Clinical advice suggests variable nature of disease means magnitude of benefits will differ
- Survey shows important improvement small sample with unclear recruitment methodology

Olipudase improved all non-neurological manifestations

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity of lungs for carbon monoxide

Key issue: Discounting rates 1.5% vs. 3.5% (3)

EAG: Lack of evidence on benefits sustained over long time

Company:

- Extension study provided follow-up data up to 6.5 years for adults and 4 years for children
- Evidence in Gaucher disease of effect of enzyme replacement therapy (ERT) maintaining up to 20 years after initiation of treatment.
- Clinical opinion provided to company and EAG states there is nothing that suggests loss of long-term efficacy

EAG comments

- Acknowledge there is evidence to support maintained effect of ERTs in Gaucher disease, but unclear if this is generalisable to olipudase alfa for the treatment of ASMD
- Relatively short-term trial data available within the ASCEND and ASCEND-Peds compared to length of the extrapolation period in economic model

Clinical experts: spectrum across ASMD respond to olipudase alfa, but advanced disease characterised by fibrosis (liver, pulmonary) not amenable to treatment.

Does the committee consider the criteria for non-reference-case of 1.5% discount rate met?

Abbreviations: ASMD, acid sphingomyelinase deficiency

Utilities (for person with ASMD)

Company: estimated utilities based on vignette study interviewing general population, [redacted] method used to elicit health state utilities

Patient utilities for each health-state

Health state	Adults	Children
ASMD without impairment	[redacted]	[redacted]
ASMD with mild/moderate impairment in DL_{CO}	[redacted]	[redacted]
ASMD with mild/moderate spleen and liver volume increase	[redacted]	[redacted]
Mild/moderate ASMD	[redacted]	[redacted]
ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]
ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]	[redacted]
ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]
ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]	[redacted]
A9: Severe ASMD	[redacted]	[redacted]

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity of lungs for carbon monoxide

Key issue: Carer disutilities (1)

EAG: uncertainties surrounding company's several assumptions on carer's disutilities

Overview: Company and EAG differ in 5 key areas, key drivers of cost-effectiveness.
Limited published evidence on ASMD carer disutility so EAG prefer more conservative assumptions

Company and EAG base-case assumptions

Company base-case	EAG preferred assumption	Company after technical engagement	EAG after technical engagement
No carer disutility for olipudase arm	Carer disutility applied to health states	Unchanged	Unchanged
Same carer's disutility value for all health states; value (-0.15); sourced from Pompe disease	Uncertain, but caution using Pompe; greater disutility in poorer health states	Unchanged; provide scenario analysis in which carer disutility differs by health-states	Unchanged
Average 1.78 carers for children, 1 for adults	1 carer for both	2.6 carers for children (to account for siblings)	Unchanged
Carer disutility (-0.5) throughout modelled time horizon if patient dies	No carer's disutility associated with patient death	Unchanged	Unchanged

Key issue: Carer disutilities (1)

EAG: applying carer disutility to BSC arm only lacks plausibility

Background Company assume no carer disutility for olipudase alfa arm whereas EAG prefer it applied according to patient health-state, irrespective of treatment

Patient expert

QoL of child increased considerably after starting olipudase alfa, regaining ability to complete many everyday life functions. Large impact on carer QoL but expects improvement in following areas if response to treatment continues

- More freedom/independence as caring requirements reduced
- Reduced stress/anxiety associated with health of child; return to a career and feel able to attend to own goals
- Social relationships decreased dramatically due to caring responsibility, feel as though they will be able to return to these , and be in better sprits around friends

EAG: carers for patients with severe health state would have reduced quality of life regardless of treatment; carer's disutility applied to health states in its preferred base case,

Does the committee consider carer's disutility should apply to BSC arm only or to health states regardless of treatment?

Abbreviations: BSC, best supportive care; QoL, quality of life

Key issue: carer's disutilities (2)

Company: sourced carer's disutility values (-0.15) from Pompe disease given limited ASMD evidence; **EAG**: preferred differential disutilities for carers

EAG:

- clinical expert advice suggests Pompe disease would have greater carer burden than ASMD; instead sourced from a variety of diseases including MS and meningitis;
- Carer disutility differs between severe vs non severe and whether patient is an adult

EAG carer utility values

Population	Non-severe	Severe (SV ≥ 15MN)
Paediatrics	-0.023 (meningitis and mild/moderate learning disability)	-0.080 (children with activity limitation)
Adults	-0.010 (overall utility from review of chronic diseases)	-0.045 (stage 2, symptomatic MS)

Patient expert:
Pompe disease different but disagree that it would have larger burden

Does the committee consider the company's or the EAG's approach appropriate to modelling carer's disutilities?

Abbreviations: MS, multiple sclerosis

Key issue: Modelling patient weight

EAG and company have different preference for modelling weight

Baseline age and weight (company base-case)

	Paediatrics (ASCEND-PEDS)	Adults (ASCEND)
Age	8 years	34 years
Weight	20.53 kg	64.52 kg

Background: Adult weight is constant over time whereas child weight changes according to z-score function estimated from SPHINGO-100 and applied to UK growth chart weights

EAG

- **Children**: UK growth charts weight low compared with 2019 Health Survey for England report
- **Adult**: weights low compared with UK average, which is likely more generalisable
- **EAG base-case used UK average weight, changing over time** (according to pattern seen by 18-year olds, as estimated by company)
- EAG expert advice: Start age in model unclear as age of diagnosis very varied. Some children will have lower weight than UK average (unclear if same is true for adults);
- Using 2019 England Health Survey not a key driver of ICER

Company following TE

- People with ASMD lighter than general population, as shown in trial data, expert interviews and data from other studies in ASMD; UK mean not representative of ASMD patients;

Patient expert: Agree normal for weight and height to be lower than peers but growth can catch up

Clinical expert: Adults seem to have similar weight distribution to UK average

Which method of modelling patient weight does the committee prefer?

Key issue: Subgroup analysis in people with severe disease

Company: acknowledge limitations in subgroup analysis, provided for illustrative purpose; issue likely unresolvable, cost-effectiveness in severe disease uncertain

Background

- Company provided subgroup analysis in people with severe disease, where all patients started in most severe health-state (SV≥15 MN and DLco<40%, stating age of children now 2-years)
- Mortality rates informed by McGovern 2013 natural history study in 42 adults and 61 children

EAG

- Transitions from most severe health-state based on overall trial populations data rather than specific clinical evidence → Expert advice suggests this may not be appropriate
- Concerns with mortality estimates, lack of transparency in approach (no rationale for choice of distribution, tests for goodness of fit not presented) – Caution when interpreting results

Company following TE

- Limitations due to small ASCEND sample size but analysis is likely conservative as it uses transition probabilities from the broad patient population

Clinical expert

- Inclusion criteria (for paediatric and adult trials) excluded the most ill patients but compassionate use of olipudase in people with more severe disease suggests even greater response to treatment

Abbreviations: DLco, diffusing capacity of lungs for carbon monoxide; MN, multiples of normal; SV, spleen volume

Company base case and EAG's exploratory analysis

Model feature	Company final base-case after correction	EAG's scenarios	Impact on ICER
Discount rate	1.5% (costs and benefits)	3.5%*	ICER Highly sensitive to change
Long term treatment effect	9 years to reach "normalised" health state then stay there until death from year 10 onwards	3 scenarios: • 1) Treatment effect frozen from year 3* • 2) treatment effect continues for olipudase alfa from year 3 • 3) treatment effect waning: olipudase alfa follows BSC transitions from year 2	ICER highly sensitive to change
Mortality	based on pooled chart review	Original method before TE: By having severe splenomegaly or not (SMR: 43.1 vs 4.3)	-
• SMR based on severe splenomegaly	• N/A	• SMR for severe splenomegaly reduced by 50% (to 21.5)	Minor impact
• Paediatric mortality	• Disease-related mortality for paediatric patients included	• Removed disease related mortality in paediatric, only background mortality included*	Minor impact

* EAG's preferred scenario and included in its base case

What are committee's preferred assumptions?

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; SMR, standardized mortality rate; TE, technical engagement

Company base case and EAG's exploratory analysis

Model feature	Company final base-case after correction	EAG's scenario(s)	Impact on ICER
Weight (paediatric)	• Weight changes over time (z-score applied to UK growth charts)	Higher weight data from general population norms (Health survey for England)	Moderate, increase ICER
Weight (adults)	Based on ASCEND mean, 64.5 kg, remains constant	2 scenario analyses: • 1) UK mean weight (gender split based on ASCEND), 77.3 kg • 2) Z-score for 18-year olds applied to UK mean, 68.5 kg*	Moderate, increase ICER
Carer disutility			
• Disutility for both arms?	BSC arm only	Disutility for health state irrespective of treatment*	Large, increase ICER
• Disutility varies by patient health state?	Same carer's disutility value (-0.15, as in Pompe disease) for all health states	Yes, but values from various diseases and differ by severe disease (vs non-severe) and adult (vs paediatric) *	Moderate/large, increase ICER
• No. carers	2.6	1*	Minor, increase ICER
• Carer disutility for patient death	-0.5 across remaining time horizon	No disutility/Removed*	Large, increase ICER

* EAG's preferred scenario and included in its base case. Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio

What are committee's preferred assumptions?

Company base case and EAG's exploratory analysis

Model feature	Company final base-case after correction	EAG's scenarios	Impact on ICER
Compliance rate	• 90% based on trials	• 100%	ICER increased by about 10%
Age starting treatment	• 8 year	• 2 year for paediatric patients; and • 28 years for adults	Minor, ICER reduced
Liver complication rates	Based on SPHINGO-302, lower probability in olipidase arm (0.3% vs. 3.4%)	3.4% probability for both arms	Minor

* EAG's preferred scenario and included in its base case. Abbreviations: ICER, incremental cost-effectiveness ratio

What are committee's preferred assumptions?

NICE National Institute for Health and Care Excellence

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and A/B) [ID 3913]

Highly Specialized Technology Appraisal Committee

[05 October 2023]

Part 2 slides

Key issues, clinical

Population representativeness:

- Does the committee consider that the population in trials represent those seen in the UK in terms of ASMD type, severity, and baseline characteristics including age and weight?

Long term treatment effect:

- What is the committee's view of olipusedase alfa's treatment effect on clinical outcomes in the long term?
- What is the committee's view of olipudase alfa's treatment effect on QoL for people with type B or A/B? Does it agree that improvement in clinical outcomes may lead to improvement in children's QoL and functioning?

Key issues: economic

Discount rate: does the committee consider the criteria for non-reference-case of 1.5% discount rate met?

Long-term treatment effect: which assumption on the long term treatment effect of olipudase alfa does the committee consider more appropriate?

Mortality: which approach is best for modelling mortality? Does the committee consider there is disease-specific mortality in paediatric patients with ASMD?

Carer's disutilities:

- apply to BSC arm only or to health states regardless of treatment?
- -0.15 for carer's disutility or, differential disutilities for carers by severity of health states and adult/children?
- 2.6 or 1 on average per child?
- -0.5 carer's disulitieis associated with patient death and for the remaining time horizon of model or not?

Weight: which method, company vs. EAG's, of modelling patient weight does the committee prefer?

QALY weighting: Does QALY weighting apply?

Others:

- Are there any equality issues that require additional consideration? If so, what are they?
- Are there any benefits not fully captured by the model?

3

Company and EAG base case assumptions

Assumptions in company and EAG base case

Model feature	Company final base-case	EAG final base-case
Discount rate	1.5% (costs and benefits)	3.5% (costs and benefits)
Long-term treatment effect	Least severe health-state from year 10	Treatment effect frozen from year 3
Carer disutility		
• Disutility for both arms?	BSC arm only	Both arms
• Disutility based on health-state	- 0.15, based on Pompe disease	Yes based on various diseases
• Number of carers	2.6	1
• If patient dies	-0.50	No disutility
Mortality & Disease-related mortality for paediatric	Based on chart review pooled data analysis; disease-related paediatric death included	Based on company's original approach; excluded disease-related paediatric death
Weight (paediatric)?	z-score applied to UK growth charts	Weight becomes UK mean from adulthood
Weight (adults)	Based on ASCEND mean, remains constant	z-score for 18-year olds applied to UK mean

EAG: company's revised base case not appropriate for decision making given uncertainties and assumptions deemed inappropriate by EAG

Company base case and EAG's exploratory analysis

Model feature	Company final base-case after correction	EAG's scenarios	Impact on ICER
Discount rate	1.5% (costs and benefits)	3.5%*	ICER Highly sensitive to change
Long term treatment effect	9 years to reach "normalised" health state then stay there until death from year 10 onwards	3 scenarios: • 1) Treatment effect frozen from year 3* • 2) treatment effect continues for olipudase alfa from year 3 • 3) treatment effect waning: olipudase alfa follows BSC transitions from year 2	ICER highly sensitive to change
Mortality	based on pooled chart review	Original method before TE: By having severe splenomegaly or not (SMR: 43.1 vs 4.3)	-
• SMR based on severe splenomegaly	• N/A	• SMR for severe splenomegaly reduced by 50% (to 21.5)	Minor impact
• Paediatric mortality	• Disease-related mortality for paediatric patients included	• Removed disease related mortality in paediatric, only background mortality included*	Minor impact

* EAG's preferred scenario and included in its base case

NICE

What are committee's preferred assumptions?

Company base case and EAG's exploratory analysis

Model feature	Company final base-case after correction	EAG's scenario(s)	Impact on ICER
Weight (paediatric)	• Weight changes over time (z-score applied to UK growth charts)	Higher weight data from general population norms (Health survey for England)	Moderate, increase ICER
Weight (adults)	Based on ASCEND mean, 64.5 kg, remains constant	2 scenario analyses: • 1) UK mean weight (gender split based on ASCEND), 77.3 kg • 2) Z-score for 18-year olds applied to UK mean, 68.5 kg*	Moderate, increase ICER
Carer disutility			
• Disutility for both arms?	BSC arm only	Disutility for health state irrespective of treatment*	Large, increase ICER
• Disutility varies by patient health state?	Same carer's disutility value (-0.15, as in Pompe disease) for all health states	Yes, but values from various diseases and differ by severe disease (vs non-severe) and adult (vs paediatric) *	Moderate/large, increase ICER
• No. carers	2.6	1*	Minor, increase ICER
• Carer disutility for patient death	-0.5 across remaining time horizon	No disutility/Removed*	Large, increase ICER

* EAG's preferred scenario and included in its base case

NICE

What are committee's preferred assumptions?

Company base case and EAG's exploratory analysis

Model feature	Company final base-case after correction	EAG's scenarios	Impact on ICER
Compliance rate	• 90% based on trials	• 100%	ICER increased by about 10%
Age starting treatment	• 8 year	• 2 year for paediatric patients; and • 28 years for adults	Minor, ICER reduced
Liver complication rates	Based on SPHINGO-302, lower probability in olipidase arm (0.3% vs. 3.4%)	3.4% probability for both arms	Minor

What are committee's preferred assumptions?

QALY weighting

EAG: does not consider appropriate to apply QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Life incremental QALY gained	Weight
Less than or equal to 10	1
11 to 29	Between 1 to 3 (equal increments)
Greater than or equal to 30	3

EAG: may not be appropriate to apply QALY weight, because;

- Lack of robust clinical data informing company's economic model given rarity of condition;
- High degree of uncertainty in company's assumptions;
- Results sensitive to assumptions on long term treatment effect, carer's disutilities, patient weight and discount rate;

Company base-case

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Treatment	Total costs (£))	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental QALYs undiscounted	ICER (£/QALY)
Original base-case corrected by EAG (deterministic: compared with BSC)							
Paediatric	[redacted]	26.43	[redacted]	26.05	[redacted]	42.68	[redacted]
Adults	[redacted]	8.91	[redacted]	17.59	[redacted]	24.03	[redacted]
Original base-case corrected by EAG (probabilistic: compared with BSC)							
Paediatric	[redacted]	26.24	[redacted]	25.06	[redacted]	40.69	[redacted]
Adult	[redacted]	8.76	[redacted]	16.32	[redacted]	22.21	[redacted]
Company updated base-case post TE (deterministic: compared with BSC)							
Paediatric	-		[redacted]	37.38	[redacted]	112.13	[redacted]
Adult	-		[redacted]	20.62	[redacted]	61.85	[redacted]

EAG base-case

EAG: does not consider QALY weighting appropriate, but provided undiscounted QALYs in appendix for consideration.

Treatment	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental QALYs undiscounted	ICER (£/QALY)
EAG base case (deterministic: compared with BSC)					
Paediatric	[redacted]	7.57	[redacted]	21.78	[redacted]
Adults	[redacted]	5.30	[redacted]	10.44	[redacted]
EAG base case (probabilistic: compared with BSC)					
Paediatric	[redacted]	7.29	[redacted]	20.83	[redacted]
Adult	[redacted]	4.83	[redacted]	9.24	[redacted]

EAG' preferred assumptions in its base case: Paediatric population

Deterministic exploratory analyses

Treatment	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Undiscounted Inc. QALYs	ICER
Company original base-case (EAG corrected)	[redacted]	26.05	[redacted]	42.68	[redacted]
EAG preferred assumptions					
3.5% discounting (costs + benefits)	[redacted]	15.36	[redacted]	N/A	N/A
No carer disutility for patient death	[redacted]	21.62	[redacted]	33.85	[redacted]
No health transitions after 2 years	[redacted]	22.57	[redacted]	37.21	[redacted]
carer disutility for both arms	[redacted]	19.22	[redacted]	32.77	[redacted]
higher carer disutility for more severe patient health-states	[redacted]	21.94	[redacted]	37.12	[redacted]
1 carer in each health-state	[redacted]	25.00	[redacted]	41.55	[redacted]
No child disease-related mortality	[redacted]	25.86	[redacted]	42.45	[redacted]
Weight on adulthood based on UK mean weight 2019	[redacted]	26.05	[redacted]	42.68	[redacted]

EAG preferred assumptions in its base case: Adult population

Deterministic exploratory analyses

Treatment	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Undiscounted Inc. QALYs	ICER
Company original base-case (EAG corrected)	[redacted]	17.59	[redacted]	40.69	[redacted]
EAG preferred assumptions					
3.5% discounting (costs + benefits)	[redacted]	12.25	[redacted]	N/A	N/A
No carer disutility for patient death	[redacted]	13.88	[redacted]	18.50	[redacted]
No health transitions after 2 years	[redacted]	13.99	[redacted]	19.25	[redacted]
carer disutility for both arms	[redacted]	13.67	[redacted]	18.92	[redacted]
higher carer disutility for more severe patient health-states	[redacted]	15.18	[redacted]	21.05	[redacted]
UK mean weight (z-score for 18-year olds applied)	[redacted]	17.59	[redacted]	24.03	[redacted]

EAG exploratory analyses

Deterministic exploratory analyses

Treatment	Paediatric population			Adult population		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company original base-case (EAG corrected)	[redacted]	26.05	[redacted]	[redacted]	17.59	[redacted]
Olipudase transition probabilities replay from year 3	[redacted]	23.71	[redacted]	[redacted]	14.63	[redacted]
Olipudase follows BSC transition probabilities from year 3	[redacted]	12.11	[redacted]	[redacted]	10.37	[redacted]
SMR for severe splenomegaly reduced by half (21.5)	[redacted]	23.87	[redacted]	[redacted]	16.04	[redacted]
UK mean weight (male/female split based on ASCEND, no z-score)	N/A	N/A	N/A	[redacted]	17.59	[redacted]

EAG exploratory analyses

Deterministic exploratory analyses

Treatment	Paediatric population			Adult population		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company original base-case (EAG corrected)	[redacted]	26.05	[redacted]	[redacted]	17.59	[redacted]
Compliance rate 100% (up from 90%)	[redacted]	26.05	[redacted]	[redacted]	17.59	[redacted]
Starting age down to 2 years (paediatric) or 28 years (adult)	[redacted]	26.40	[redacted]	[redacted]	19.50	[redacted]
Olipudase alfa same rates of liver complications as BSC (up from 0.3% ,to 3.4%)	[redacted]	25.87	[redacted]	[redacted]	17.49	[redacted]

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Managed access

Considerations: how much uncertainties can be resolved by ongoing studies, and would further qualitative data for carer's disutilities useful for decision making

Company: Studies either ongoing or planned to address uncertainties in evidence

- **For long term treatment effect and understanding of ASMD patients in the UK, ongoing studies:**
  - ❑ Long-term extension study KTS13632 (n=25), up to 9-year follow up;
  - ❑ ASCEND (n=36), extension treatment period, open-label up to 4-year;
  - ❑ International Niemann-Pick Disease registry (INPDR);
- **For carer's QoL and burden of the illness, planned studies include:**
  - ❑ Qualitative interviews of ASMD caregivers;
  - ❑ A-third part study jointly sponsored by ASMD registries in different countries including the US and UK;

Managed access team: potential candidate for MAA but uncertainties remain

- **Long term treatment effect and weight**:
  - ❑ 5-year time frame for MAA, both extension studies finishing in Q2 2024, may be not long enough to resolve all uncertainties relating to long-term treatment effect or weight;
- **Carer's QoL**:
  - ❑ qualitative data to be collected but value of resolving uncertainties (number of carers, carer's disulities, carer's disutilites relating to patient death) in model unclear; may be subject to small sample size;
- **Disease specific mortality in paediatric patients**:
  - ❑ data may be available from INPDR during appraisal, could be retrieved outside of managed access;

Other considerations

Managed Access

Is the technology considered a potential candidate for managed access?	Yes	Treatment is a candidate for the IMF. Currently no treatments for this indication and it can provide large QALY gains for children and adults.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Uncertainties could be resolved with further data from ongoing trials but some uncertainty is likely to remain. Several uncertainties need committee input.
Can data collection be completed without undue burden on patients or the NHS system	Unclear	Some burden is likely to fall on clinicians.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	Yes - Minor	Agreeing a DCA that includes data collection from the registry may impact timelines. Unclear whether this treatment would be given a routine recommendation based on its clinical effectiveness data.

Is olipudase alfa suitable for managed access?

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID3913]:

A Highly Specialised Technology Appraisal

Produced by

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Brian O'Toole	Lead for the EAG's appraisal of the economic evidence, drafted economic sections of the report, writing and editorial input
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Helen Coelho	Critical appraisal of the clinical evidence and drafted sections of the report
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Dawn Lee	Quality appraisal of the company's economic model and senior guidance on economic analyses
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
Edward Wilson	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report. Guarantor of the report

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Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ASMD	Acid sphingomyelinase deficiency
AST	aspartate aminotransferase
BSC	best supportive care
CCL18	Cc chemokine ligand 18
CI	confidence interval
CS	company submission
CV	cardiovascular
EAG	External assessment group
EED	Economic Evaluation Database
EMA	European Medicines Agency
ERT	enzyme-replacement therapy
FDA	Food and Drug Administration
FEV1	forced expiratory volume
FVC	forced vital capacity
HDL	high-density lipoprotein
HRQoL	health-related quality of life
HS	health state
HST	highly specialised technology
ICER	incremental cost-effectiveness ratio
IAR	infusion associated reaction
ITT	intention to treat
LDL	low-density lipoprotein
LY	life-year
MeSH	medical subject heading
mITT	modified intention to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPD	Niemann-Pick Disease
NR	not reported
O^2	oxygen
ONS	Office for National Statistics
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PSA	probabilistic sensitivity analysis
PSS	personal social services
QALY	quality-adjusted life year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation

AE	adverse event
SE	standard error
SLR	systematic literature review
SMR	standardised mortality ratio
SoC	standard of care
SRS	Splenomegaly related score
TDABC	time driven activity-based costing approach
TEAE	treatment emergent adverse event
TP	transition probability
TTO	time-trade-off
VN	voretigene neparvovec

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3 to 1.6.

Table 1: Summary of key issues

Key issue	Summary of issue	Report sections
Discounting	The company used differential discounting, which is not consistent with the NICE reference case	4.2.5
Olipudase alfa treatment efficacy	The company's long-term efficacy assumption was not supported by robust clinical data.	4.2.6
Carer HRQoL	The EAG disagreed with several of the company's assumptions used to model carer HRQoL	4.2.9.1
Mortality	There was uncertainty surrounding the company's approach to modelling mortality	4.2.8
Modelled patient weight	Where was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	4.2.3
Uncertainty surrounding the company's economic analyses in those with severe disease	The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations.	4.2.3.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Discounting	Discounted costs at 3.5% and benefits at 1.5%	Discounted both costs and benefits at 3.5%	4.2.5
Treatment efficacy	From 2-years onwards all patients on olipudase alfa transitioned into the least severe health states (based on spleen volume and DLco)	To freeze TPs in the olipudase alfa arm at 2-years	4.2.6
Carer HRQoL	• The company applied carer disutility to health states in the BSC arm only i.e. carers of patients receiving olipudase alfa did not experience a negative impact on HRQoL • The company assumed carer disutility did not differ according to health state severity i.e. a carer disutility of -0.15 is applied to both the least severe and most severe modelled health states • The source of carer disutility was a published study in people with Pompe disease, (estimated to be -0.15) [1] • The company assumed 1.78 carers for children and 1 carer for adults, based on a prior NICE HST appraisal (HST11: voretigene neparvovec for inherited retinal dystrophies caused by RPE65 gene mutations) [2] • The company applied a carer disutility associated with patient death (assumed to be -0.5, applied for the entire duration of the modelled time horizon	• Application of carer disutility to model health states (irrespective of treatment) • A dynamic disutility approach i.e. applied higher disutility to severe states and lower disutility for other states. Differential carer disutilities were used for adult and paediatric populations • The EAG used alternative published literature sources for carer disutility • One carer was assumed for all health states in both adults and children • Carer disutility associated with death was removed	4.2.9.1
Mortality	The company model included disease-specific mortality for the paediatric population.	Based on UK clinical opinion to the EAG, disease-related mortality was not apparent in paediatric patients. For the paediatric population,	4.2.8

		disease-related mortality was removed and patients were assumed to follow background mortality until they reached adulthood.	
Modelled patient weight	Weight was not based on the mean weight of UK patients.	The EAG preferred to use the mean UK population weight (based on Health Survey England data), and use the z-score for 18-year olds (as estimated by the company) to account for reduced weight due to ASMD	4.2.3

Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; HRQoL, health-related quality of life; HST, highly specialised technology; TP, transition probability; UK, United Kingdom

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- **Improved treatment efficacy**. The incremental QALY gain associated with olipudase alfa was primarily driven by the company's long-term efficacy assumption i.e. from two years onwards all patients on olipudase alfa transition into the least severe health states (spleen volume SV<6MN and DLco>80), where they experience a relatively high utility value and remain until death (see Section 4.2.6). For the adult and paediatric populations respectively, approximately [redacted] and [redacted] of the incremental gain stems from patients remaining in this health state.
- **Reducing mortality**. The company modelled disease mortality based on the presence or absence of 'severe splenomegaly' using data from the observational study SPHINGO-100 (see Section 4.2.8). Due to the modelled efficacy associated with olipudase alfa, fewer patients died relative to those on best supportive care (BSC), resulting in an increase in life-years gained and QALYs.
- **Reducing the HRQoL burden on carers**. Due to the company's assumptions surrounding carer health-related quality of life (HRQoL; see Section 4.2.9.1), fewer caregiver QALYs are modelled to be lost in the olipudase alfa arm.
- **Discounting benefits at 1.5%.** The company applied differential discounting in their base case i.e. used 3.5% for costs and 1.5% for benefits. The lower discount rate

applied to benefits had a substantial impact on QALYs accrued (see Section 4.2.5 and 6.2.9).

Overall, the technology is modelled to affect costs by:

- Increasing treatment-related costs. Drug acquisition costs were the primary driver of olipudase alfa incremental costs (accounting for [redacted] of total costs). Annual drug costs were estimated based on patient weight and their compliance with the treatment.

The modelling assumptions that have the greatest effect on the ICER are:

- The company conducted one-way sensitivity analyses varying parameters arbitrarily by +/- 20%. The parameters/assumptions with the largest impact on the ICER were patient weight, drug unit costs, compliance and starting age. Discounting costs at 1.5% also had a high upward impact on the ICER in both populations, as well as the inclusion of a discontinuation rate at week 80 and a higher compliance rate of 95%. Based on the EAG scenario analyses, the ICER was most sensitive to alternative long-term effectiveness assumptions for olipudase alfa, the application of carer disutility to model health states (irrespective of treatment), the removal of carer disutility associated with death, and the use of reference case discounting.

1.3. The decision problem: summary of the EAG's key issues

The EAG did not identify any key issues related to the decision problem.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

There are limitations in the clinical evidence base for olipudase alfa, which may be expected given the rare nature of the condition. However, the EAG did not identify any key issues with the clinical effectiveness evidence.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The EAG identified six key issues with the cost effectiveness evidence for olipudase alfa.

Key Issue 1: Non-reference case discounting may not be appropriate

Report sections	Section 4.2.5 and Section 6.2
Description of issue and why the EAG has identified it as important	In the company's base case analysis, costs were discounted at 3.5% and benefits were discounted at 1.5%.

	The EAG did not consider the application of non-reference case discounting to be appropriate.
What alternative approach has the EAG suggested?	The EAG conducted a scenario analysis whereby both costs and benefits were both discounted at 3.5%. This was included in the EAG's preferred base case analysis.
What is the expected effect on the cost-effectiveness estimates?	The ICER was highly sensitive to this analysis.
What additional evidence or analyses might help to resolve this key issue?	This issue was resolved.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio

Key Issue 2: Uncertainty surrounding olipudase alfa long-term treatment effect

Report sections	Section 4.2.6 and Section 6.2
Description of issue and why the EAG has identified it as important	In the company's base case analysis, 100% of patients who receive olipudase alfa were assumed to transition to the least severe health states (SV<6MN and DLco≥80%) and remain there for the duration of the modelled time horizon (subject to mortality). In contrast, patients in the BSC arm were assumed to transition in every cycle until the end of the time horizon or death. Clinical experts advised the EAG that the long-term efficacy assumption for olipudase alfa may be plausible (see Section 4.2.6). However, due to the lack of long-term treatment effectiveness data and the potential for the assumption to overestimate the incremental QALY gain associated with olipudase alfa, the EAG considered there to be a high degree of uncertainty surrounding this assumption.
What alternative approach has the EAG suggested?	The EAG conducted several scenario analyses to test uncertainty surrounding the long-term treatment effect associated with olipudase alfa. These included the following: • observed benefit is frozen at 2 years • observed benefit is maintained (transition probabilities in year 2+ are replayed) • treatment effect waning (from 2 years, assume that all olipudase alfa patients follow BSC transitions)
What is the expected effect on the cost-effectiveness estimates?	All three scenarios resulted in an upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Long-term clinical effectiveness data would help to reduce modelled uncertainty. These data are not currently available, therefore uncertainty surrounding long term treatment effect remains.

Abbreviations: DLco, diffusing capacity for carbon monoxide; EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; SV, spleen volume

Key Issue 3: Uncertainty surrounding modelled carer disutility

Report sections	Section 4.2.9.1 and Section 6.2
Description of issue and why the EAG has identified it as important	The EAG disagreed with the following assumptions regarding carer disutility that were included in the company base case: • The company applied carer disutility to health states in the BSC arm only i.e. carers of patients receiving olipudase alfa did not experience a negative impact on HRQoL. The EAG did not consider that the company justified this approach, and considered it more plausible to associate carer disutility with the health state of the patient, regardless of treatment arm • The company assumed that carer disutility did not differ according to health state severity i.e. a carer disutility of -0.15 was applied to both the least and most severe modelled health states. The EAG did not consider this to be plausible, as carer disutility would be expected to be greater for patients in more severe health states • Data on carer disutility in people with ASMD types B and A/B were not available. The source of carer disutility used by the company was based on a population with Pompe disease (estimated to be -0.15). [1] Clinical advice to the EAG was that Pompe disease is not sufficiently similar to ASMD types B and A/B, and it would be expected to have overall greater carer burden. • The company assumed 1.78 carers for children and 1 carer for adults. The EAG did not consider that the company had provided sufficient justification for the number of carers in the paediatric population, and clinical advice suggested that this may be an overestimation. • The company applied a carer disutility associated with patient death (assumed to be -0.5 and applied for the entire duration of the modelled time horizon). The EAG did not consider that the company had provided justification for this approach.
What alternative approach has the EAG suggested?	Based on clinical expert opinion to the EAG and a review of published literature, several scenario analyses were conducted, including the following: • Carer disutility was applied to model health states (irrespective of treatment) • A dynamic disutility approach was used i.e. higher disutility was applied to severe states and lower disutility for other states. Differential carer disutilities were applied for adults and paediatric populations

	• Alternative published literature sources were used for carer disutility (see Section 4.2.9.1 for alternative values used) • One carer was used for all health states in adult and paediatric populations • carer disutility associated with death was removed
What is the expected effect on the cost-effectiveness estimates?	All scenario analyses had an upward impact on the ICER (in both populations). Results were most sensitive to the application of carer disutility to health states (irrespective of treatment) and the removal of carer disutility associated with death. See Section 6.2 for results.
What additional evidence or analyses might help to resolve this key issue?	The EAG explored alternative carer disutility assumptions to assess uncertainty surrounding this modelled assumption. Collection of HRQoL data in carers of people with ASMD types B and A/B would help to reduce uncertainty.

Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio

Key Issue 4: Uncertainty surrounding modelled mortality rates

Report sections	Section 4.2.8 and Section 6.2
Description of issue and why the EAG has identified it as important	In the company's base case analysis, mortality was modelled according to whether patients did or did not have severe splenomegaly. The company estimated SMRs using data from the SPHINGO-100 observational study. [3] The EAG identified the following key uncertainties surrounding the company's handling of mortality in the model: • SPHINGO-100 is an older study that included a small sample and reported few deaths (n=9), and therefore is not a robust source for mortality risk. • The company's model included disease-specific mortality for the paediatric population, however clinical advice to the UK is that disease-related mortality was not apparent in the paediatric ASMD population.
What alternative approach has the EAG suggested?	The EAG conducted the following scenario analyses to determine whether results were sensitive to a change in mortality assumptions: • the SMR associated with severe splenomegaly was reduced by 50% • disease-related mortality in the paediatric population was removed and patients were assumed to follow background mortality until they reached adulthood.
What is the expected effect on the cost-effectiveness estimates?	Reducing the SMR by 50% had a relatively minor upward impact on the ICER in both patient populations. Removing

	paediatric mortality had a minor downward impact on the ICER for the paediatric population.
What additional evidence or analyses might help to resolve this key issue?	The EAG requested additional mortality data from the International Niemann-Pick Alliance (INDPA). These data may become available at a later stage during the NICE appraisal.

Abbreviations: ASMD, acid sphingomyelinase deficiency; EAG, External Assessment Group; SMR, standardised mortality ratios

Key Issue 5: There is some uncertainty surrounding the company's approach to modelling patient weight

Report sections	4.2.3 and 6.2
Description of issue and why the EAG has identified it as important	The EAG noted some uncertainty surrounding the company's estimation of patient weight in the model. Paediatric population • The company derived the z-score function based on data from the SPHINGO-100 trial. The z-score function (which estimates the change in paediatric weight over time) was applied to weight from UK growth charts. The EAG noted that weights from the UK growth chart appeared low compared to weight data from Health Survey for England (2019). Adult population • Patient weight for adults appeared low (64.5kg) relative to the average UK adult weight, and the mean weight estimated by the company for patients aged 18-years (62kg). Given that olipudase alfa dosing is weight based, an increase in the starting weight of patients results in higher drug costs for olipudase alfa. If drug costs are underestimated in the CS, the ICER will likewise be underestimated.
What alternative approach has the EAG suggested?	The EAG undertook the following scenario analyses: • For children, patient weights based on UK growth charts were replaced with weight data from general population norms in the Health Survey for England report (2019). [4] • For adults, two scenario analyses were conducted a) the UK mean weight was used (estimated from the male/female split from ASCEND) b) the UK mean weight was used and the z-score for 18-year olds (as estimated by the company) was applied. This was to account for patients potentially having a lower weight than the

	general population as a result of ASMD. The EAG incorporated this scenario into their preferred base case
What is the expected effect on the cost-effectiveness estimates?	The ICER was sensitive to assumptions about patient weight. The EAG scenario analyses had an upward impact on the ICER due to a corresponding increase in drug costs
What additional evidence or analyses might help to resolve this key issue?	High-quality evidence for the average weight of the target population would allow for drug costs to be more accurately estimated in the model. The EAG was uncertain to what extent patient weight may change following treatment with olipudase alfa; for example, it is plausible that children who respond to treatment may be more likely to meet normal growth milestones over time. Long-term follow-up data for weight in those treated with olipudase alfa would provide clarity.

Abbreviations: EAG, External Assessment Group

Key Issue 6: Uncertainty surrounding the company's economic analysis for those with severe disease

Report sections	Section 4.2.3.1 and 5.3.3
Description of issue and why the EAG has identified it as important	The company provided economic results for a population subgroup in both children and adults with severe disease. There were several uncertainties surrounding the company's approach to modelling the severe population that significantly undermine the validity of the findings: • Clinical effectiveness data used to inform transitions were not derived from trial participants with severe ASMD. Rather, the company assumed 100% of patients began in the severe health state and used transition probabilities from the overall trial population. Based on clinical opinion to the EAG, this assumption may not be appropriate • Instead of using trial data, the company estimated mortality amongst the severe population using a published literature source (McGovern et al).[5] The EAG had concerns about the reliability of these data for estimating mortality, and there was a lack of transparency in the company's approach to estimating survival i.e. for both the adult and paediatric populations the company applied a Weibull distribution to the mortality data, however rationale for this curve selection was not provided, AIC/BIC statistics were not presented and no attempt was made to discuss visual fit of alternative functions. • No sensitivity analysis was presented in the CS for the severe subgroup, increasing uncertainty in the base case results.

What alternative approach has the EAG suggested?	The EAG were unable to resolve this issue with the current evidence base, and no additional analysis was conducted.
What is the expected effect on the cost-effectiveness estimates?	The EAG cannot determine whether transition probabilities used in the company's severe subgroup analysis are representative of the true population. Clinical advice to the EAG was that this may not be the case, and therefore the EAG considered that the subgroup analysis for the severe population was subject to extreme uncertainty and may not be appropriate for decision making.
What additional evidence or analyses might help to resolve this key issue?	The EAG considered that the company had used the best available evidence for the severe subgroup given that very few people in the company trials were considered to have severe disease at baseline. However, as this evidence is limited, robust subgroup data with respect to treatment effect, impact on mortality and HRQoL in both paediatric and adult populations would help to alleviate uncertainty. The EAG also considered that further information from the company regarding their methods for estimating survival in the severe subgroup would help to reduce uncertainty.

Abbreviations: EAG, External Assessment Group

1.6. Other key issues: summary of the EAG's views

The EAG did not identify any further key issues.

1.7. Summary of EAG's preferred assumptions and resulting ICER

The EAG's preferred assumptions and deterministic and probabilistic ICERs for the adult and paediatric populations are summarised in Table 3 to Table 6. The EAG noted that there were differences between the deterministic and probabilistic results in both the adult and paediatric populations. This occurs in non-linear models, and probabilistic analyses provide the expected costs and outcomes in these cases. However, probabilistic sensitivity analysis (PSA) is subject to Monte Carlo error (simulation noise). The PSA was run for 1000 iterations. When the EAG ran the PSA for 10,000 simulations, the ICERs remained stable. The EAG therefore considered that the deterministic results should be interpreted with caution.

Modelling errors identified and corrected by the EAG are described in 6.1. For further details of the exploratory and sensitivity analyses conducted by the EAG, see Section 6.2.

Table 3: EAG's deterministic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.95	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	26.05	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	15.36	[redacted]	[redacted]
Removed carer disutility associated with death of patient	6.2.3	[redacted]	21.62	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	22.57	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	19.22	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.94	[redacted]	[redacted]
• Assume 1 carer in each health state	6.2.3	[redacted]	25.00	[redacted]	[redacted]
Removed disease-related mortality (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	25.86	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	26.05	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.57	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 4: EAG's probabilistic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.07	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	25.06	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	14.90	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.29	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	21.86	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.41	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	20.87	[redacted]	[redacted]
• Assume 1 carer in each health state	6.2.3	[redacted]	24.21	[redacted]	[redacted]
Removed disease-related mortality removed (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	24.81	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	25.20	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.29	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 5: EAG's deterministic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	16.44	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	17.59	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually) 6.2.1					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	12.25	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.88	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2-years	6.2.1	[redacted]	13.99	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	13.67	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	15.18	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	17.59	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	5.30	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 6: EAG's probabilistic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	15.39	[redacted]	[redacted]

EAG corrected company base case	6.1	[redacted]	16.32	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually)					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	11.46	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.33	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.36.2.1	[redacted]	13.74	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	12.48	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	13.60	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	16.27	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	4.83	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Sanofi in support of olipudase alfa for treating acid sphingomyelinase deficiency (ASMD) types B and A/B (otherwise known as Niemann-Pick disease types B and A/B).

2.2. Critique of the company's description of the underlying health problem

2.2.1. Epidemiology

The company provided an overview of the literature related to the epidemiology of ASMD (CS B.1.3). The EAG agreed with the company's characterisation of ASMD as a very rare disease: the CS reported that there are approximately 40–50 prevalent children and adults currently in the UK, which was is in line with clinical expert advice to the EAG and with comments from Niemann-Pick UK (NPUK) during scoping for this appraisal (NPUK support 37 UK patients, who make up 90% of the known UK population). The CS also stated that most people in the UK with ASMD have type B or A/B, with the majority being type B. This is likely due, in part, to the higher mortality risk associated with type A compared with type A/B and B. There is also an increased risk of mortality amongst people with ASMD type A/B compared with type B.

The company used data from six studies (based in Australia, Czech Republic, Netherlands, Portugal, United Arab Emirates [UAE] and the United States [US]) to inform rates of ASMD type B and A/B (see CS B.1.3, Table 5). Incidence rates in these studies ranged from 0.1 to 0.25 per 100,000 live births for type B and from 0.33 to 0.9 per 100,000 live births for type A/B. The differences in estimates of type A/B across these studies are likely due to population differences across the studies. Indeed, the EAG agreed that the incidence of ASMD would be expected to vary according to population/country and that there are numerous potential reasons for this including: the genetic, recessive nature of the condition; phenotypic variation amongst those with the same genotype and early mortality amongst those with severe presentation; differing prevalence of populations with specific genetic mutations; and diagnostic screening programmes that are present in some countries and not others (not currently present in the UK). These factors may contribute to the lower incidence of ASMD (and in the case of diagnostic screening programmes, to the possibility of under-diagnosis) in the UK.

The EAG noted that, of the six studies presented in CS B.1.3 Table 5, only two were identified by the company's systematic literature review (SLR; Pinto et al., 2004[6] and Burton et al., 2017[7]). The company's searches did not retrieve the other four studies and it is unclear how these were identified. The EAG also highlighted that one of the studies included in CS B.1.3, Table 5 (Poorthuis et al., 1999[8]) did not clearly provide incidence data for type B or A/B either alone or in combination. The data from this study appeared, therefore, to be outside of the scope of this appraisal. The EAG checked the lists of included and excluded studies from the company's SLR (CS Appendix D Tables 84 and 85) and did not identify any additional studies providing relevant epidemiologic data.

2.3. Critique of the company's overview of current service provision

The CS provided an overview of the current service provision for the diagnosis and management of ASMD types B and A/B. Overall the EAG considered the summary provided by the company to be accurate, though noted the following additions:

- The company correctly stated that there is no diagnostic test to differentiate between subtypes of ASMD, though advice to the EAG was that type A is clearly differentiated from types B and A/B at an early stage, due to the speed of progression and severity of symptoms. The EAG therefore considered that the target population for olipudase alfa would be clearly recognisable to clinicians.

- The company correctly noted that most people with ASMD are diagnosed in childhood. Expert advice to the EAG indicated that diagnosis is frequently earlier in those children with a familial history of ASMD, due to earlier recognition of symptoms and/or diagnostic screening. The EAG were also advised that those without familial history who have mild disease may not be diagnosed until adulthood, but this is infrequent, meaning that the incident population eligible for olipudase alfa will include a small minority of adults.

- The company provided an overview of the background treatments that people with ASMD types B and A/B may receive. These treatments may be medical or non-medical and are targeted to treat the symptoms and health consequences of the condition. Advice to the EAG was that these treatments would be expected to reduce if an effective treatment for ASMD was identified.

2.4. Critique of company's definition of decision problem

The company stated that their submission was consistent with the NICE scope for this appraisal. The EAG appraisal of the company's definition of the decision problem is outlined in Table 7. In general, the EAG agreed with the company assessment though noted that several outcomes specified in the NICE scope were not represented in the company's evidence base. In addition, the EAG were concerned that at clarification the company were unable to confirm that trials of olipudase alfa included participants with ASMD type A/B. The EAG assumed this was the case due to estimates provided in the report of olipudase alfa by the European Medicines Agency (EMA), though these estimates were not provided separately for each arm, and the EAG was unclear where these data were derived from. This issue is discussed further in Sections 3.2.2.2 and 3.2.3.1.

Table 7: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with acid sphingomyelinase deficiency (also known as Niemann-Pick disease type B or type AB)	As per scope	N/A	The CS was consistent with the population described in the NICE scope, although the EAG noted that the company were uncertain about how many participants in the included trials met criteria for a diagnosis of ASMD type A/B. In its assessment, the EMA reported the number of participants in ASCEND and ASECEND-Peds with type A/B, however given the company could not provide this (clarification QA15) the EAG assumed that this was an estimate based on baseline characteristics. On the basis of expert advice, the EAG expected that olipudase alfa was likely to have a similar effect on visceral symptoms of ASMD for each subtype. However, neurological symptoms experienced by people with ASMD type A/B would not be expected to be responsive to treatment with olipudase alfa, and it's feasible that broader outcomes related to functioning and HRQoL may vary between subtypes.
Intervention	Olipudase alfa	As per scope	N/A	No comment
Comparator(s)	Best supportive care (BSC)	As per scope	N/A	There was no alternative treatment for ASMD types B and A/B and the EAG agreed that BSC, consisting of treatments to manage the symptoms and complications of ASMD, was the main comparator to olipudase alfa. In its response to clarification (QA4) the company stated that they did not include evidence for purely non-pharmacological interventions in the CS. The EAG understood that non-pharmacological interventions may be commonly used by people with ASMD, though noted that these would have been permitted during the trials for all participants.

Outcomes	• change in spleen volume • change in lung function • change in liver function and volume • change in physical observations (including observations or measurements from examination of the skin, head, eyes, ears, nose and throat; lymph nodes; heart, vital signs, lungs and abdomen; bone marrow; extremities and joints) • change in weight, height and onset of puberty in children and young people • change in neurological observations (including observations or measurements from examination of coordination; cranial nerves; extrapyramidal features; fundoscopy; gait; motor skills; peripheral nervous system; reflexes; sensory nervous system; strength and mental status) • change in biomarkers (including high sensitivity c-reactive protein; ceramide; iron; cardiac troponin I; ferritin; CCL18 levels; lysophingomyelin, oxysterols, lipid profile)	Partial	None provided	Advice to the EAG was that key outcomes measured by the company trials were highly relevant to understanding the potential efficacy of olipudase alfa for treating ASMD types B and A/B, including change in organomegaly, pulmonary function, liver function, HRQoL and functioning, and AEs. The EAG therefore concluded that the evidence reported was sufficient for judging the key benefits of olipudase alfa, though the absence of some outcomes has limitations for inputs within the company model.

	• Change in fatigue and exercise tolerance • Mortality • Adverse effects of treatment • Health-related quality of life • Carer quality of life			
Economic analysis	Analysis expected to be consistent with the NICE reference case	As per scope	N/A	The company submitted a cost utility analysis, which was appropriate. The EAG noted that the company's base case differed to the NICE reference case regarding discounting (see Section 4.2.5). Furthermore, the company made several assumptions with respect to carer disutility that did not align with NICE guidance (see Section 4.2.9.1).
Subgroups	None specified	N/A	N/A	ASMD types B and A/B are heterogeneous conditions with broad variation in the age of diagnosis, disease severity and symptom profile across the population. These differences are related to the various genetic mutations responsible for the condition, though there is currently no validated marker of disease severity or prognosis. The EAG considered that subgroup analyses that compared the effect of olipudase alfa between meaningful groups, such as according to genetic markers, age of onset, or baseline severity would be of interest to provide more information about the effect of olipudase alfa and how it may be used in practice. However, the EAG accepted that this is a very rare condition, and the company evidence consisted of very little comparative evidence from which to conduct analyses. In response to a request from the FDA, the company conducted subgroup analyses comparing a small number of clinical outcomes in ASCEND according to markers of disease severity at baseline, the results of which are reported in the CS. As expected, these analyses were limited due to the available sample size, and so at this

				time the EAG considered that the current evidence base for olipudase alfa was not sufficient to fully explore potential variation in the effect of treatment across the population. The company provided economic results for the severe population. This analysis was subject to a number of limitations (see Section 4.2.3.1 and 5.2).
Special considerations including issues related to equity or equality	None specified	N/A	N/A	Treatment with olipudase alfa was not anticipated to affect inequity in protected groups.

Abbreviations: AE, adverse event; ASMD, acid sphingomyelinase deficiency; CS, company submission; EAG, External Assessment Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; HRQoL, health-related quality of life; N/A, not applicable; NICE, National Institute for Health and Care Excellence

3. CLINICAL EFFECTIVENESS

The sections below provide the EAG appraisal of the evidence submitted by the company in support of the clinical effectiveness and safety of olipudase alfa for the treatment of children and adults with ASMD Type B or A/B.

The EAG reviewed the details provided on:

- the methods implemented to identify, screen, extract data and assess the risk of bias in the relevant evidence
- the clinical efficacy of olipudase alfa for the stated indication and
- the safety profile of olipudase alfa for the stated population.

Detailed information from the CS is only provided where the EAG disagreed with the company's assessment or proposal, or where there was a particular area of concern that the EAG considered necessary to highlight to the NICE committee. Otherwise, the EAG signpost to the relevant part of the CS.

3.1. Critique of the methods of the review

The company undertook a single SLR to identify evidence reporting on the efficacy/effectiveness and safety of olipudase alfa for the treatment of children or adults with ASMD types B or A/B.

A summary of the EAG's critique of the methods implemented in the SLR is presented in Table 8. Overall, the EAG found the SLR to be of reasonable quality and it was likely that the key studies relevant to the company's decision problem were identified.

The EAG was concerned about the quality appraisal conducted by the company and disagreed with the company's overall ratings of trial quality. This issue is discussed further in section 3.2.2.6.

Table 8: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	CS B.2.1, Table 9	The EAG was broadly satisfied that searches identified all relevant literature, however, the EAG

	CS Appendix D.1.1 Company clarification response to questions A1 – A3.	noted the following limitations: the subject heading for Niemann-Pick Diseases was not exploded to include narrower terms in the MeSH hierarchy; and the use of 'Article' and 'Article in Press' limits excluded conference abstracts from Embase search results. At clarification, the company provided additional information about methods for searching grey literature sources. The EAG considered that these methods missed some relevant sources, and restrictions on search terms and limits in clinicaltrials.gov could have resulted in missing relevant evidence. However, the EAG conducted additional searches (see Section 3.4.1) and did not identify any relevant studies that should have been included.
Inclusion criteria	CS Appendix D.1.1, Table 83 Company clarification response to questions A4–A5	Inclusion and exclusion criteria were broad, and reasonably aligned with the company's decision problem. The EAG noted that the broad inclusion criteria (i.e. including all non-medical interventions) resulted in the inclusion of a study (NCT00410566) where olipudase alfa was not given at the licensed maintenance dose. The EAG also noted that the comparator in the NICE scope was best supportive care, but non-medical comparators were excluded from the SLR for clinical and safety outcomes. Following clarification, the company provided justification for this: non-medical interventions aim to reduce symptom burden rather than treating ASMD. The EAG noted that concomitant non-medical interventions would have been permitted for participants in the included trials. Additionally, the EAG agreed that it is unlikely any studies focusing on a non-medical intervention as a comparator were available and excluded from the SLR.
Screening	CS B.2.1, Table 9 CS Appendix D.1.1	Standard appropriate methods. The EAG highlighted that the SLR included studies reporting the population of interest as a subgroup, or for which 80% of the population matched the population of interest. Given the rarity of the condition, the EAG agreed that this was methodologically appropriate.
Data extraction	CS B.2.1, Table 9 CS Appendix D	Standard appropriate methods.
Tool for quality assessment of included study or studies	CS B.2.1, Table 9 CS Appendix D Company clarification response to question A6	The EAG noted that whilst appropriate methods were used to assess the ASCEND trial, the ROBINS-I was used to assess the single-arm trials. The ROBINS-I was designed for non-randomised comparative studies and was, therefore, not the best choice of tool to evaluate

		and highlight the constraints of single-arm studies. The EAG had concerns with the critical appraisal ratings determined by the company and considered that the evidence base for olipudase alfa was limited in ways not considered in the company assessment.
Evidence synthesis	CS B.2.1, Table 9 CS Appendix D	The EAG agreed that, due to the paucity of studies, data pooling across studies was not feasible.

Abbreviations: CS, Company submission; EAG, Evidence Assessment Group

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described four trials of olipudase alfa (Table 9). Three of the trials included unique patient populations: ASCEND (a double-blind RCT with adults), [9,10] ASCEND-Peds (an open-label single arm trial with children) [11,12] and DFI13412 (an open-label single arm trial with adults). [13] The fourth trial, LTS13632, was an open-label extension of the latter two trials (ASCEND-Peds and DFI13412). [14] The company reported clinical effectiveness and safety data for all four trials: data for ASCEND (and its extension), ASCEND-Peds and DFI13412 were reported in Section B.2.6. of the CS. Data for LTS13632 were reported in Section B.2.11 of the CS.

The EAG noted that further data are being collected for olipudase alfa and/or for outcomes relevant to understanding the humanistic burden and potential value of olipudase alfa for treating ASMD type B and A/B. Data collection for LTS13632 is ongoing and is expected to generate data at four- and 6.5-year follow-up for paediatric and adult participants, respectively (within the CS, data were reported at 6.5-years for five adult participants, and at four-years for spleen and liver volume in seven paediatric participants). In addition, the company was conducting a prospective/retrospective cohort study to map disease course, disease burden, HRQoL, resource use, and to validate patient-reported outcome measures (PROs) in ASMD, which was expected to complete in April 2023 [NCT04106544]. Finally, the EAG understood that olipudase alfa was being reimbursed in France as part of an early access program with evidence generation, which will complete in January 2025 [NCT05359276].

Table 9: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Follow-up	Study type
ASCEND DFI12712 [NCT02004691] [10,15,16]	Double-blind international RCT plus double-blind extension (all participants receiving placebo switched to treatment)	Adults with ASMD type B (N=36)	Olipudase alfa	Placebo	52 weeks plus 1-year extension	Phase II/III efficacy and safety evaluation
ASCEND-Peds DFI13803 [NCT02292654] [11,12]	Open-label international single-arm	Children with ASMD not identified as type A (N=20)	Olipudase alfa	NA	52 weeks	Phase I/II efficacy and safety evaluation
DFI13412 [NCT01722526] [13,17]	Open-label, single arm trial	Adults with ASMD (N=5)	Olipudase alfa	NA	26 weeks	Phase I safety and tolerability evaluation
LTS13632 [NCT02004704] [14,18-21]	Open-label extension to ASCEND-Peds and DFI13412	Participants from selected centres recruited to ASCEND-Peds and DFI13412 (N=25)	Olipudase alfa	NA	4- and 6.5-years for paediatric and adult participants, respectively	Phase II long-term efficacy and safety evaluation. Trial ongoing (expected completion July 2024)

Abbreviations: ASMD, acid sphingomyelinase deficiency; CS, company submission; NA, not applicable; RCT, randomised controlled trial

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

For adults, the CS reported an RCT evaluating olipudase alfa (ASCEND) alongside a small single-arm study (DFI13412) and a single-arm extension study involving the DFI13412 participants (LTS13632).

The company stated that an RCT design was not considered appropriate for those <18 years of age for ethical reasons. The paediatric evidence base for olipudase alfa was, therefore, limited to a single-arm study (ASCEND-Peds) from which participants were also eligible to enter the extension study LTS13632. Key design features of these studies are provided in Table 10.

Table 10: Summary of key olipudase alfa study design characteristics

	ASCEND	ASCEND-Peds	DFI13412	LTS13632
Design	Double-blind RCT	Single-arm	Single-arm	Single-arm extension
Blinding	During PAP + ETP	Open-label	Open-label	Open-label
Comparator	Placebo (0.9% sodium chloride)	None	None	None
Total N	36	20	5	25
ASMD Type	B[a]	A/B and B	B	A/B and B
Adult/Paediatric	Adult	Paediatric [b]	Adult	Both
Location(s)	17 countries in North and South America, Australasia, Europe, and Asia	6 countries (Brazil, France, Germany, Italy, the UK, US)	2 countries (UK, US)	7 countries (Brazil, Belgium, France, Germany, Italy, the UK, US)
Sites	23 (one in the UK)	6 (one in the UK)	2 (one in the UK)	9 (two in the UK)
PAP	52 weeks (randomly allocated treatment period)	52 weeks	26 weeks	Ongoing[c]
ETP	52 weeks (all participants switched to olipudase alfa)	Eligible to participate in LTS13632	Eligible to participate in LTS13632	NA

Abbreviations: PAP, primary analysis period; ETP, extension period; NA, not applicable.
Notes: [a] Although the summary of product characteristics (SmPC) for olipudase alfa reported that 25% of participants in ASCEND had neurological symptoms consistent with a clinical diagnosis of ASMD type A/B; [b] Split into three age groups: adolescents (n=4), children (n=9), and infants/early children (n=7); [c] Data reported in the CS were principally available at 6.5 years for adult and 4 years for paediatric populations.

A discrepancy in the information provided by the company was noted in that an additional study location was reported for LTS13632 despite all participants having been recruited from the ASCEND-Peds and DFI13412 studies.

The company defined multiple different analysis sets for both ASCEND and ASCEND-Peds, including a modified-ITT (m-ITT) population, a per protocol set, a safety set, and outcome-specific analyses using patients with available data. At clarification (question A20) the company confirmed that all clinical data reported in the CS from these trials were based on the mITT population and all safety data were based the safety population, but that these populations were identical (no participant received a treatment other than the one they were allocated to receive).

The EAG considered that the data from LTS13632 may be unreliable due to the small number of participants reaching the 6.5-year and four-year time points and the high levels of missing data in the paediatric population at the latest data cut prior to this appraisal (data were available for 7/20 participants [35%]). In response to clarification (question A18) the company also reported a high rate of missing data for key outcomes at 2-year follow-up (see Section 3.2.2.5). Additionally, the EAG highlighted that, in the CS (p.169), the company claimed that data up to 9-years were available from LTS13632, but all data reported in the CS were from the earlier time points. Clarification on this was requested (question A23), but no further explanation was provided.

Overall, the EAG considered that the best quality data for olipudase alfa were available at up to one year in both adult and paediatric participants (see Section 3.2.2.6 for the EAG critical appraisal of the included trials).

3.2.2.2. Population

The CS reported limited population eligibility criteria for the included trials. Following clarification (question A16) the company did not provide this information but indicated that this information was not deemed confidential. The EAG, therefore, report further eligibility criteria from the four trial CSRs (Table 11).

No record was made in the trials of ASMD type (A/B or B). The company stated (response to clarification question A15) that this was not necessary because the marketing authorisation for olipudase alfa was for people with either ASMD types A/ B or B. The EAG disagreed with this statement on the basis that it is important to demonstrate effectiveness of olipudase alfa in both conditions covered by the marketing authorisation. Indeed, expert advice to the EAG suggested that the effect of olipudase alfa may differ between these subtypes (the absence of an effect on neurological symptoms may lead to a differential impact on outcomes such as functioning and quality of life). The company also reported that the risk of mortality may be higher for those with ASMD type A/B than type B. The EAG ascertained (response to clarification question A15) that

both adult and paediatric participants with a clinical presentation consistent with type A/B were eligible for inclusion in both ASCEND and ASCEND-Peds (and by default in the paediatric population in LTS13632), and confirmed this using information from the summary of product characteristics (SmPC) for olipudase alfa (produced by the EMA). The SmPC reported that 25% of participants in ASCEND and 40% of participants in ASCEND-Peds had neurological symptoms consistent with a clinical diagnosis of ASMD type A/B (SmPC[22] pages 11 and 14). Despite this, there remains a lack of separate evidence for each ASMD type.

The company reported (document B, Section 2.3) that in ASCEND, 62 people were screened but only 38 were considered eligible for inclusion (i.e. 24 people were excluded at this stage). The EAG requested confirmation that those excluded all had ASMD types B or A/B.

[redacted]. Two people did not provide informed consent and one person was recorded as unable to adhere to study requirements. The remaining exclusions were due to not meeting clinical inclusion criteria, such as spleen volume, lung diffusion capacity, comorbid conditions, adequate platelet count, or liver function. Clinical advice to the EAG was that the eligibility criteria were particularly stringent in permitted DLco levels and may have excluded people with higher disease severity. Requirements may also have excluded those at a higher risk of adverse events. Clinical advice also suggested that the trials may have excluded those with mild disease severity. Subgroup analyses conducted within ASCEND did not find an effect of baseline severity on two outcomes (splenomegaly and lung diffusion capacity), though the sample size in subgroup analyses were limited in size. There were mixed views amongst clinicians about whether the treatment effect of olipudase alfa may vary according to disease severity, though there was some speculation that this may be true for some outcomes and not others (for example, some symptoms may be irreversible where there has been extensive organ damage). Overall, the EAG considered it plausible that the treatment effect of olipudase alfa and its adverse event profile may vary in those excluded in the trial but had no data to substantiate this. The EAG also considered it plausible that the risk of adverse events may be higher in those patients not eligible for the clinical trials.

Table 11: Summary of key inclusion/exclusion criteria for the included trials

	Inclusion criteria	Exclusion criteria
ASCEND	Adults aged ≥18 years with a clinical diagnosis of ASMD type B and: DLco ≤70% of predicted normal value Spleen volume ≥6 multiples of normal SRS ≥5 Platelet count ≥ 60 x 103 /μL INR ≤ 1.5 Not pregnant and using effective contraception	Any serious medical condition or a medical condition including significant cardiac disease, hypertension, active hepatitis B or C, HIV, malignancy within the past 5 years Received any major organ transplant Scheduled for surgery during the trial Unwilling to abstain from alcohol around the time each treatment is administered, and unwilling or unable to abstain from certain medications around the time of liver biopsy (at baseline, week 52 and week 104). Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications Patient requires ventilatory support (any invasive or non-invasive for more than 12 hours daily while awake) Patient is breast-feeding
ASCEND-Peds	Children aged <18 years with ASMD without acute or rapidly progressive neurological abnormalities Spleen volume ≥5 multiples of normal Platelet count ≥ 60 x 103 /μL alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤250 IU/L or total bilirubin ≤1.5 mg/dL INR ≤1.5 Height of -1 z score or lower Not pregnant and using effective contraception	Any serious medical condition or a medical condition including significant cardiac disease, active hepatitis B or C, HIV, malignancy within the past 5 years Delayed gross motor skills Received any major organ transplant Scheduled for surgery during the trial Patient requires ventilatory support (any invasive or non-invasive for more than 12 hours daily while awake) Unwilling to abstain from alcohol around the time each treatment is administered Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications

	Inclusion criteria	**Exclusion criteria**
DFI13412	Adults aged 18 – 65 years with documented non-neuronopathic ASMD DLco >20% and ≤80% of predicted normal value Spleen volume ≥6 multiples of normal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤250 IU/L or total bilirubin ≤1.5 mg/dL Receiving a stable dose of lipid-lowering therapy (e.g. statins) Not pregnant and using effective contraception	Any serious medical condition or a medical condition including significant cardiac disease, active hepatitis B or C, HIV, cirrhosis, or malignancy within the past 5 years Received any major organ transplant Unwilling to abstain from alcohol around the time each treatment is administered, and unwilling or unable to abstain from certain medications around the time of liver biopsy Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications Body mass index >30
LTS13632	Patients who completed the treatment period of ASCEND-Peds or DFI13412 and with an acceptable safety profile Not pregnant and using effective contraception	Patient has a new condition or worsening of an existing condition that would make the patient unsuitable for enrollment or would interfere with the patient completing the trial Unwilling to abstain from alcohol around the time each treatment is administered, and unwilling or unable to abstain from certain medications around the time of liver biopsy Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity for carbon monoxide; INR, international normalised ratio; SRS, splenomegaly related score

Source: Trial CSRs

3.2.2.3. Intervention

The evaluated intervention in all included trials was olipudase alfa. Details of the treatment administered, including background care, were not reported in the CS. At clarification (question A17) the EAG requested that the company provide information of the dose received, mean dose duration, dose modifications, and background care received by participants in all trial arms. In response, the company provided some of this information, as follows:

- The mean [redacted] and median [redacted] cumulative dose of olipudase alfa received by patients in the initial trial period of olipudase alfa (i.e. not the extension phase), and the number and proportion of participants not achieving the target olipudase alfa dose of 3mg/kg (n=1; 5.6%).
- The mean [redacted] and median [redacted] number of infusions received by participants in ASCEND-Peds (i.e. not the mean/median dose received, as requested by the EAG), and the number and proportion of participants not achieving the target olipudase alfa dose of 3mg/kg (n=0).
- A table summarising concomitant treatments during the initial ASCEND trial period (Table 4 in the company response to clarification question A17), and during ASCEND-Peds (Table 5 in the company response to clarification question A17). People with ASMD typically experience a range of comorbid conditions resulting from the impact of their condition, and the background care received by participants in ASCEND and ASCEND-Peds provided by the company at clarification (question A17) appeared to be consistent with this. The EAG noted some differences in background care between the trial arms in ASCEND but considered that these likely due to the small absolute numbers of participants.

3.2.2.4. Comparator

Only one of the trials (ASCEND) used a comparator, which was a matched placebo. The EAG highlighted that the lack of a comparator in the remaining three trials seriously increased the risk of bias in these studies (see Section 3.2.2.6).

3.2.2.5. Outcomes

The outcomes measured in the four trials, and where these data can be found in the CS, are summarised in Table 12. Key outcomes specified in the NICE scope were available for all four

studies, although data from DFI13412 and LTS13632 were primarily used to supplement safety data from ASCEND and ASCEND-Peds.

The company conducted subgroup analyses on data for two outcomes in ASCEND: for DLco, the company compared the outcome according to baseline DLco severity, baseline ALT or AST abnormality, and total bilirubin abnormality; for spleen volume, the company compared the outcome according to baseline ALT or AST abnormality, total bilirubin abnormality, spleen severity, and the presence of portal hypertension. At clarification (question A25) the EAG requested that the company provide a rationale for why these subgroups were selected over other prognostic or demographic markers. The company did not provide a rationale for the selected subgroups, instead stating that the subgroup analyses were requested by the FDA without explanation. Expert advice to the EAG was that these subgroups were appropriate for consideration and provided some indication of whether the effect of treatment may vary according to disease severity and organ damage. However, a broader range of analyses may have been informative as there was no universally accepted measure of disease severity and there are other markers of organ damage. Furthermore, clinical advice was that baseline severity may affect response to some outcomes over others, and therefore subgroup analyses across a broader range of outcomes may have been more informative.

Table 12: Map of the location of outcomes data in the company submission

Outcome	ASCEND	ACSEND-Peds	DFI13412	LTS13632
% change in DLco	CS Document B, Table 22, Figure 6, Figure 13, Figure 14	CS Document B, Table 29, Figure 10	Not reported in CS	CS Document B, Figure 19
% change in spleen volume	CS Document B, Table 23, Figure 7, Figure 15, Figure 16	CS Document B, Table 30, Figure 11	CS Document B, Table 34, CS Appendix M.1.4	CS Document B, Figure 17
% change in liver volume	CS Document B, Table 24, Figure 8	CS Document B, Table 31, Figure 12	CS Document B, Table 34, CS Appendix M.1.4	CS Document B, Figure 18
% change in platelet counts	CS Document B, Table 25, Figure 9	Not reported	Not reported in CS	CS Document B.2.11
% change in liver function (ALT and AST)	CS Document B, Table 26, CS Appendix N.6	CS Document B, Table 32, CS Appendix N.6	Not reported in CS	CS Appendix O.1
% change in lipid profile (cholesterol and triglycerides)	CS Document B, Table 26, Appendix N.6	CS Document B, Table 32, CS Appendix N.6	Not reported in CS	Not reported in CS
% change in Pulmonary function (FVC, FEV1, lung capacity, and O2 uptake during exercise)	CS Document B, Table 26, Appendix N.6	CS Document B, Table 32, CS Appendix N.6	Not reported in CS	Not reported in CS
Biomarker reduction (chitotriosidase, angiotensin enzyme, CCL18, safety biomarkers)	CS Document B, Table 26, CS Appendix N.6 and N.8	CS Document B, Table 32, CS Appendix N.6 and N.8	Not reported in CS	CS Appendix O.5
HRQoL	CS Document B, Tables 27-28; CS Appendix N.7	CS Document B, Table 33	Not reported in CS	CS Appendix O.6
Adverse effects	CS Document B, Tables 35 and 36	CS Document B, Tables 37 and 38	CS Document B, Table 34, CS Appendix M.1.6	CS Document B, Table 41
Neurological and physical observations and imaging	CS Appendix N.1-N.4	CS Appendix N.1-N.4	Not reported in CS	CS Appendix O.3 and O.4
Paediatric physical outcomes (height, weight, puberty onset)	Not applicable	CS Document B, Table 32 CS Appendix N.5 and N.6	Not applicable	CS Appendix O.2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCL18, chemokine ligand 18; CS, company submission; DLco, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume; FVC, forced vital capacity; HRQoL, health-related quality of life;

In response to clarification (question A18), the company reported that the availability of follow-up data in ASCEND varied across outcomes due to participant non-attendance or technical faults with certain assessments. The company further reported the number of participants available at follow-up for some outcomes (shown in Table 13). These data showed that attrition of ≥30% was present for key clinical outcomes in the olipudase alfa arm at year two (spleen volume, DLco, liver volume, platelet count), with attrition particularly high (50%) for DLco. The EAG considered this to be a high rate of attrition for these key outcomes, and considered this issue in its appraisal of the quality of the trial (see Section 3.2.2.6).

Table 13: Number of participants available at follow-up timepoints in ASCEND

Outcome	Follow-up timepoint	Number of participants available			
		Placebo/olipudase alfa N=18		**Olipudase alfa/olipudase alfa N=20**	
% predicted DL_{CO}	Year 1	17	94.4%	17	85.0%
	Year 2	10	55.6%	10	50.0%
Spleen volume (MN)	Year 1	17	94.4%	18	90.0%
	Year 2	11	61.1%	14	70.0%
Liver volume (MN)	Year 1	17	94.4%	17	85.0%
	Year 2	11	61.1%	14	70.0%
Platelet count (10^9/L)	Year 1	16	88.9%	18	90.0%
	Year 2	15	83.3%	13	65.0%
Lung HRCT ground glass appearance score	Year 1	17	94.4%	18	90.0%
	Year 2	14	77.8%	16	80.0%
ALT (IU/L)	Year 1	16	88.9%	18	90.0%
	Year 2	15	83.3%	12	60.0%
HDL cholesterol (mg/dL)	Year 1	16	88.9%	18	90.0%
	Year 2	14	77.8%	12	60.0%
LDL cholesterol (mg/dL)	Year 1	15	83.3%	18	90.0%
	Year 2	14	77.8%	12	60.0%

Source: Company response to clarification A18. The table was amended by the EAG to show the percentage of participants available.

Abbreviations: ALT, alanine aminotransferase; DLco, diffusing capacity of carbon monoxide; HDL, high-density lipoprotein; HRCT, high-resolution computed tomograph; LDL, ow-density lipoprotein; MN, multiples of normal

3.2.2.6. Critical appraisal of the design of the studies

The company usedthe Cochrane risk-of-bias (RoB) tool version 2.0 to assess the quality of ASCEND, and the ROBINS-I to assess the remaining three olipudase alfa studies. Three additional single-arm studies used to inform inputs in the company's economic analysis were also assessed using the ROBINS-I: Bembi 1992 (amniotic epithelial cell implantation), [23] Liu 2019 (liver transplantation) [24] and NCT00410566 (olipudase alfa). [25]

The EAG broadly agreed with the company's assessment that ASCEND was at a low risk of bias as assessed using the Cochrane RoB 2.0 (CS Appendix D.1.3, Table 2). [26] However, the EAG highlighted two additional considerations:

- At clarification (question A9), the company confirmed that overall quality appraisal ratings were considered relevant to all trial outcomes. However, as noted in Section 3.2.2.5, there was a high rate of missing participants at 2-year follow-up for several key clinical outcomes (attrition ≥30% in the olipudase alfa arm at year 2 for spleen volume, DLco, liver volume and platelet count; attrition 50% for DLco.). The company did not consider this in their quality appraisal. Based on the Cochrane risk of bias tool v2, the EAG considered these outcomes to be at severe risk of bias. This rating is based on the view that it is plausible that missingness in these outcomes could relate to the outcome, for example high rates of participant non-attendance could be due to the effect of treatment. The severe rating remains even though the EAG did not have sufficient information to judge whether this was likely.

- There were no baseline data provided for ASCEND on the number of participants with type A/B ASMD in each of the trial arms. It is, therefore, unclear whether an imbalance between trial arms exists in this baseline characteristic.

With regard to the single-arm studies, the EAG considered that the company's assessment that these (ASCEND-Peds, DFI13412 and LTS13632) were at a low risk of bias was incorrect. This was largely because the assessments did not fully account for the lack of a comparator in these trials. The ROBINS-I tool[27] used to assess these studies was initially developed to appraise the quality of non-randomised comparative trials rather than single-arm studies. It is, therefore, not possible for the trial analyses to fully account for confounders in a way required by the tool criteria. Furthermore, the EAG did not consider that the company had provided sufficient justification for its statements that ASCEND-Peds was representative of the target patient

population, accounted for confounding factors, and that the findings were sufficiently precise. Data available to the EAG suggested that these statements were questionable.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Baseline characteristics of participants in the included trials

The CS presented baseline characteristics of participants included in ASCEND, ASCEND-Peds, and DFI13412 (see Table 12). Baseline data for LTS13631 were not presented in the CS (participants were those included in ASCEND-Peds and DFI13412). Table 14 summarises the key baseline data from the four trials. Demographic data presented in the CS from the olipudase alfa trials were judged to be generally consistent with the population in UK clinical practice (as far as it is possible to ascertain for such a rare condition). However, the EAG identified several considerations:

- As noted in Section 3.2.2.2, a breakdown of participants by ASMD subtype was not presented for any of the trials. Although the SmPC reported that 25% of participants in ASCEND and 40% in ASCEND-Peds exhibited neurological symptoms consistent with type A/B ASMD, these rates were not provided separately for the trial arms in ASCEND. The EAG could not, therefore, determine whether ASMD type was balanced between the trial arms.

- Baseline weight of participants in the trials was lower than would be expected for the general population in England and Wales. For ASCEND, weight data for trial participants was reported in the CS but were not available in the CSR and could not be verified. Clinical expert advice indicated that although some people with ASMD are slightly smaller than the average population, this would not necessarily lead to a major difference in weight across the population. With successful treatment, growth may be expected to be comparable to the general population.

- Baseline age at first infusion reported for the paediatric and adult populations in LTS13631 were not consistent with those given for ASCEND-Peds and DFI13412 (see Table 14). This may simply be due to rounding errors.

- Age at diagnosis was higher in ASCEND than in the adult population in DFI13412 (see Table 14). Clinical expert advice to the EAG indicated that a lower age at diagnosis may be

expected with time (due to improvements in understanding of the condition and cascade testing of asymptomatic siblings).

- In ASCEND, when compared with controls, a numerically higher proportion of participants in the olipudase alfa arm had severe splenomegaly (>15 MN) at baseline (27.8% versus 16.7%), although this is likely due to the small numbers of participants involved (n=5 versus n=3).

Table 14: Key baseline characteristics for the included trials

	ASCEND		**ASCEND-Peds**	**DFI13412**	**LTS13631**	
	Olipudase alfa N=18	Placebo N=18	N=20	N=5	Paediatric N=20	Adult N=5
Age, mean years (SD), range	36.2 (12.7), 18.8 – 59.9	33.5 (17.1), 18.6 – 65.9	8.2 (4.4), 1.5 – 17.5	32.6 (9.4), 23 - 48	[redacted]	[redacted]
Weight (kg), mean (SD)	67.4 (14.1)	61.6 (13.4)	23.4 (10.8)	[redacted]	As per ASCEND-Peds	As per DFI13412
Sex, n (%)	Male 9 (50%) Female 9 (50%)	Male 5 (28%) Female 13 (72%)	Male 10 (50%) Female 10 (50%)	Male 3 (60.0%) Female 2 (40.0%)	As per ASCEND-Peds	As per DFI13412
Race, n (%)	White 16 (89%) Asian 1 (6%) Other 1 (6%)	White 16 (89%) Asian 1 (6%) Other 1 (6%)	White 17 (85%) SE Asian 2 (10%) Other 1 (5%)	White 5 (100%)	As per ASCEND-Peds	As per DFI13412
Ethnicity, n (%)	Not Hispanic or Latino 12 (67%) Hispanic or Latino 5 (28%) NR 1 (6%)	Not Hispanic or Latino 12 (67%) Hispanic or Latino 6 (33%)	Not Hispanic or Latino 19 (95%) Hispanic or Latino 1 (5%)	Not Hispanic or Latino [redacted] Hispanic or Latino [redacted]	As per ASCEND-Peds	As per DFI13412
Age at ASMD diagnosis, mean years (SD), range	21.4 (20.3), [redacted]	14.6 (16.1), [redacted]	2.5 (2.5), [redacted]	7.2 (5.0), [redacted]	As per ASCEND-Peds	As per DFI13412
Severe splenomegaly (>15 MN), n (%)	5 (27.8%)	3 (16.7%)	12 (60%)	[redacted]	NR	NR
Severely reduced DLco (<40%), n (%)	3 (16.7%)	4 (22.2%)	1 (11.1%)	[redacted]	NR	NR

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity for carbon monoxide; kg, kilogram; MN, multiples of normal; NR, not reported; SD, standard deviation. Source: Trial CSRs[10,11,13,14]; Wasserstein et al. 2022[15]

3.2.3.2. Clinical effectiveness results

Percentage change in DLco

Participants who received olipudase alfa in all included trials showed an overall improvement in lung diffusion capacity. By year one all groups showed a mean improvement of >20%, and there was an apparent trend for DLco to increase over time (though longer follow-up points included small numbers of participants, DLco exceeded 30% for adults and 40% for children). In comparison, no change in DLco was evident for adults who received placebo. The EAG therefore concluded that olipudase alfa had an overall clear clinical benefit in improving lung diffusion capacity compared to BSC.

A remaining uncertainty for the EAG was the number of participants in the trials who did not respond to treatment or did not achieve a clinically significant improvement in DLco (defined by the company as an improvement ≥15%). The EAG understood that the effect of treatment may vary across the population, for example due to baseline symptom severity or time since diagnosis (as this may affect the extent to which organs have experienced irreversible change). The company conducted a responder analysis showing that only 5/18 (27.8%) of adult participants in ASCEND had shown a clinically significant improvement in DLco by year one (the group LS mean change was 21.97 (95% CI 15.18, 28.76)). While mean improvements in DLco continued to improve over the trial follow-ups, it is uncertain whether this effect was shown in all participants as the company conducted no further responder analyses.

Percentage change in spleen volume

Participants who received olipudase alfa across all the included trials showed a mean reduction in spleen volume. After 6-months of treatment, mean reductions in spleen volume were greater than 25% in all groups, and reductions were stable or reduced further over following timepoints. In comparison, there was no change in spleen volume for adult participants in ASCEND who received placebo. Almost all adult participants (described in the CS as 94.4%, which the EAG assumed was a typo for 16/17 participants [94.1%]) in ASCEND showed a clinically meaningful reduction in spleen volume by 12-months (specified by the company as a change ≥15%). Absolute spleen volume at the longest follow-up stabilised for both adult and child participants at approximately six multiples of normal. Based on the trend in the data showed in Figure 1 below (taken from the CS, p.150), the EAG considered it plausible that spleen volume would remain at this level, at least in the months immediately following the end of trial follow-up. If spleen volume was to remain elevated at this level for the rest of a person's life, clinical experts to the EAG considered that this would nevertheless offer a meaningful clinical benefit to patients' functioning and mental wellbeing.

Figure 1: Spleen volume in long-term follow-up

Percentage change in liver volume

Participants who received olipudase alfa in all included trials showed a mean reduction in liver volume. Mean reductions exceeded 20% following 6-months of treatment, and continued to improve over subsequent follow-up timepoints (see Figure 2 taken from the CS p.151). In contrast, no change in liver volume was evident for participants who received placebo. No responder analysis was conducted by the company to determine how many participants receiving olipudase alfa experienced a clinically meaningful reduction in liver volume.

Figure 2: Liver volume in long-term follow-up

Percentage change in platelet counts

Mean platelet counts increased in adults receiving olipudase alfa in ASCEND, while there was no change amongst participants receiving placebo. There were no data for platelet count for children in ASCEND-Peds, though overall platelet counts for children continuing into LTS13632 did show an increase (N=5). A figure of change in platelet counts in both adult and paediatric participants in ASCEND and ASCEND-Peds was provided in appendices to the LTS13632 trial CSR. [14] The figure showed that adult platelet counts remained fairly stable until final follow-up, though in children mean platelet counts showed high variance and appeared to reduce back towards baseline measurements in the last few months of follow-up. Given the small sample size available in the long-term follow-up, and the increased stability of platelet counts in the

adult population, the EAG were hesitant to conclude that the effect of olipudase alfa on platelet count reduced after four-years. However, the EAG considered that the effect of olipudase alfa for platelet counts may vary across paediatric participants for unclear reasons, and that further data collection is needed to reduce uncertainties in the effect of treatment beyond four years.

Additional efficacy outcomes

Additional efficacy outcomes measured in ASCEND suggested that participants receiving olipudase alfa also showed improved liver function (ALT and AST), reduced cholesterol and triglyceride, and improved pulmonary function (FVC and O^2 uptake during exercise). Data for disease markers showed [redacted] in chitotriosidase, there was also a [redacted] angiotensin enzyme and CCL18, though [redacted]

Positive findings were also reported for additional outcomes measured in ASCEND-Peds, though there was no comparison group and variance was high, particularly in age-specific groups where sample sizes were small. Improvements were shown in liver function (ALT and AST), pulmonary function (FVC), cholesterol and triglyceride, and exercise capacity. Data for disease markers also showed [redacted].

The EAG did not have validated thresholds to determine whether changes in the above outcomes in the adult and paediatric populations were clinically meaningful. Clinical advice to the EAG was that in the paediatric population, these effects may lead to overall improved functioning, which would have benefits for children's school life and wellbeing.

Health-related quality of life

In ASCEND, HRQoL at baseline for each treatment arm was below the general population norms for all subscales. At six- and 12-months, there was no difference between treatment arms in HRQoL measured either by the EQ-5D or the SF-36. The company argued that these findings were inconsistent with improvements in clinical outcomes and with statements by participants who received olipudase alfa and described benefits of treatments for fatigue, productivity and pain. The EAG agreed that the lack of a change in HRQoL seemed inconsistent with improvements in clinical outcomes such as reductions in splenomegaly and platelet count, which may be expected to impact on fatigue. The company argued that clinical benefits of olipudase alfa improve HRQoL through reductions in fatigue and pain, and through increased ability to function; however, the EAG noted that measures selected by the company to assess

these outcomes showed no difference between treatment arms at up to one year follow-up. The EAG considered it possible that while olipudase alfa may have clinical health benefits for adult participants, the impact of these changes on their overall HRQoL had not been demonstrated.

In ASCEND-Peds, participants exhibited an improvement in HRQoL that in many cases exceeded established minimally important differences (MIDs) for the PedsQL generic outcome.[28,29] For children aged 5-7 years' old the effect was not present until after one year of treatment, and mean improvement in HRQoL hovered close to the MID threshold. However, children between eight and 18-years of age showed mean improvements in HRQoL above the MID by six-months, with a further increase by 12-months. Given the company's argument that generic HRQoL measures are insensitive to change in the adult population, at clarification (QA26) the EAG asked the company if they had a rationale for why this may be different for the paediatric population. The company responded that they considered generic HRQoL in both adults and paediatric patients to be insensitive, and that without a comparator arm in ASCEND-Peds they were unable to conclude whether there is a real effect of treatment on HRQoL. The EAG accepted that there was no control arm and therefore it was not possible to ascribe the improvements in HRQoL shown in paediatric participants to the benefits of olipudase alfa. The EAG also noted that HRQoL measures completed within open-label trials present a significant risk of bias (see Section 3.2.2.6). However, the EAG nevertheless considered these data to suggest that improvements in clinical outcomes shown in ASCEND-Peds may have meaningful benefits in HRQoL, particularly for children over 5-years of age. This was consistent with advice from experts to the EAG, who suggested that improvements in clinical outcomes would be expected to improve children's functioning at school and home.

Subgroup analyses

Subgroup analyses comparing outcomes between those with severe DLco and spleen volume at baseline were highly limited due to the small number of participants in ASCEND who were considered to have severe symptoms (DLco: three and four participants in the olipudase alfa and placebo arms, respectively; spleen volume: five and three participants in the olipudase alfa and placebo arms, respectively). Other analyses had a more balanced sample size, though were still limited by small samples. Subgroup analyses did not show a clear difference in effect based on baseline severity in the outcome or other subgroup categories.

Adverse effects

The CS primarily reported adverse reactions to olipudase alfa that occurred in the ASCEND and ASCEND-Peds trials (CS B.2.10). Adverse events data were also provided from LTS13632 (CS B.2.11, Table 41) and DFI13412 (CS B.2.6, Table 34). The EAG have checked the data provided in the CS against the CSRs for the four studies.

Treatment-emergent adverse events (TEAEs)

Overviews of the safety data from ASCENDS and ASCEND-Peds were provided in CS B.2.10, Tables 35 and 37 respectively, with summaries of the most common TEAEs provided in CS B.2.10, Tables 36 and 38 respectively.

CS B.2.10 stated that all participants in both the ASCEND safety population and the ASCEND-Peds safety population experienced at least one TEAE. In ASCEND, treatment-related TEAEs were more common in the olipudase alfa group than in the placebo group (n=12 (67%)) versus n=6 (33%) respectively), but serious TEAEs were similar across the two groups and none were thought to be related to the study drug. The EAG noted that this applied to the primary analysis period for the study, and that the ASCEND CSR[10] specified that one participant (previously in the placebo group but switched to olipudase alfa as part of the study extension) experienced a serious TEAE of extrasystoles that was related to the study drug. This participant had pre-existing cardiomyopathy. In ASCEND-Peds, five participants experienced 12 serious adverse events. Five of these (in three participants) were treatment-related serious adverse events. These all occurred in the youngest study cohort (infant/early child).

For brevity, the EAG consolidated the data on the most commonly observed adverse events observed in ASCEND (primary analysis period) and ASCEND-Peds (see Table 15). For a breakdown of the ASCEND-Peds results by age category, refer to CS B.2.10 Table 38. In ASCEND, headache was the most frequently observed TEAE during the primary analysis period with infections and infestations being the most commonly observed organ class of adverse events. In ASCEND-Peds pyrexia occurred in more participants than any other TEAE during the treatment period.

Table 15: Summary of the most common treatment-emergent adverse events in ASCEND PAP and ASCEND-Peds

	ASCEND				**ASCEND-Peds**	
	N (%)	Events	N (%)	Events	N (%)	Events
Any class†	18 (100%)	270	18 (100%)	242	20 (100%)	798
Pyrexia	--	--	--	--	15 (75.0%)	56
Contusion	--	--	--	--	6 (30.0%)	88
Scratch	--	--	--	--	4 (20.0%)	44
Infections and infestations	15 (83.3%)	36	15 (83.3%)	45	--	--
Nasopharyngitis	6 (33.3%)	8	8 (44.4%)	18	11 (55.0%)	28
Upper RTI	4 (22.2%)	6	6 (33.3%)	8	8 (40.0%)	17
Nervous system disorders	9 (50.0%)	40	13 (72.2%)	71	--	--
Headache	8 (44.4%)	32	12 (66.7%)	64	8 (40.0%)	38
Musculoskeletal and connective tissue disorders	11 (61.1%)	26	12 (66.7%)	23	--	--
Arthralgia	3 (16.7%)	3	4 (22.2%)	10	--	--
Respiratory, thoracic, and mediastinal	5 (27.8%)	15	9 (50.0%)	14	--	--
Cough	2 (11.1%)	3	5 (27.8%)	5	14 (70.0%)	31
Nasal congestion	--	--	--	--	6 (30.0%)	18
Epistaxis	--	--	--	--	4 (20.0%)	17
Urticaria	--	--	--	--	4 (20.0%)	24
Rash	--	--	--	--	3 (30.0%)	17
Vomiting	--	--	--	--	12 (60.0%)	38
Diarrhea	--	--	--	--	11 (55.0%)	22
Stomach pain	--	--	--	--	6 (30.0%)	20

Abbreviations: PAP, primary analysis period; PT, preferred term; RTI, respiratory tract infection; SOC, system organ class

† Includes treatment-emergent adverse events with percentages of events >= 2% and number of patients >= 2; --Not reported in the CS for this study. Source: CS B.2.10, Table 36 and Table 38

CS B.2.6, Table 34 reported that there were no serious TEAEs in DFI13412, with 97% of TEAEs assessed as mild, which was consistent with the data in the CSR. The CSR specified that the

most common TEAEs in DFI13412 were headache (n = 18), arthralgia (n = 16), abdominal pain (n = 14), and nausea (n = 14) and that there were six moderate events in two participants (pyrexia, abdominal gas pain, spleen pain, nausea, headache, and migraine). LTS13632 included the five participants from DFI13412, and separate longer-term data from DFI13412 were provided in CS B.2.11, Table 41.

For the LTS13632 study as a whole, CS B.2.11, Table 41 reported that [redacted] (99.7%) of TEAEs (in the adult and paediatric population) were of mild or moderate severity (data up until 78 months.

[redacted]

[redacted] Details of these serious TEAEs were not provided in the CS, but were given in the CSR:

[redacted]

Adverse events of special interest

In ASCEND, the percentage of patients with a protocol defined infusion associated reaction (IAR) was higher in the olipudase alfa group compared with the placebo group (44.4% and 27.8%, respectively; CS B.2.10, Table 35). CS B.2.10, Table 37 states that 55% of the participants in ASCEND-Peds had a protocol defined IAR. The CSR for LTS13632 reported that 80% of adult and 65% of paediatric participants experienced a protocol-defined IAR, with the most common protocol-defined IAR events being headache, nausea, and arthralgia in adults and urticaria, pyrexia, and vomiting in children. These events were highest during year one of treatment and declined gradually. The CSR for DFI13412 reported that 80% of participants experienced an IAR (55 events in four participants), with the most commonly reported IAR events being headache, nausea, abdominal pain, and musculoskeletal pain.

CS B.2.10, Table 35 reported that there were no treatment-emergent pregnancies or symptomatic overdoses in either group of the ASCEND study or in the ASCEND-Peds study. The CSR for LTS13632 reported that there were no pregnancies or symptomatic overdoses during the study.

Discontinuations and dose reductions

The CS reported that there were no discontinuations or withdrawals due to TEAEs in any of the four studies reporting adverse events data (ASCEND, ASCEND-Peds, DFI13412 and LTS13632). Following clarification, the company confirmed that there were no discontinuations due to the study drug in ASCEND (of the two discontinuations in people receiving olipudase alfa, [redacted]).

CS B.2.10 stated that three out of the 18 participants in each safety group of ASCEND experienced a TEAE that lead to a temporary interruption in treatment. In ASCEND-Peds, two of the 20 participants experienced an event that led to the visit being stopped (but then continued and completed the study) and three participants experienced 25 events where infusions had to be paused and resolved.

CS B.2.10 also reported that, in ASCEND, one participant in the olipudase alfa group experienced a TEAE (alanine aminotransferase increased) that led to a temporary dose reduction and in ASCEND-Peds, there were eleven dose reduction events. For LTS13632, CS B.2.11, Table 41 specified that there were [redacted] These data were consistent with the CSRs for these studies.

Deaths

CS B.2.10 stated that no deaths occurred in the ASCEND or ASCEND-Peds trials, CS B.2.6, Table 34 stated that there were no deaths in DFI13412, and CS B.2.11, Table 41 reported no TEAEs leading to death in LTS13632. This was consistent with the CSRs for these studies.

Safety biomarkers

Safety biomarker data (ceramide levels in plasma, calcitonin, high sensitivity C-reactive protein (hsCRP), ferritin, IL-6, IL-8, iron and cardiac troponin) were provided in CS Appendix N.8, Tables 30 and 31 for ASCEND and ASCEND-Peds respectively.

For ASCEND, the company reported that mean hsCRP, iron, ferritin, calcitonin, cardiac Troponin I, and IL-8 [redacted] In ASCEND-Peds there were three participants who experienced acute phase reactions [redacted]

[redacted]The company also noted that, at 52-weeks in ASCEND, plasma ceramide was increased in the olipudase alfa arm compared with the placebo arm at both 24- and 48-hours post-infusion. In the ASCEND-Peds trial, there was an increase in plasma-ceramide from pre-infusion to 24 hours and 48 hours post-infusion, but there was no control group in this study for comparison.

3.3. Critique of the indirect comparison and/or multiple treatment comparison

No other comparators to olipudase alfa were identified, and therefore no indirect comparison was feasible.

3.4. Additional work on clinical effectiveness undertaken by the EAG

The EAG conducted searches of Ovid MEDLINE and Embase (17th August 2022) to confirm that the company's literature searches had identified all relevant studies. The MEDLINE search used the exploded subject heading for Niemann-Pick Diseases to include the relevant MeSH term for Niemann-Pick Disease, Type B/, but this search did not retrieve any additional studies. The Embase search tested the impact of the use of 'Article' or 'Article in Press' limits (full search strategies are available in Appendix A). This search identified 19 conference abstracts that were not retrieved by company searches, however, the EAG was satisfied that these abstracts did not provide any further information, and that all relevant studies had been included.

The EAG also noted inconsistent use of terms in grey literature searches for conference abstracts. The EAG completed additional searches of listed sources with missing terms and did not identify any further studies.

3.5. Conclusions of the clinical effectiveness section

Based on the evidence presented by the company, the EAG concluded that olipudase alfa resulted in benefit to clinical outcomes for children and adults with ASMD types B and A/B. These benefits were most notable for outcomes related to splenomegaly and hepatomegaly, but benefits were also demonstrated for respiratory function and platelet count. The benefits of olipudase alfa on clinical outcomes were not reflected in similar benefits in HRQoL and functioning, though clinical advice to the EAG was that the reported change in clinical outcomes would nevertheless have a meaningful benefit to people's functioning and quality of life. The EAG considered it plausible that measures of quality of life and functioning may not be sensitive to change resulting from improvement in the clinical outcomes of ASMD types B and A/B,

though the company did not present evidence to substantiate this. Clinical advice to the EAG was that as ASMD types B and A/B are heterogeneous conditions, the magnitude of benefits of treatment to some outcomes may vary across the target population. The adverse event profile of olipudase alfa appeared acceptable, though the EAG highlighted a high rate of adverse events particularly in very young children treated in ASCEND-Peds. Clinical advice to the EAG was that this may be due to the tapering regimen used in the trial and suggested that more experience with administering olipudase alfa at a slower rate may reduce the number of AEs in this group.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted SLRs to identify existing cost-effectiveness evidence, health-related quality of life (HRQoL) evidence, and cost and resource use evidence for olipudase alfa and comparator interventions. A summary of the EAG's critique of the methods implemented by the company to identify relevant cost effectiveness, HRQoL and healthcare resource use and costs evidence is presented in Table 16. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 16. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence, HRQoL and health care resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	CS Appendix D.1.1	The EAG was broadly satisfied that searches identified all relevant literature, however, the EAG noted the following limitations: the subject heading for Niemann-Pick Diseases was not exploded to include narrower terms in the MeSH hierarchy; and the use of 'Article' and 'Article in Press' limits excluded conference abstracts from Embase search results. The EAG conducted additional searches (see Section 3.4.1) and did not identify further studies.
Inclusion criteria	CS Appendix D.1.1	No issues identified. Health economic evaluations, clinical trials and observational studies were included. The company excluded case reports, non-systematic reviews, pre-clinical studies, non-medical intervention studies, commentary and letters.
Screening	CS Appendices D.1.1, G, H and I	No issues identified. Two independent investigators trained in the objectives of the review screened abstracts and full-text papers to identify relevant studies based on the inclusion/exclusion criteria. Any disagreements were resolved by a third reviewer.
Data extraction	CS Appendices D.1.1, G, H and I	Extraction methods were not explicitly defined, however the company stated that the SLR was conducted in accordance with the high-quality standards required by NICE and reported in accordance with the standards defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
QA of included studies	CS Appendices D.1.1, G, H and I	No economic evaluations of treatments for ASMD were identified in the SLR. No utility values were identified in the SLR. For healthcare resource use and costs, one

		study was identified (SPHINGO-302).[30] The EAG noted that this was not used in the economic analysis, as annual frequencies of resource use were reported to have been derived from a retrospective cohort analysis conducted using IQVIA Open Claims. Full details of the company's SLR methods can be found in appendices G to I.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment; SLR, systematic literature review

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 17: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate and captured the health benefit to patients. Carer disutility was incorporated into the company's model.
Perspective on costs	NHS and PSS	NHS and PSS as appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis. The analysis contained a single comparator and therefore a fully incremental analysis was not required.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model incorporated a lifetime horizon (100-years) for both the paediatric and adult populations. The EAG considered this to be sufficiently long enough to capture important differences in costs and benefits between the treatment arms.
Synthesis of evidence on health effects	Based on systematic review	Modelled transition probabilities used in the economic analysis for both olipudase alfa and BSC treatment arms were estimated from the following key clinical data sources: • ASCEND • ASCEND-peds • SPHINGO-100 • DF131412 • LTS13632

Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs were used as appropriate. The company collected HRQoL data directly from participants in the ASCEND and ASCEND-Peds trials, however data from these trials were not used in the company's base case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utilities for both adult and paediatric patients were derived from a vignette study. Carer disutility was derived from published literature and assumption.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The vignette study was based on [redacted] members of the [redacted] general population. The study appropriately elicited preferences using [redacted]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As part of their base case, the company provided results with unweighted QALYs, which the EAG deemed appropriate. However the company also presented QALY weighted results. The EAG had concerns about the appropriateness of applying QALY weighting, and considered that the NICE committee should determine whether the application of QALY weighting was appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use and costs were largely based on NHS reference costs (2019/20), as appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs were discounted at 3.5% and benefits were discounted at 1.5%. The EAG noted that a differential discount rate is not standard practice.

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal; TTO, time-trade-off

4.2.2. Model structure

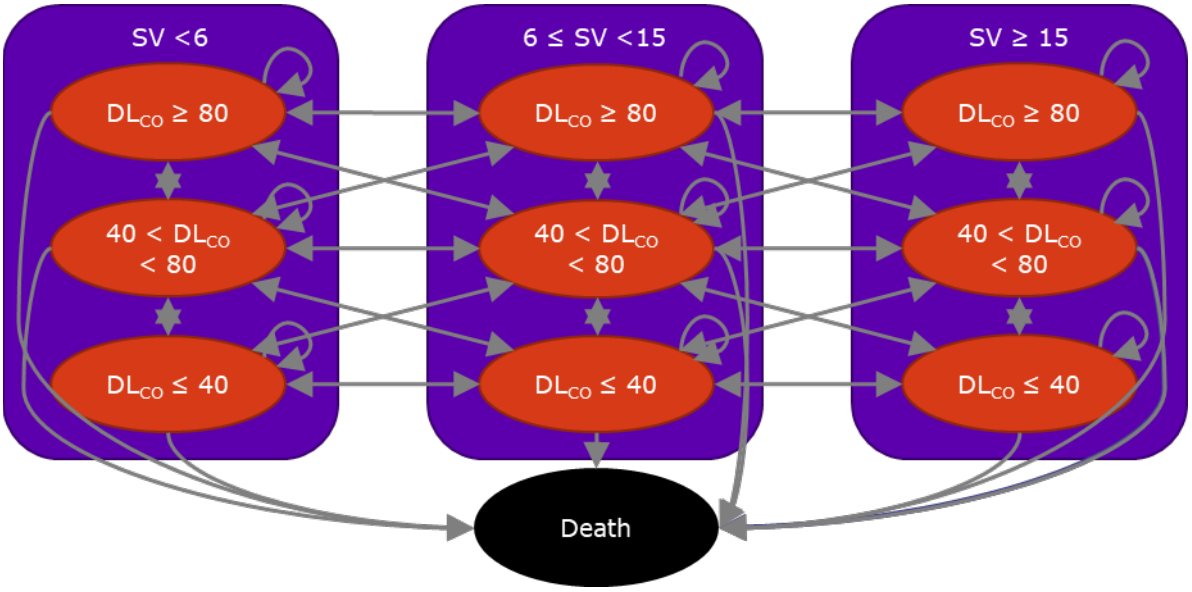
The company presented a cohort-based Markov model whereby patients moved through a series of health states associated with specific costs and utilities. The company defined health states via a combination of patients' spleen volume (splenomegaly) and lung capacity to diffuse carbon monoxide (DLco). The EAG noted that due to the combined nature of the health states, disease severity health states cannot be categorised explicitly according to mild, moderate or severe. However, when considered individually, the model implicitly assumes three levels of spleen volume severity, for example SV <6 MN could be considered mild, SV 6-15 MN as moderate and ≥15 MN as severe. Similarly, the model assumed there to be three levels of

DLco, defined as mild reduction (≥ 80%), moderate reduction (40-80%) and severe reduction (≤40%).

Defining health states via a combination of patients' spleen volume and DLco resulted in nine modelled health states (see Figure 3 below). Patients entered the model according to their baseline distribution in the ASCEND or ASCEND-Peds studies (see Table 19 below). The same model structure was used to model both the adult and paediatric cohort. As outlined in Figure 3, patients could remain in each health state, could improve (i.e. experience a reduced spleen volume and/or increased DLco), or could get worse (i.e. experience an increase in spleen volume and/or decreased DLco). Death could occur in any health state.

The clinical data used to derive transition probabilities in the model were derived from four clinical studies, and was further guided by company assumptions. These are discussed further in Section 4.2.6.

Figure 3: Model structure



On p.165 of the CS, the company stated that spleen volume (splenomegaly) and the lung's capacity to diffuse carbon monoxide (DLco) were selected to inform model health states "*as they are important predictors of disease progression, with a severe impact on the level of disability and QoL of patients, and thus are the primary efficacy endpoints from the ASCEND trial".* The company further stated that the model structure was validated by UK clinical experts with experience in treating ASMD. The EAG noted the lack of cost effectiveness models for ASMD and therefore sought clinical opinion to determine the appropriateness of the model

structure and whether splenomegaly and lung function should be used to inform modelled health states. Clinical opinion to the EAG was somewhat mixed, however, on balance experts considered that both spleen volume and DLco may be reasonable markers of overall disease severity. Impairment in liver functioning was also suggested as a potential indicator of general patient health, though it was noted that liver functioning may also be affected by other conditions, and that impairment in liver function due to ASMD was likely to coincide with spleen enlargement. The EAG noted that two published papers by Jones et al (2020) and Eskes et al (2020), which reviewed prognostic markers of mortality, reported that both spleen volume and DLco were predictors of long term health outcomes.

Overall the EAG considered that the company's approach of defining health states according to spleen volume and DLco was likely to be appropriate, however, the lack of absolute consensus amongst clinicians shold be noted.

4.2.3. Population

Modelled baseline characteristics for paediatric and adult patients are outlined in Table 18, and the distribution of patients across modelled health states is outlined in Table 19. These data were derived from the pivotal studies ASCEND and ASCEND-Peds. The EAG noted that weight for both adults and children was low relative to the general population. Clinical experts to the EAG were unable to clarify the anticipated weight of the target population, though suggested that some children with ASMD types B and A/B may exhibit a lower weight than the general population. However, this would not be expected to be the case in children treated successfully for their condition. Clinical experts were unable to comment on whether adult weight varied from the general population mean, and if so, how this would change with effective treatment.

Table 18: Patient baseline characteristics

	ASCEND-Peds (paediatrics)	**ASCEND (adults)**
Starting age	8 years	34 years
Weight	20.53 kg	64.52 kg

Abbreviations: kg, kilogram

Table 19: **Baseline distribution of patients in the model**

Health state	ASCEND-Peds (paediatrics)	ASCEND (adults)
DL_{CO} ≥80%	0%	0%
DL_{CO} 40 – 80%	88.9%	80.6%
DL_{CO} ≤40%	11.1%	19.4%
Spleen volume <6 MN	0%	0%
Spleen volume 6–15 MN	40%	77.8%
Spleen volume ≥15 MN	60%	22.2%

Abbreviations: DLco, diffusing capacity for carbon monoxide; MN, multiples of normal

Based on one-way sensitivity analysis provided by the company, results were highly sensitive to variation in patient weight and moderately sensitive to patients' starting age (see p.220 and p.221 of the CS). The EAG noted that for adult patients, weight was assumed to be constant over the time horizon. For paediatric patients, the company derived the z-score function based on data from the SPHINGO-100 trial (for children at 8 years; see p.168 in the CS). The EAG considered there to be uncertainty surrounding the company's approach to modelling patient weight in both populations:

- The company used a z-score function to estimate the change in paediatric weight over time (see p.168 and p.169 of the CS). The z-score function (which estimates the change in paediatric weight over time) was applied to weight from UK growth charts. The EAG noted that weights from the growth chart appeared low compared to patient weight data from Health Survey for England (2019).[4] In order to explore uncertainty in patient weight, the EAG conducted a scenario analysis that used patient weight from Health Survey for England. See Section 6.2 for results.

- The patient weight for adults appeared somewhat low relative to mean UK weight and the mean weight estimated by the company for the paediatric equation at 18 years (62kg). Clinical opinion to the EAG was that adults with ASMD types B and A/B were likely to have lower weight compared to the general population mean in the UK. In order to explore uncertainty surrounding modelled adult patient weight, the EAG conducted two scenario analyses. These are discussed further in Section 6.2.

In terms of starting age of patients in the model, clinical opinion to the EAG was that age of diagnosis varied widely across the population. For example, diagnosis will occur earlier in those with more severe disease and in those where there is familial history. Clinical advice to the EAG suggested that diagnosis may commonly occur between two- and six-years of age, though those with mild symptoms may be diagnosed in adulthood. Consistent with heterogeneity in the severity of ASMD across the population, the range in age of diagnosis in the clinical trials was broad, ranging from 0.02 to 11.09 years for children and 1.0 to 58 years for adults. Clinical experts confirmed that typical age of diagnosis for children varies, with experts suggesting average ages ranging between two- to six-years. Clinical experts were unable to determine a representative starting age for adults in clinical practice because of heterogeneity in the population. One expert further noted that diagnosis of those with milder symptoms may occur earlier if a treatment for ASMD became available. In order to explore uncertainty surrounding starting age, the EAG has conducted scenario analyses which reduces the starting age to two-years (in the paediatric population) and 28-years (in the adult population). Section 6.2 for further discussion.

4.2.3.1. Severe patient subgroup

The company provided results for a severe population subgroup (see Section 5.2), though did not provide a rationale for conducting the analysis. In response to clarification question B.3, the company stated that "*patients with severe disease have the poorest prognosis and are likely to benefit most from treatment with olipudase alfa. They would therefore be expected to have differential cost-effectiveness."* The EAG noted that subgroup analyses were conducted for a small number of outcomes in ASCEND, showing no clear difference in effect according to baseline severity. However, it should be noted that the sample size in ASCEND was small and a limited range of outcomes were assessed. Outcomes that may be less amenable to change due to pre-existing damage may not have been included.

The company's approach to modelling the severe population differed to the base case analysis in several respects. For this analysis, 100% of patients were assumed to start in the most severe subgroup SV≥15 MN and DLco<40%. The starting age of paediatric patients was assumed to be two-years (as opposed to eight in the company's base case). The EAG accepted this approach on the basis that those with more severe disease are likely to manifest symptoms earlier and therefore be more likely to receive a diagnosis at a younger age. The company also opted to model mortality using data from McGovern et al (2013), [5] whereby the company

estimated survival by treatment via a parametric extrapolation using a Weibull distribution. The EAG noted several concerns surrounding the subgroup analysis:

- The clinical effectiveness data used to inform transitions were not derived from patients with severe ASMD. Instead, the company assumed that 100% of patients began in the severe health state and applied transition probabilities from the overall population. Based on clinical opinion to the EAG, this assumption did not appear to be appropriate, see Section 4.2.7

- The company used an alternative published literature source to estimate mortality for severe patients (McGovern et al, [5] see Section 4.2.8 for further description). The EAG considered there to be a lack of transparency in the company's approach to estimating survival. For both the severe adult and paediatric populations, the company did not justify use of a Weibull distribution to the mortality data, AIC/BIC statistics were not presented, and no attempt was made to discuss visual fit of alternative functions.

- Limited sensitivity analyses were conducted i.e. the company tested uncertainty via probabilistic sensitivity analysis (PSA), however no scenario analysis or one-way sensitivity analysis (OWSA) was presented in the CS for this subgroup.

Overall, the EAG considered there to be significant uncertainty surrounding the severe population subgroup and considered that results should be interpreted with caution.

4.2.4. Interventions and comparators

There were no alternative curative treatments for ASMD in the UK. The company therefore compared olipudase alfa (plus BSC) to best supportive care (BSC). Within the economic model, BSC consisted of routine care including healthcare professional visits, monitoring and laboratory tests, medications, vaccinations and organ transplants (lung and liver). Clinical opinion to the EAG confirmed that BSC as outlined by the company was the appropriate comparator. The intervention, olipudase alfa, is administered as an IV infusion at a recommended maintenance dose of 3mg/kg every 2 weeks. Clinical advice to the EAG was that treatment would likely be administered in hospital initially, but that after a period of time some people may prefer to be treated at home. See Section 4.2.10 regarding assumptions with respect to treatment dosing and administration.

4.2.5. Perspective, time horizon and discounting

The economic analysis was conducted from an NHS and PSS perspective as consistent with the NICE reference case. The time horizon used in the economic analysis was 100-years for both adult and paediatric populations. The EAG considered this to be reasonable and sufficiently long enough to capture the differences in costs and effects between treatment arms. The cycle length used in the analysis was six-monthly (for the first year) and then yearly thereafter. The company stated that this is broadly reflective of monitoring in UK clinical practice. Based on clinical input to the EAG, there was some variability with respect to monitoring, however using a yearly cycle length was considered to be broadly appropriate.

The EAG noted that non-reference case (differential) discounting was used in the company's base case: costs were discounted at 3.5% and benefits were discounted at 1.5%. The company justified this approach on the basis that it reflected HM Treasury Green Book advice. [31] Whilst the EAG acknowledged the advice in the HM Treasury Green Book, differential discounting was nevertheless inconsistent with the NICE process and methods manual (2022), [32] as per the NICE reference case. Differential discount rates typically improve the cost effectiveness of most medical interventions, particularly treatments with high upfront costs or delayed benefits. Differential discounting could therefore potentially allow for the higher pricing of treatments, thus increasing NHS costs. As outlined in a 2020 report by the Centre for Health Technology and Evaluation (CHTE), this methodology remains an area of academic debate.

The company provided a scenario analysis where both costs and benefits were discounted at 1.5%, resulting in an increased ICER in both paediatric and adult populations (see Section 5.3.3). The NICE process and methods manual (2022) specified that the reference case may be supplemented with alternative analyses to apply a discount rate of 1.5% to both costs and benefits if all of the following criteria are met:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

On p.10 of the 2017 NICE interim process and methods guidance for HSTs[33] it is stated that *"a discount rate of 1.5% for costs and benefits may be considered by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are*

likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs".

The EAG did not consider the use of a 1.5% discount rate to be appropriate given the lack of robust long term data supporting the impact of olipudase alfa on patient morbidity and mortality (see Section 4.2.6 and 4.2.8). The EAG preference was therefore for a 3.5% discount rate to be used for costs and benefits.

4.2.6. Treatment effectiveness and extrapolation

The clinical data used to derive treatment probabilities for adult and paediatric patients in the olipudase alfa and BSC arms were derived from trials of olipudase alfa (ASCEND[10,16], ASCEND-Peds[11,34], LTS13632[14] and DF131412[13]) and from an observational study of outcomes in people with ASMD (SPHINGO-100)[35].

For paediatric patients, olipudase alfa transition probabilities in the first year were calculated based on ASCEND-Peds trial data. For BSC, these were estimated based on the paediatric patients in the SPHINGO-100 study. For subsequent years, olipudase alfa transition probabilites were estimated by combining data from ASCEND-Peds and LTS13632. For subsequent year BSC transitions, data from SPHINGO-100 was used.

For adult patients in year one, transition probabilities for olipudase alfa were estimated by combining data from ASCEND and DF131412, whereas for BSC, ASCEND and SPHINGO-100 were used. For subsequent years, olipudase alfa transition probabilites were estimated by combining data from ASCEND and LTS13632, and BSC transitions were estimated from SPHINGO-100. Olipudase alfa transition probabilies used in the model are presented in Table 20 and Table 21 (see p.172 and p.173 of the CS for BSC transitions).

Table 20: Olipudase alfa transition probabilities for spleen volume

Start state		End state		
		<6 MN	**6–15 MN**	**≥15 MN**
0–6 months				
Children	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	26.2%	73.8%	0.0%
	≥15 MN	7.9%	43.6%	48.5%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	36.2%	63.9%	0.0%

	≥15 MN	21.3%	64.5%	14.2%
6–12 months				
Children	<6 MN	97.6%	2.4%	0.0%
	6–15 MN	11.3%	88.7%	0.0%
	≥15 MN	4.3%	59.3%	36.5%
Adult	<6 MN	97.5%	2.5%	0.0%
	6–15 MN	12.5%	87.5%	0.0%
	≥15 MN	3.5%	45.2%	51.3%
Year 2+				
Children	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	100.0%	0.0%	0.0%
	≥15 MN	100.0%	0.0%	0.0%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	100.0%	0.0%	0.0%
	≥15 MN	100.0%	0.0%	0.0%

Abbreviations: MN, multiples of normal; SV, spleen volume.
Source: Company submission (p.160 and p.161)

Table 21: Olipudase alfa transition probabilities for DLco

Start state		End state		
		≥80%	**40–80%**	**≤40%**
0–6 months				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
6–12 months				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	24.7%	75.3%	0.0%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	6.3%	93.7%	0.0%
	≤40%	2.9%	72.0%	25.1%

Year 2+				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	100.0%	0.0%	0.0%
	≤40%	100.0%	0.0%	0.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	100.0%	0.0%	0.0%
	≤40%	100.0%	0.0%	0.0%

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide.
Source: Company submission (p.160 and p.161)

4.2.7. Long term extrapolation of treatment effectiveness

In the company's base case analysis, 100% of patients who receive olipudase alfa are assumed to transition to the least severe health state (SV<6MN and DLco≥80% health states) from year two and remain there for the duration of the modelled time horizon (subject to mortality). In contrast, patients in the BSC arm are assumed to transition in every cycle until the end of the time horizon or death. The company did not provide justification for this assumption in the CS. Based on clinical expert opinion to the EAG, the long-term efficacy assumption for olipudase alfa may be plausible. Stable, long-term efficacy has been shown for enzyme-replacement therapy (ERT) in gaucher disease, which is another lysosomal storage disorder. Not all ERTs have shown long-term efficacy, though clinicians advising the EAG were hopeful that olipudase alfa may be as effective as for gaucher disease. However, two clinical advisers suggested that there may be a reduced effect (some treatment waning) in severe patients due to antibody resistance.

The EAG considered it to be plausible that olipudase alfa may have long-term benefit for the target population, though due to the lack of long-term treatment effectiveness data and the potential for the assumption to overestimate the incremental QALY gain associated with olipudase alfa, there was a high degree of uncertainty surrounding this assumption. The EAG conducted three scenario analyses using alternative long-term efficacy assumptions for olipudase alfa (see Section 6.2.1). As part of the EAG preferred base case, it was assumed that transition probabilities for patients receiving olipudase alfa would be frozen at two-years.

4.2.8. Mortality

Mortality was modelled via standardised mortality ratios (SMRs) using clinical data from the SPHINGO-100 study, [3] the prospective longitudinal study which collected disease related morbidity and mortality data over an 11-year period. The company estimated mortality according

to the presence or absence of severe splenomegaly: for patients without severe splenomegaly, the SMR was estimated to be 4.3, whilst for those with severe splenomegaly the SMR was 43.1 (i.e. patients with severe splenomegaly have a death rate 10 times higher than those without severe splenomegaly). These SMRs were estimated by comparing the observed mortality in the SPHINGO-100 study, with the expected mortality of the general US population (using US life tables). In order to calculate adjusted survival probabilities in the model, the SMR was applied to the mortality rates of the general UK population, as a multiplier.

The EAG noted several issues with the company's approach to modelling mortality, including the following:

- The EAG queried the company's decision to use splenomegaly as the key determinant of mortality (given ASMD impacts multiple organs including liver and lung function) during clarification. In response to question B.11, the company stated that "*all available clinical parameters were tested as potential predictors of survival, defined as the time from the date of birth to the date of last visit or death. The only parameter that presented a statistically significantly association with survival was severe splenomegaly as defined using the published threshold of 15 multiples of normal".* Clinical advice to the EAG about the validity of this approach was somewhat mixed, however on balance splenomegaly appeared to be a reasonable proxy/beacon of disease severity. While an enlarged spleen may not be a common cause of death, there is a positive correlation between an enlarged spleen and disease severity (including lung and liver involvement). Furthermore, the EAG noted two recently published papers, which examined prognostic markers for mortality, identified splenomegaly as a predictor of survival; Jones et al (2020) [36] and Eskes et al (2020). [37]

- Clinical opinion to the EAG suggested that there was uncertainty surrounding the company's assumption that paediatric patients die from ASMD. Two clinicians treating paediatric patients were unable to recall any deaths amongst children with ASMD types B or A/B in their care.

- The EAG noted that data from SPHINGO-100 were derived from a small sample (n=58) with correspondingly low event rates (e.g. deaths n=9), which may lead to unreliable estimates of risk. Three deaths occurred in the paediatric population, which represented 33.3% of deaths within the study. The primary cause of death for all three deaths was pneumonia. To validate these data, the EAG sought to identify additional mortality data from the international Niemann-Pick Disease Alliance (INPDA), who manage a data registry

including people with ASMD types B and A/B. These data were not available during the timeframe of the EAG appraisal, though the evidence may become available to the EAG and/or NICE committee at a later stage during this appraisal.

Overall, the EAG considered there to be some uncertainty surrounding the mortality data used in the company's base case and considered that the incremental life-years gained reported for olipudase alfa should be interpreted with caution. In order to test the impact of mortality on the base case ICER, the EAG conducted a scenario analysis in which the SMR for severe splenomegaly was reduced by 50%. Results were not sensitive to this change (see Section 6.2). Furthermore, on the basis of clinical opinion, a scenario analysis was conducted in which disease-related mortality in the paediatric population was removed i.e. only backgroud mortality was considered (until the patient reached adulthood). This analysis was included as part of the EAG preferred base case (see Section 6.2 and 6.3).

As part of a scenario analysis (and for the subgroup analysis in the severe population), the company used an alternative mortality data source, a published study by McGoven et al (2013).[5] This natural history study, which included 103 patients with ASMD type B, assessed morbidity and mortality. At entry, 61 participants were considered paediatric (≤21 years) and 42 were adults. Eighteen patients died during the study, of whom 12/18 (67%) were children and 6/18 (33%) were adults, leading to a mortality rate of 19% and 14%, respectively.

The EAG identified the following concerns surrounding the use of McGovern et al. as a source of alternative mortality data, and in the company's modelling approach in general:

- A significant minority of the deaths reported in the trial were due to complications following treatment (bone marrow and stem cell transplants, 25%) rather than due to the disease itself. The EAG noted that these may not reflect routine operational procedures for people with ASMD types B and A/B within the NHS.The McGovern study was also reasonably dated (conducted from 1992-2012), and the EAG queried whether care will have changed substantially since that time so that health outcomes are no longer generalisable. There were differing views amongst clinical experts as to whether care and health outcomes had changed substantially in the past ten- or twenty-years.

- The study did not report whether participants had 'severe disease', and did not categorise participants according to spleen volume or lung function (as per the company's base case approach). In the paper the authors stated that the mortality data suggested that there were

two cohorts: those with more severe disease who have a higher mortality rate during childhood and those with milder disease who are more likely to survive into adulthood. The EAG noted that this assumption introduced uncertainty given that data were not derived from a population with confirmed severe status based on important prognostic factors like spleen volume and DLco.

- The EAG considered there to be a lack of transparency surrouding the company's approach to extrapolating overall surivival data. The company stated that a Weibull parametric function was used, however no rational or supporting evidence was provided for selecting the Weibull i.e. curve selection did not appear to be validated using clinical opinion, AIC/BIC statistics or visual inspection. The EAG considered this to introduce considerable uncertainty into the analysis, as it was a veritable 'black box'.

For the reasons outlined above, the EAG considered the mortality estimates from McGovern et al. to be subject to uncertainty and may overestimate mortality, particulalry in the paediatric cohort.

4.2.9. Health-related quality of life

There was a lack of published HRQoL data for people with ASMD types B and A/B. The company collected HRQoL data directly from participants in the ASCEND and ASCEND-Peds trials. The company stated that HRQoL in the ASCEND trial was assessed after 52-weeks of olipudase alfa treatment, using the EQ-5D-5L and SF-36 generic preference-based measures. The company also presented data for a disease-specific measure named the NPB-HAQ, which reportedly assessed fatigue, pain, respiratory, abdominal complaints and quality of life (as well as questions specific to ASMD symptoms and physical activity). HRQoL-specific data from the NPB-HAQ were not included in the company's model. No citation for the NPB-HAQ was provided by the company (and the EAG were unable to locate one), therefore the EAG were unclear whether this measure had been appropriately developed and validated before use in the trial. The company stated that the primary instruments (EQ-5D-5L or SF-36) lacked sensitivity to change in adults with ASMD, noting that there was no statistically significant difference in HRQoL following treatment with olipudase alfa despite change in disease severity markers. As noted on p.177 of the CS, the company stated that neither instrument (EQ-5D-5L or SF-36) assessed the "*important aspects*" of ASMD, such as spleen volume and pulmonary function, and further noted that the utilities derived from both instruments produced counterintuitive results e.g. baseline utilities from both instruments were lowest for the least severe health

states. The company suggested that one potential reason for counterintuitive results was that the small sample size may not be sufficiently large enough to reflect the different health states within ASMD, or because patients may adjust to their condition over time. Overall, the EAG considered that the company's decision to not use HRQoL data for adults from the ASCEND trial in the economic analysis trial may be appropriate given the short follow up in the trial (which the EAG considered partly explained the counterintuitive HRQoL results). Using the trial results within the model was likely to have introduced further uncertainty to the analysis.

In the ASCEND-Peds trial, treatment with olipudase alfa resulted in a significant improvement in the PedsQL Generic Core Scale and Multidimensional fatigue scale for the majority of subsets at week-52 compared to baseline. However, the company did not use HRQoL data from the trials in their economic model. The company stated that despite the improvement in HRQoL noted in the ASCEND-Peds trial, they nevertheless considered that generic HRQoL measures were insensitive to change in the population. Furthermore, in their response to clarification (question A26), the company noted that the paediatric trial did not have a comparator arm, thereby preventing the evaluation of the treatment related benefit on HRQoL.

Due to the limitations surrounding the trial HRQoL data, the company conducted a vignette study[38] to generate HRQoL data for the economic model. In the absence of robust trial data (and values in published literature), well-conducted vignette studies are an appropriate means for eliciting health state values and are in line with the NICE manual for process and methods (2022). [32] In this instance, the company's vignette study appeared reasonably well-conducted: the study included a pilot phase (including [redacted] patients) to test the validity of the planned methodology and health states; and adult and child health state descriptions used in the main study were based on discussions with clinicians, patients, carers, and on the basis of data from literature reviews and clinical trials. In order to validate health state descriptions (and how well they match the modelled health states), the EAG sought clinical expert opinion (see Table 22 below for health state descriptions). Based on clinical input to the EAG, the vignette health states were considered to be broadly appropriate and were reflective of the modelled states.

Table 22: Modelled health states (corresponding to vignette states)

Modelled health state	Vignette health states
Spleen volume (1-6): DLco (100-80)	ASMD without impairment
Spleen volume (1-6): DLco (80-40)	ASMD with mild/moderate impairment in DL_{CO}

Spleen volume (6-15): DLco (100-80)	ASMD with mild/moderate spleen and liver volume increase
Spleen volume (6-15): DLco (80-40)	Mild/moderate ASMD
Spleen volume (>15): DLco (100-80)	ASMD without DL_{CO} impairment with severe spleen and liver volume increase
Spleen volume (1-6): DLco (<40)	ASMD with severe DL_{CO} impairment and without spleen and liver volume increase
Spleen volume (>15): DLco (80-40)	ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase
Spleen volume (6-15): DLco (<40)	ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase
Spleen volume (>15): DLco (<40)	Severe ASMD

The main study[38] included [redacted] participants and interviews were conducted in-person. The [redacted] was used to elicit health state utilities The EAG noted several benefits of using the vignette study rather than using HRQoL data from the trials:

- the study included [redacted] only
- the relatively large number of respondents may be likely to produce more robust estimates (versus the small number of patients included in the trials).
- eliciting values from the [redacted].

Health state utility values used in the model are outlined in Table 23. Given the lack of published utility values for ASMD, the EAG sought clinical expert opinion on the face validity of these values. Based on clinical opinion to the EAG, values for both populations appeared to make logical sense (decreasing with disease severity) and could be considered broadly reasonable. However, one of the EAG's clinical experts who had experience with paediatric patients stated that utility values for people with Gaucher disease (a lysosomal storage disorder that has similarities with ASMD types B and A/B) were lower. The EAG attempted to identify utility values for Gaucher disease used in the NICE HST appraisal of eliglustat (HST5 for treatment of type 1 Gaucher disease), but these were redacted and could not be provided by NICE. Therefore, it was not possible to cross-validate values using this appraisal.

Table 23: Health state utilities (derived from the vignette study)

Health state	Adults	Children
A1: ASMD without impairment	[redacted]	[redacted]
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]	[redacted]
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]	[redacted]
A4: Mild/moderate ASMD	[redacted]	[redacted]
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]	[redacted]
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]	[redacted]
A9: Severe ASMD	[redacted]	[redacted]

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity for carbon monoxide

4.2.9.1. Carer disutility and disutility associated with death

The model included carer disutility for health states in the BSC arm only. On p.180 of the CS, the company stated that this treatment-specific approach to carer disutility was justified *"given the treatment-mediated impact on patients' symptoms and manifestations, and the potential reduction in caregiver burden this brings".* For each health state, a disutility of -0.150 was applied. The carer disutility chosen by the company was based on a published study by Simon et al., [1] which estimated health utilities and parental quality of life for three rare conditions in new-borns (Krabbe disease, Pompe disease and Pheylketonuria). Specifically, the company opted to use the parental disutility for Pompe disease (non-ventilator dependent infants) stating that Pompe disease and ASMD share similarities including respiratory issues, reduced growth and fatigue. Furthermore, the company made two key assumptions with respect to carer disutility: the implementation of a carer disutility associated with patient death (assumed to be -0.50); and the number of carers (1.8 for paediatric patients and 1 for adults).

The EAG had several key concerns surrounding the company's approach to estimating carer disutility in the model:

- Clinical opinion to the EAG was that the disease burden of Pompe disease is greater than in ASMD, as most patients with Pompe are immobile and unable to feed, unlike those with ASMD. The EAG therefore considered that the expected burden on these families and carers would be considerably higher and that the disutility selected by the company appeared to overestimate the impact of ASMD on carer HRQoL.

- The EAG considered the application of carer disutility only to the BSC arm to lack plausibility, given that carer HRQoL will depend on the severity of the patient's disease rather than the treatment received. That is, carers for patients in the severe health state (who are receiving either olipudase alfa or standard of care) will have reduced quality of life. The EAG conducted a scenario analysis whereby carer disutility was applied to all modelled health states regardless of treatment (see Section 6.2). The EAG incorporated this approach into its preferred base case.

- The EAG considered the company's decision to apply a single disutility to all modelled health states to be a simplifying assumption that was not adequately justified. For example, a carer disutility of -0.15 was applied to all health states including the least severe health state (where a patient has spleen volume of 1-6 MN and DLco 100-80). This implied that carers of patients with mild symptoms will experience a severe disutility of -0.15). Clinical opinion to the EAG was that this assumption did not appear to be appropriate, and that the HRQoL burden for carers was likely to increase with respect to disease severity. It was considered that a more plausible approach would be to use dynamic disutilities, whereby a separate (higher) carer disutility is applied to the most severe state and lower disutilities are applied for mild/moderate health states. The EAG conducted scenario analyses to explore this (see Section 6.2.3).

- In the base case analysis, the company assumed that paediatric patients (patients <18 years) would require 1.78 carers (based on the UK average number of parents per child)[39] and adults would require one carer. The company stated that this assumption was in line with a prior HST appraisal of voretigene neparvovec (HST 11)[2] for treating inherited retinal dystrophies caused by RPE65 gene mutations. Children eligible for treatment with voretigene neparvovec have significant visual impairment and for this appraisal the EAG considered that a school-age child would typically require more than one carer. In the

absence of data, a mean of 1.78 carers using the same source was used.[39] The EAG did not consider that the conditions were sufficiently similar with respect to disease activity, and therefore did not consider it appropriate to assume generalisability with respect to carer burden.

Furthermore, the 'QALY penalty' associated with caring responsibilities can be thought of as comprising two components: (i) the impact of caring duties themselves, and (ii) the emotional burden of caring for a sick child. With respect to (i), the EAG felt that where there are two parents, the caring duties would be divided between both parents rather than doubled: the sum total of carer burden would be the same irrespective of whether there was one or two parents. Clinical advice to the EAG was that an assumption of one carer was likely appropriate with regards to caring responsibilities. With respect to (ii) the EAG accepted that the emotional burden would, of course, fall on both parents. However, it would also affect siblings, extended family and friends. To inform a fair comparison to allocate finite resources across the NHS, the EAG proposed that such impacts be limited to a single carer rather than an arbitrary higher number. On this basis and informed by clinical expert advice, the EAG considered that 1.8 carers per child was likely to be an overestimation and preferred to assume one carer would be standard in its base case.

- The company's model included a carer disutility associated with patient death. The company assumed this to be -0.50 and applied this as a multiplier to the number of deaths in each cycle (which was assumed to continue over the entire modelled time horizon). As a means of justifying this disutility, the company stated that this value had been used in published cancer models, referring to a study by Hornberger et al. (2012).[40] Upon review the EAG noted that this study (which was a cost effectiveness analysis of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia) applied a carer utility decrement of 0.60 if the patient died and assumed a one-year bereavement period). This carer disutility assumption was notably different to that used by the company within this appraisal, whereby the disutility value of -0.50 was applied throughout the modelled time horizon. For the paediatric population, this assumption contributed to a total loss of [redacted] QALYs in the olipudase alfa arm, and [redacted] QALYs in the BSC arm. For the adult population, this assumption contributed to a total loss of [redacted] QALYs in the olipudase alfa arm and a total loss of [redacted] QALYs in the BSC arm. The EAG also noted that within Hornberger et al., it was not clear how carer

decrements were calculated as no information was provided regarding carer disutility elicitation methods.

Sources (published literature and HTA assessments) have explored the impact of including carer disutility associated with patient death, including a published study (Song et al.)[41] and NICE TA588 (Nusinersen for treating spinal muscular atrophy, where a disutility of -0.04 was applied). However, the inclusion of carer disutility associated with patient death was not an approach recommended by NICE at the time. Ultimately, the EAG considered it to be a highly speculative assumption that potentially biased the analysis in favour of olipudase alfa (given the higher mortality rate in the BSC arm in the model). The EAG conducted a scenario analysis that removed carer disutility associated with death. This scenario analysis was incorporated into the EAG base case (See Section 6.2 and 6.3 for results).

Overall, the EAG considered the company's approach to modelling carer disutility included numerous inappropriate assumptions. Based on the scenario analyses conducted by the EAG, carer disutility was considered to be a key driver of results (see Section 6.2).

4.2.9.2. Disutility associated with complications and adverse events

The model included disutilities associated with common complications of ASMD B and A/B, shown in Table 24. Complications were modelled as one-off events (assigned at the start of the event). The company noted that this is likely to be a conservative assumption, given that ASMD complications are likely to have lasting long-term effects. The duration of adverse events was assumed to be one-year for all complications, apart from hospitalised pneumonia.

Due to the paucity of utility data with respect to ASMD-related complications, modelled values were derived from numerous published literature sources (UK and non-UK):

- respiratory complications: disutility was derived from a study in pneumococcal disease (disutility is reflective of having hospitalised pneumonia)[42]
- liver disease complications: disutility was assumed to reflect decompensated cirrhosis in hepatitis C[43]
- Spleen complications: disutility was assumed to reflect splenectomy in patients with immune thrombocytopenic purpura[44]

- cardiovascular disease complications: disutility was assumed to reflect angina in patients with diabetes-related chronic conditions[45]

- major bleeding: disutility was assumed to reflect thrombocytopenia in patients with immune thrombocytopenic purpura in the UK.[46] The company stated that thrombocytopenia was chosen as the closest proxy, as bleeding in patients with ASMD is also related to thrombocytopenia, as a result of splenomegaly

The EAG considered that the use of disutility data from diseases the company considered 'analogous' to ASMD introduced uncertainty as it was unclear whether these disease complications could be considered sufficiently similar to ASMD. However, in the absence of robust ASMD data, the approach of using proxy values to capture the impact of complications on patient HRQoL was reasonable. The company tested disutility associated with complications via one-way sensitivity analysis (varying parameters by +/- 20%), however results were not sensitive to this. The EAG did not consider disutility associated with complications to be a key driver of incremental results.

Table 24: Disutility associated with complications

Complication	Utility decrement	Source
Respiratory	-0.034	Galante et al (2011)[42]
Liver disease	-0.237	McLernon et al (2008)[43]
Spleen	-0.080	Snyder et al (2008)[44]
Cardiovascular disease	-0.230	Sullivan et al (2016)[45]
Major bleeding	-0.129	Szende et al (2010)[46]

Finally, the company did not include disutilities due to adverse events in the base case and justified this on the basis that these events were not assumed to have a long-term impact on patients' quality of life. The EAG considered that the approach was not consistent with the company's approach to modelling costs, whereby adverse event costs associated with olipudase alfa were included in the model. However, due to short duration of treatment-emergent adverse events, it was considered that including adverse event disutility was likely to have a minimal impact on the results.

4.2.10. Resources and costs

4.2.10.1. Drug costs

The model included drug acquisition costs for olipudase alfa. The list price for a 20mg vial was stated to be [redacted]. A patient access scheme (PAS) discount for olipudase alfa that reduced the list price by [redacted] was agreed with NHS England and included in the company analyses. Including the PAS discount, the price per 20mg vial of olipudase alfa was [redacted]. There were no active treatment costs applied to the BSC arm in the model, which was considered reasonable given that no active comparator to olipudase alfa was available and background care interventions would be received by participants in both arms.

Olipudase alfa is administered via IV infusion every two-weeks. For both adult and paediatric patients, the model estimated drug costs for two periods, a dose escalation period and a maintenance period. On p.163 of the CS (Document B), the company reported that the dosing corresponds to the ASCEND and ASCEND-Peds trials (see Table 25). The EAG noted that there was an error in the company's estimation of paediatric dosing in the model i.e. the company overestimated the mg/kg for weeks 6, 10, 12 and 14. The EAG amended this error, however this did not have a material impact on the ICER (see Section 6.1). Once patients entered the maintenance period, it was assumed that they receive 3mg/kg for the duration of treatment (which is considered the highest tolerated dose). The EAG noted that the proportion of patients achieving the highest tolerated dose was derived from the ASCEND and ASCEND-Peds trials for the adult and paediatric populations, respectively i.e. 94.40% of adults and 100% of paediatric patients achieved the highest tolerated dose.

Table 25: Dosing used in the model

Dose	Adults (≥18 years old)	Paediatrics (0 to < 18 years old)
First dose (Day 1/Week 0)	0.1 mg/kg	0.03 mg/kg
Second dose (Week 2)	0.3 mg/kg	0.1 mg/kg
Third dose (Week 4)	0.3 mg/kg	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg	0.3 mg/kg
Fifth dose (Week 8)	0.6 mg/kg	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg	0.6 mg/kg
Seventh dose (Week 12)	2 mg/kg	1 mg/kg

Eighth dose (Week 14)	3 mg/kg (recommended maintenance dose)	2 mg/kg
Ninth dose (Week 16)	-	3 mg/kg (recommended maintenance dose)

For both the paediatric and adult populations, annual drug acquisition costs for olipudase alfa were calculated based on the estimated total annual dose and compliance rate (see Table 59 on p.185 of the CS, Document B). The compliance rate used in the analysis was 90% for both populations, based on data from ASCEND and ASCEND-Peds. Based on clinical opinion to the EAG, 90% may represent a reasonable minimum compliance rate as, like other ERTs, olipudase alfa may ultimately be administered at home by a clinician and missed doses may be uncommon. As an exploratory analysis, the EAG conducted a scenario analysis that increased the compliance rate to 100%. See Section 6.2 for further details and results.

The EAG also noted that the model did not assume the occurrence of drug wastage. Based on the company's response to clarification question A11, ERT doses are routinely rounded to the nearest vial to avoid wastage. For example, if weight is halfway between two vials, clinicians would round down the dose one week and round up the dose the following week in order to avoid wastage. Based on clinical opinion to the EAG, this assumption was considered to be reasonable.

4.2.10.2. Administration and monitoring

The company included administration costs associated with infusion of olipudase alfa for the dose escalation phase and the maintenance phase. In the dose escalation phase, the annual cost was calculated from the biweekly cost of dose escalation consisting of a physician visit and any monitoring (until the highest tolerated dose is achieved). The cost was estimated to be £135 per visit, which appeared to reflect the hourly administration cost for a hospital outpatient clinic setting.

For the maintenance phase, administration costs were based on the mean duration of infusion, which was estimated to be 220 minutes or 3.66 hours (see Table 62 on p.187 of the CS Document B). Clinical expert opinion to the EAG confirmed that the estimated time to administer treatment appeared reasonable. Once on maintenance treatment, 100% of adult and paediatric patients were assumed to have treatment administered at home with a nurse. The hourly cost

for nurse administration was estimated to be £44 and unit costs were derived from Personal Social Services Research Unit (PSSRU) 2020 costs as appropriate.

Annual costs for administering olipudase alfa are shown in Table 26. Administration costs were not considered to be a key driver of the ICER, accounting for just [redacted] of total costs in the olipudase alfa arm.

Table 26: Olipudase alfa annual cost of administration

	Annual cost
Children	
Year 1 (escalation and maintenance)	£3,561.90
Subsequent years (maintenance)	£3,788.16
Adults	
Year 1 (escalation and maintenance)	£3,567.87
Subsequent years (maintenance)	£3,788.16

4.2.10.3. Health state costs

Costs associated with the medical management of ASMD were included in the model, representing health state costs. These applied to both the olipudase alfa and BSC (see Tables 64 to 66 on p.189 to p.192 of the CS). Annual frequencies were derived from a retrospective cohort analysis using IQVIA open claims for patients with confirmed and potential (high probability) ASMD type B. Unit costs were based on 2019/20 NHS reference costs. [47]

The EAG noted that using a retrospective 'activity based costing' approach introduced some uncertainty, and that using a time driven activity-based costing approach (TDABC) or a fuzzy logic (FL) TDABC approach within prospective trials would lead to more accurate resource use estimates, accounting for variation in time. However, this may be considered to be a conservative approach to resource use estimation, as there was assumed to be no difference in healthcare resource use between treatment arms in healthcare visits, laboratory tests, monitoring, medication and vaccine use etc. Clinical opinion to the EAG was that patients on olipudase alfa arm would likely have reduced healthcare resource use in practice, due to the efficacy of treatment.

4.2.10.4. Adverse event and complication costs

The annual costs of treating serious treatment-emergent adverse events were included in the model for the olipudase alfa arm only (see Table 67, p.193 of the CS). Based on the company's model the annual probability of experiencing serious adverse events for children was estimated to be 8.30% in all years, based on incidence data from ASCEND-peds and the long-term extension study LTS13632. This accounted for events such as alanine aminotransferase increase, rash, anaphylactic reaction, urticaria and hypersensitivity, and resulted in an annual cost of £25.66 for olipudase alfa. For adults, the annual probability of experiencing serious adverse events was estimated to be 1.02% in all years, based on the occurrence of serious extrasystoles from ASCEND PAP and ETP. This resulted in an annual cost of £10.51 for olipudase alfa. Unit costs were derived from NHS reference costs 2019/20, as appropriate. Overall, modelled treatment emergent adverse event costs were not a key driver of cost effectiveness, as these were minor relative to the large drug cost associated with olipudase alfa.

The model also included complication costs of respiratory, bleeding (as a result of increased spleen volume), liver, spleen and cardiovascular complications. In each modelled health state, the probability of experiencing complications was based on base annual rate data from SPHINGO-302[30] and odds ratios from SPHINGO 100. [3] The EAG noted that the only difference in complication rates between olipudase alfa and BSC was with respect to liver complications. The annual probability of liver complication was estimated to be 0.3% and 3.4% for olipudase alfa and BSC respectively. To explore uncertainty surrounding modelled complication rates, the EAG conducted a scenario analysis that assumed no difference in liver complication rates between treatment arms. Results were not sensitive to this analysis (see Section 6.2).

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1.1. Company base case results

The discounted results reported by the company including the PAS discount for olipudase alfa are shown in Table 27 to Table 29. The incremental QALY gain associated with olipudase alfa in both the paediatric and adult populations was primarily driven by modelled treatment efficacy i.e. a high proportion of patients were assumed to remain in the SV <6 MN, DLCO ≥80% health state and therefore experience lower mortality (increased life-years) and higher utility relative to patients on BSC (see CS Appendix J for disaggregated results). The QALY loss associated with BSC was due primarily to carer QALY loss (see Section 4.2.9.1 for the EAG's critique of the company's approach to modelling carer HRQoL). In terms of incremental costs, these are driven by olipudase alfa drug costs. The company presented results for a mixed population (weighted average of adult and paediatric patients). The EAG did not consider a mixed population to be appropriate for decision making, however for completeness, results are presented in Table 29.

The company provided supplementary base case results using QALY weighting, however no justification was provided for this. In response to clarification question B.12, the company stated that the approach was in line with NICE guidance and that *"olipudase alfa offers significant QALY gains, with discounted QALY gains of* [redacted] *in paediatric patients and* [redacted] *in adult patients despite likely conservative assumptions regarding mortality and patient and family/carer utilities".* The EAG noted that based on NICE guidance (Interim Process and Methods of the Highly Specialised Technologies Programme, 2017), [33] in order for QALY weighting to be considered there would need to be compelling evidence that the treatment offered significant QALY gains. As discussed in Sections 4.2.6, 4.2.8 and 4.2.9.1, the EAG highlighted considerable uncertainty surrounding modelled assumptions including long-term treatment efficacy, impact on mortality, and patient and carer utilities. The EAG, therefore did not consider that it was appropriate to apply QALY weighting given the uncertainty surrounding the incremental QALY gain associated with olipudase alfa. However, for completeness, the results incorporating undiscounted QALYs are reported in Appendix B.

Table 27: Company base case results (paediatric population)

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
Olipudase alfa	[redacted]	[redacted]	24.41	[redacted]	[redacted]	24.95	[redacted]
BSC	[redacted]	[redacted]	-0.54	[redacted]	[redacted]	-	
Company probabilistic base case							
Olipudase alfa	[redacted]	[redacted]	24.22	[redacted]	[redacted]	24.07	[redacted]
BSC	[redacted]	[redacted]	0.15	[redacted]	[redacted]	-	

Abbreviations: QALYs, quality adjusted life years; LYs, life years; BSC, best supportive care

Table 28: Company base case results (adult population)

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
Olipudase alfa	[redacted]	[redacted]	6.66	[redacted]	[redacted]	16.44	[redacted]
BSC	[redacted]	[redacted]	-9.77	[redacted]	[redacted]	-	
Company probabilistic base case							
Olipudase alfa	[redacted]	[redacted]	6.56	[redacted]	[redacted]	15.39	[redacted]
BSC	[redacted]	[redacted]	-8.83	[redacted]	[redacted]	-	

Abbreviations: QALYs, quality adjusted life years; LYs, life years; BSC, best supportive care

Table 29: Company base case results- Mixed population (paediatrics and adults)

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
Olipudase alfa	[redacted]	[redacted]	15.54	[redacted]	[redacted]	20.69	[redacted]
BSC	[redacted]	[redacted]	-5.16	[redacted]	[redacted]	-	
Company probabilistic base case							
Olipudase alfa	[redacted]	[redacted]	15.39	[redacted]	[redacted]	19.73	[redacted]

BSC	[redacted]	[redacted]	-4.34	[redacted]	[redacted]	-	

Abbreviations: QALYs, quality adjusted life years; LYs, life years; BSC, best supportive care

5.2. Subgroup analysis

As discussed in Section 4.2.3.1, the company presented a subgroup analysis in patients with severe disease. The company's results for this subgroup, including the PAS discount for olipudase alfa, are presented in Table 30. As previously noted, these results are considered highly uncertain and should be interpreted with caution.

Table 30: Company base case results (Severe subgroup)

	Incremental costs	Incremental LYs	Incremental QALYs	ICER	ICER (weighted)
Paediatric	[redacted]	[redacted]	47.42	[redacted]	[redacted]
Adult	[redacted]	[redacted]	17.83	[redacted]	[redacted]
Mixed population	[redacted]	[redacted]	32.62	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years; LYs, life years; BSC, best supportive care

5.3. Company's sensitivity analyses

5.3.1. One-way sensitivity analysis (OWSA)

The company conducted OWSA for both adult and paediatric populations that varied certain model parameters by +/- 20% including baseline patient characteristics, drug administration and acquisition costs, maintenance costs, complication costs, compliance rates, treatment related adverse events, routine care costs and utilities. Results were presented via tornado diagrams (see p221 and p.222 in the CS Document B). The EAG noted that although the company provided a separate model for the subgroup population, OWSA results for the severe subgroup were not provided in the CS.

The EAG noted that parameters such as caregiver disutilities, number of caregivers and mortality were omitted from the company's sensitivity analysis. There were also discrepencies in the calcualtion of boundaries of the sensitivity analysis for respiratory complication rate and carer disutility parameters. After resolving the general discrepencies of the model and amending the company's OWSA, the results were most sensitive to variation in adult patient weight, drug

unit costs, compliance, number of caregivers for adults, mortality ratios, starting age, and utilities.

5.3.2. Probabilistic sensitivity analysis

The company conducted probabilistic sensitivity analysis (PSA) for both the paediatric and adult populations. Distributions used for model parameters can be found in Table 73 on p.213 of the CS Document B. As with the company's OWSAs, the EAG noted that parameters such as caregiver disutilities, number of caregivers and mortality had been excluded from the company's PSA. Threre were also discrepencies in the formulas used to caclulate the PSA sample number for carer disutility. After resolving general discrepencies in the model and implementing the EAG PSA corrections, the model was run for 1000 simulations. The results showed that for the paediatric population, olipudase alfa had a [redacted] probability of being cost effective at a willingness to pay of £300,000. For adults, olipudase alfa had a [redacted] probability of being cost effective at a willingness to pay of £300,000. The maximum willingness to pay threshold for HSTs is £100,000. Using this threshold, there is a [redacted] probability of olipudase alfa being cost effective in either adults or children.

5.3.3. Scenario analyses

A limited number of scenario analyses were provided by the company in the CS (see Table 74, p.222 of the CS Document B). For both the paediatric and adult populations, the company conducted the following scenario analyses:

- Discounting costs at 1.5%. When both costs and benefits were discounted at 1.5% the ICER increased i.e. olipudase alfa became less cost effective due to higher total costs (see question B.17 of the company clarification response).
- Alternative mortality assumptions based on a published study by McGovern et al (2013).[5] This analysis resulted in improved cost effectiveness for olipudase alfa i.e. there was a minor downward impact on the ICER for the adult population and a large downward impact on the ICER for the paediatric population (resulting from a large incremental LY and QALY gain). As noted in Section 4.2.8, the EAG considered the company's approach to extrapolating survival using McGovern et al, to be associated with considerable uncertainty.

- Treatment discontinuation in week 80 (at a rate of 5.56%). The company stated that this reflected the participants in the ASCEND trial who discontinued during the extended trial period. This resulted in an increased ICER for olipudase alfa in both adults and children.
- Patient compliance increased to 95%. Increasing compliance to olipudase alfa resulted in increased ICERs in both adults and paediatric patients as a result of higher drug costs (see question B.17 of the company clarification response).

Although the company provided rationale for testing each of the aforementioned scenarios, it was unclear why a limited subset of results were presented to the EAG. The EAG noted that several key drivers of cost effectiveness uncertainty, including treatment effect and HRQoL assumptions (for both patients and carers), were not tested in the company's scenario analyses. Initially, the company only provided scenario analyses results based on a weighted average population (of paediatric and adults), however during clarification the EAG requested that results be provided seperately for each population (see clarification response B.17).

Overall, the EAG did not consider the scenario analyses conducted by the company to be sufficient to address key aspects of modelled uncertainty.

5.4. Model validation and face validity check

On p.229 of the CS (Document B) the company stated that *"the cost-effectiveness model has undergone validation within a UK advisory board conducted in May 2022 by Sanofi. Five clinical experts participated in the advisory board. Any issues identified were considered in the final model and discussed with a clinical expert".* The company also noted that two external health economists quality-assured the model. However, despite the company's review process, the EAG identified errors within the company's model which were then corrected (see Section 6.1 for a complete list).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The EAG identified limitations with the company's base case and therefore explored the impact of using alternative parameter values and assumptions.

Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis.

The scenario analyses presented in Section 6.2 focused on exploring the following issues and uncertainties:

- **The extrapolation of the olipudase alfa treatment effect**. The company assumed that 100% of patients who receive olipudase alfa transition to the SV <6MN and DLco ≥80% health states from year 2 onwards i.e. all patients move into the least severe health state and remain there for the duration of the modelled time horizon (subject to mortality). The EAG explored alternative long-term effectiveness assumptions for olipudase alfa (discussed in Section 4.2.6).
- **Mortality in paediatric patients**. The company assumed that paediatric patients die due to ASMD-related complications. The EAG explored the impact of removing disease-related mortality in paediatric patients (discussed in Section 4.2.8).
- **The SMR associated with severe splenomegaly**. The company estimated the SMR for severe splenomegaly to be 43.1. The EAG assessed the impact of using a reduced SMR of 21.5, an approximately 50% reduction (discussed in Section 4.2.8).
- **Modelled carer disutility assumptions**. The EAG assessed the impact of assuming alternative model carer disutility assumptions (discussed in Section 4.2.9.1).
- **Compliance rates**. The company modelled treatment compliance based on rates within the clinical trials ASCEND and ASCEND-Peds. In this scenario the EAG assessed the impact of assuming 95% compliance i.e. no missed/interrupted doses (discussed in Section 4.2.10.1).

- **Discounting of costs and benefits**. The company employed differential discounting in their base case analysis (costs were discounted at 3.5% and benefits at 1.5%). In this scenario analysis both costs and benefits were discounted at 3.5%.
- **Age of starting treatment**. For this scenario the EAG assumed a lower treatment starting age (reducing the age by six years in both adult and paediatric patients).
- **Liver complication rates**. The EAG assumed no difference in liver complication rates between olipudase alfa and BSC.

In Section 6.3, the EAG preferred base-case is presented incorporating a combination of the exploratory analyses presented in Section 6.2.

6.1. EAG corrections and adjustments to the company's base case model

The EAG identified errors within the company's model. These included the following:

- general population utility was updated based on the latest NICE algorithm[48];
- an inappropriate correction for cycle length for the two first cycles in AE calculations;
- an inappropriate use of probabilities rather than rates in calculation of complications;
- an inappropriate correction for cycle length for the first two cycles for liver, spleen and CV complications;
- an inappropriate formula to calculate complication QALYs for all types of complications;
- dosing escalation data for children for week 6, 10, 12 and 14 were incorrectly inputted in the model.

The EAG corrected company base case results are outlined in Table 31. The costs and QALYs reported in all tables are for olipudase alfa.

Table 31: EAG-corrected company base case results and impact of model corrections (paediatric population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
Model corrections					

General population utility	[redacted]	26.44	[redacted]	[redacted]	[redacted]
AE calculation	[redacted]	24.41	[redacted]	[redacted]	[redacted]
Respiratory complications	[redacted]	24.40	[redacted]	[redacted]	[redacted]
Liver complications	[redacted]	24.41	[redacted]	[redacted]	[redacted]
Spleen complications	[redacted]	24.41	[redacted]	[redacted]	[redacted]
CV complications	[redacted]	24.41	[redacted]	[redacted]	[redacted]
Bleeding complications	[redacted]	24.41	[redacted]	[redacted]	[redacted]
Dosing (children)	[redacted]	24.41	[redacted]	[redacted]	[redacted]
EAG corrected company base case	[redacted]	26.43	[redacted]	[redacted]	[redacted]
EAG corrected company probabilistic base case					
Model corrections					
General population utility	[redacted]	26.26	[redacted]	[redacted]	[redacted]
AE calculation	[redacted]	24.25	[redacted]	[redacted]	[redacted]
Respiratory complications	[redacted]	24.23	[redacted]	[redacted]	[redacted]
Liver complications	[redacted]	24.29	[redacted]	[redacted]	[redacted]
Spleen complications	[redacted]	24.22	[redacted]	[redacted]	[redacted]
CV Complications	[redacted]	24.25	[redacted]	[redacted]	[redacted]
Bleeding Complications	[redacted]	24.24	[redacted]	[redacted]	[redacted]
Dosing (Children)	[redacted]	24.24	[redacted]	[redacted]	[redacted]
EAG corrected company base case	[redacted]	26.24	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CV, cardiovascular; EAG, external assessment group; QALYs, quality adjusted life years

Table 32: EAG-corrected company base case results and impact of model corrections (adult population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
Model corrections					
General population utility	[redacted]	8.91	[redacted]	[redacted]	[redacted]
AE calculation	[redacted]	6.66	[redacted]	[redacted]	[redacted]
Respiratory complications	[redacted]	6.66	[redacted]	[redacted]	[redacted]
Liver complications	[redacted]	6.67	[redacted]	[redacted]	[redacted]
Spleen complications	[redacted]	6.66	[redacted]	[redacted]	[redacted]
CV complications	[redacted]	6.66	[redacted]	[redacted]	[redacted]
Bleeding complications	[redacted]	6.66	[redacted]	[redacted]	[redacted]
Dosing (children)	[redacted]	6.66	[redacted]	[redacted]	[redacted]
EAG corrected company base case	[redacted]	8.91	[redacted]	[redacted]	[redacted]
EAG corrected company probabilistic base case					
Model corrections					
General population utility	[redacted]	8.71	[redacted]	[redacted]	[redacted]
AE calculation	[redacted]	6.52	[redacted]	[redacted]	[redacted]
Respiratory complications	[redacted]	6.61	[redacted]	[redacted]	[redacted]
Liver complications	[redacted]	6.59	[redacted]	[redacted]	[redacted]
Spleen complications	[redacted]	6.58	[redacted]	[redacted]	[redacted]
CV complications	[redacted]	6.51	[redacted]	[redacted]	[redacted]

Bleeding complications	[redacted]	6.55	[redacted]	[redacted]	[redacted]
Dosing (children)	[redacted]	6.53	[redacted]	[redacted]	[redacted]
EAG corrected company base case	[redacted]	8.76	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CV, cardiovascular; EAG, external assessment group; QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted a list of scenario analyses to test the impact of alternative model assumptions on the ICER. These are discussed in the Sections below.

6.2.1. Olipudase alfa long term treatment effect

As noted in Section 4.2.6, there was a lack of long-term data supporting the company's assumption of effect of olipudase alfa after two years i.e. 100% of patients who received olipudase alfa were assumed to transition to the best health states (SV <6MN and DLco ≥80%) from year two onwards. The EAG considered that this assumption was subject to uncertainty and potentially overestimated the QALY gain associated with olipudase alfa. To explore the impact of alternative effectiveness assumptions, the EAG conducted the following scenarios:

- **Observed benefit was frozen for olipudase alfa**: In this scenario patients on olipudase alfa remained in the same health state they were in after two years' of treatment. Given the lack of long-term effectiveness data, the EAG considered this effectiveness assumption to be more plausible than the assumption used by the company in their base case, which may be optimistic. Results were highly sensitive to this analysis. This analysis was incorporated into the EAG preferred base case.

- **Observed benefit continued for olipudase alfa**: In this scenario analysis transition probabilities were replayed in the olipudase alfa arm at two years i.e. after year two patients moved through health states based on the transition probabilities observed in year two of the trials. Results were sensitive to this analysis.

- **Treatment effect waning**: In this scenario it was assumed that all patients receiving olipudase alfa followed BSC transitions from year two onwards. The EAG considered this

scenario to be exploratory and pessimistic as there was no empirical basis to support the assumption that treatment effectiveness would be equivalent to BSC after year two. Results were highly sensitive to this analysis.

6.2.2. Mortality

To test the impact of alternative mortality assumptions, the EAG conducted the following scenario analyses:

- **Removed mortality associated with ASMD (for paediatric patients)**. Based on clinical advice that the risk of mortality was very low in children with ASMD types B and A/B (see Section 4.2.8), in this scenario paediatric patients were assumed to follow general background mortality until the age of 18, whereupon ASMD mortality would re-apply. Results were not very sensitive to this scenario, resulting in a minor increase in the ICER. This analysis was incorporated into the EAG preferred base case.
- **Reduced the SMR associated with severe splenomegaly**. As discussed in Section 4.2.8, the EAG noted limitations surrounding the SPHINGO-100 study used to estimate SMRs in the model. In this scenario, the EAG reduced the SMR for severe splenomegaly by 50%, to 21.5. This analysis had a small upward impact on the ICER in both populations.

6.2.3. Modelled carer disutility assumptions

As noted in Section 4.2.9.2, the EAG conducted scenario analyses to test the impact of alternative/more plausible carer disutility assumptions on the ICER.

- **Application of carer disutility to model health states (irrespective of treatment)**. This scenario analysis had a large upward impact on the ICER for both populations. As noted in Section 6.2.8, the EAG considered this assumption to be more appropriate for decision-making. This analysis was incorporated into the EAG preferred base case.
- **Application of a dynamic disutility approach** i.e. applied higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility). The EAG considered this assumption to be more appropriate for decision-making. For the paediatric population, the disutility for mild/moderate health states was derived from Al Janabi et al. (where the value reflected carer disutility for patients with meningitis who have mild/moderate learning disability), [49] whilst disutility for the severe health state was from Wittenberg et al. (*reflecting carer disutility for patients of children with*

activity limitation).[50] For adult patients, the disutility for mild/moderate health states was derived from Wittenberg et al. (where carer disutility is representative of all chronic conditions within the Wittenberg systematic review),[50] whilst disutility for the severe health state was from Acaster et al. (reflecting carer disutility for patients with Stage 2 MS; patients who are symptomatic).[51] The disutilities selected by the EAG are outlined in Table 33. For this scenario analysis the EAG made several assumptions: first, the severe health state was assumed to be defined by SV ≥15 MN and all other health states were considered under the category 'mild/moderate'; second, the disutilities associated with these proxy conditions were assumed to be generalisable to people with ASMD. Finally, carer HRQoL was not assumed to adapt over time. One expert comment to the EAG noted that carer HRQoL may change over time due to an adaptation effect. The EAG acknowledged that whilst this may happen, incorporating such an additional assumption into the model (without robust data) would introduce further uncertainty. A simplifying assumption was therefore made that assumed that carer disutility would remain constant. This scenario analysis had a moderate/large upward impact on the ICER. This analysis was incorporated into the EAG preferred base case.

Table 33: Dynamic carer disutility values used by the EAG

Population	Mild/moderate health states (all health states other than severe)	Severe health state (SV ≥ 15MN)
Paediatrics	-0.023	-0.080
Adults	-0.010	-0.045

Abbreviations: SV, spleen volume

- **Remove carer disutility associated with death of patient**. This scenario analysis had a large upward impact on the ICER. The EAG considered this assumption to be more appropriate for decision-making. This analysis was incorporated into the EAG preferred base case.

- **Assume 1 carer in each health state (for paediatric patients)**. This scenario analysis had a relatively minor upward impact on the ICER. The EAG considered this assumption to be more appropriate for decision-making. This analysis was incorporated into the EAG preferred base case.

6.2.4. Compliance rate

As noted in Section 4.2.10.1, the company used a compliance rate of 90% in both the paediatric and adult populations (data from the ASCEND and ASCEND-Peds trials). The EAG noted that altering compliance in the model to 100% impacted on costs only i.e. QALYs were not affected. Based on this analysis, the ICER increased by approximately 10% in the paediatric population and 11% in the adult population.

6.2.5. Discount rate

The EAG did not consider the use of differential discounting to be appropriate (see Section 4.2.5). This scenario analysis applied NICE reference case discounting (3.5%) to both costs and benefits. The ICER was highly sensitive to this analysis, resulting in a large upward impact. This analysis was incorporated into the EAG preferred base case.

6.2.6. Starting age

To explore uncertainty surrounding the starting age, the EAG reduced the starting age in both subgroups. The starting age for paediatric patients was reduced to two years and the starting age of adults was reduced to 28-years. Results were not sensitive to this analysis and the ICER decreased in both populations. The EAG noted that for the paediatric population, this scenario resulted in reduced incremental costs, which appeared to be due to differential discounting (of costs and benefits).

6.2.7. Liver complication rate

In the company's base analysis, the annual base rate for spleen, liver and CV complications were derived from SPHINGO-302. [30] The EAG noted that both olipudase alfa and BSC were modelled to have the same probability of spleen and CV complications, however for olipudase alfa, the company estimated a lower complication probability for liver complication (0.3% vs 3.4%). In this scenario, the EAG assumed no difference in liver complication rates between arms i.e. the rate was set to 3.4% for both olipudase alfa and BSC. Results were not overly sensitive to this analysis.

6.2.8. Modelled Patient weight

The EAG noted some uncertainty surrounding the company's modelling of patient weight in both the paediatric and adult populations (see Section 4.2.3). As dosing of olipudase alfa is weight-

based, assumptions about population weight may be influential on drug costs. The following scenario analyses were conducted to test the impact of using alternative weight assumptions.

For paediatrics:

- In order to explore the impact of using an alternative source to estimate paediatric weight in the model, the EAG opted to use weight data from paediatrics in the Health Survey for England report 2019.[4] This scenario analysis had a moderate upward impact on the ICER.

For the adult population:

- Mean patient weight was updated based on UK general population estimates (using data from Health Survey for England report 2019).[4] The UK mean weight was adjusted to reflect the male/female split from the ASCEND trial. This resulted in a mean weight of 77.27kg. The ICER was sensitive to this analysis.

- Mean patient weight was updated based on UK general population estimates (using data from Health Survey for England report 2019).[4] Based on clinical input to the EAG, patients with ASMD may be likely to have lower weight than the UK average population. To account for reduced weight as a result of ASMD, the z-score for 18-year olds (as estimated by the company) was applied, resulting in a weight of 68.52 kg. This scenario analysis had a moderate upward impact on the ICER. This analysis was incorporated into the EAG preferred base case.

6.2.9. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.8. Each change was made individually. The results of the EAG's exploratory analyses are provided in Table 34.

Table 34: Deterministic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	26.05	[redacted]	[redacted]
Olipudase alfa long-term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	22.57	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	23.71	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	12.11	[redacted]	[redacted]
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	25.86	[redacted]	[redacted]
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	23.87	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	19.22	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.94	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.62	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	25.00	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	26.05	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	15.36	[redacted]	[redacted]
Starting age					
Reduced to 2 years	6.2.6	[redacted]	26.40	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	25.87	[redacted]	[redacted]
Modelled patient weight				[redacted]	

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	26.05	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 35: Probabilistic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	16.1	[redacted]	25.06	[redacted]	
Olipudase alfa long-term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	21.60	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	23.03	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	11.52	[redacted]	[redacted]
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	24.88	[redacted]	[redacted]
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	23.26	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.28	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature	6.2.3	[redacted]	20.94	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
sources used for carer disutility)					
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.28	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	23.94	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	25.20	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	15.01	[redacted]	[redacted]
Starting age					
a. Reduced to 2 years	6.2.6	[redacted]	25.77	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	25.26	[redacted]	[redacted]
Modelled patient weight				[redacted]	
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	25.15	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 36: Deterministic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	17.59	[redacted]	[redacted]
Olipudase alfa long-term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	13.99	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	14.63	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	10.37	[redacted]	[redacted]
Mortality					

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	16.04	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	13.67	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	15.18	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.88	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	17.59	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	12.25	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	19.50	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	17.49	[redacted]	[redacted]
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	17.59	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	17.59	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 37: Probabilistic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	16.32	[redacted]	
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	12.84	[redacted]	[redacted]
b. Observed benefit continues: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	13.57	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	9.42	[redacted]	[redacted]
Mortality					
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	15.10	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	12.32	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	13.69	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.25	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	16.36	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	11.47	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	18.15	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	16.22	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	16.37	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	16.57	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

6.3. EAG's preferred assumptions

The EAG preferred deterministic and probabilistic base case ICERs are provided in Table 38 to Table 41. Incremental costs and QALYs are discounted (undiscounted QALYs are provided in Appendix B.

Table 38: EAG's deterministic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.95	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	26.05	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	15.36	[redacted]	[redacted]
Removed carer disutility associated with death of patient	6.2.3	[redacted]	21.62	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	22.57	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	19.22	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e.	6.2.3	[redacted]	21.94	[redacted]	[redacted]

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)					
c. Assume 1 carer in each health state	6.2.3	[redacted]	25.00	[redacted]	[redacted]
Removed disease-related mortality (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	25.86	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	26.05	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.57	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 39: EAG's probabilistic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.07	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	25.06	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	14.90	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.29	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	21.86	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.41	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e.	6.2.3	[redacted]	20.87	[redacted]	[redacted]

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)					
c. Assume 1 carer in each health state	6.2.3	[redacted]	24.21	[redacted]	[redacted]
Disease related mortality removed (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	24.81	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	25.20	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.29	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 40: EAG's deterministic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	16.44	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	17.59	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually) 6.2.1					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	12.25	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.88	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2-years	6.2.1	[redacted]	13.99	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	13.67	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e.	6.2.3	[redacted]	15.18	[redacted]	[redacted]

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)					
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	17.59	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	5.30	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 41: EAG's probabilistic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	15.39	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	16.32	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually)					[redacted]
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	11.46	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.33	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.36.2.1	[redacted]	13.74	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	12.48	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative	6.2.3	[redacted]	13.60	[redacted]	[redacted]

published literature sources used for carer disutility)					
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	16.27	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	4.83	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

6.4. Conclusions of the cost-effectiveness section

There was a lack of robust clinical data to inform the company's economic model, which the EAG considered was largely due to the rarity of the condition. Consequently, however, the company's base case analysis contained assumptions that the EAG considered to be associated with a high degree of uncertainty. Key model inputs and assumptions were tested by the EAG via scenario analysis, as noted in Section 6.2, which showed that results were sensitive to alternative treatment efficacy, carer HRQoL, patient weight and discounting assumptions.

Based on the EAG preferred base case results, olipudase alfa was not considered to be cost effective compared to BSC at a willingness to pay threshold of £100,000 in either adults or children. Although the EAG did not consider QALY weighting to be appropriate, an appendix is provided which contains undiscounted QALYs for NICE's consideration.

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Appendix A: Search strategies for Ovid MEDLINE and Embase

A summary of additional searches completed by the EAG are reported in 3.4.

Search strategy for Ovid MEDLINE:

1	niemann pick disease/	1711
2	(acid sphingomyelinase deficien$ or ASMD or Niemann-Pick).ti,ab,kw.	4078
3	1 or 2	4489
4	type C*.ti.	17610
5	3 not 4	3320
6	5 not ((exp animal/ or nonhuman/) not exp human/)	2794
7	(case report or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	870892
8	case report/ or case study/ or case reports.jw.	2322536
9	6 not (7 or 8)	2338
10	(ephemera or "introductory journal article" or news or "newspaper article" or editorial or comment or overall).pt. or in vitro techniques/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3254601
11	9 not 10	2178
12	review.pt. not (guideline/ or practice guidelines/ or practice guidelines as topic/ or guideline.ti. or (((systematic or meta) and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.)	2878862
13	11 not 12	1692
14	Niemann-Pick Diseases/	1711
15	Niemann-Pick Disease, Type B/	95
16	((visceral or neurovisceral) adj2 NPD).ti,ab.	3
17	(ASM adj deficien*).ti,ab.	94
18	Niemann-Pick.ti,ab,kw.	3983
19	niemann pick.ti,ab,kw.	3983
20	NiemannPick.ti,ab.	3
21	14 or 15 or 16 or 17 or 18 or 19 or 20	4451
22	21 not 3	44

Search strategy for Ovid Embase:

1	niemann pick disease/	5043
2	(acid sphingomyelinase deficien$ or ASMD or Niemann-Pick).ti,ab,kw.	5336
3	1 or 2	6837
4	type C*.ti.	19792
5	3 not 4	5227
6	5 not ((exp animal/ or nonhuman/) not exp human/)	4301
7	(case report or woman or man or child or adolescent or female or male or bou or girl or infant).ti.	952339
8	case report/ or case study/ or case reports.jw. or case reports.jx.	2854453
9	6 not (7 or 8)	3651

10 (ephemera or "introductory journal article" or news or "newspaper article" or editorial or comment or overall).pt. or in vitro techniques/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti. 3433333
11 9 not 10 3343
12 limit 11 to (article or article in press) 1498
13 review.pt. not (guideline/ or practice guidelines/ or practice guidelines as topic/ or guideline.ti. or (((systematic or meta) and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.) 2721272
14 12 not 13 1498
15 ((visceral or neurovisceral) adj2 NPD).ti,ab. 6
16 (ASM adj deficien*).ti,ab. 132
17 Niemann-Pick.ti,ab,kw. 5186
18 niemann pick.ti,ab,kw. 5186
19 NiemannPick.ti,ab. 12
20 15 or 16 or 17 or 18 or 19 5253
21 20 not 3 54
22 type B.ti,ab. 33907
23 4 and 22 118
24 2 and 23 9
25 11 not 12 1845 [results not retrieved by use of Article, Article in Press limit]
26 olipudase alfa/ 49
27 olipudase alfa.ti,ab. 38
28 26 or 27 53
29 25 and 28 31
30 (prevalence or incidence or natural history or complication* or mortality).ti. 719318
31 25 and 30 17
32 exp health economics/ 974892
33 exp economic evaluation/ 338707
34 exp "health care cost"/ 323866
35 exp pharmacoeconomics/ 221790
36 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 1285287
37 (expenditure$ not energy).ti,ab. 47306
38 (value adj2 money).ti,ab. 2809
39 budget$.ti,ab. 44444
40 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 1900228
41 (metabolic adj cost).ti,ab. 1749
42 ((energy or oxygen) adj cost).ti,ab. 4850
43 ((energy or oxygen) adj expenditure).ti,ab. 35485
44 41 or 42 or 43 40910
45 40 not 44 1891789
46 25 and 45 88
47 Quality-Adjusted Life Years/ 32388
48 (quality adjusted or adjusted life year$).ti,ab,kf. 31254
49 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 25008
50 (illness state$1 or health state$1).ti,ab,kf. 13601
51 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2866
52 (multiattribute$ or multi attribute$).ti,ab,kf. 1414
53 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 29594
54 utilities.ti,ab,kf. 14100

55 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. 28068
56 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 8184
57 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 43549
58 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. 3295
59 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. 30688
60 quality of life/ and ec.fs. 53881
61 quality of life/ and (health adj3 status).ti,ab,kf. 19411
62 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 6492
63 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 231876
64 25 and 63 22
65 overall survival.ti. 13772
66 25 and 65 1
67 randomized controlled trial/ 727333
68 random*.ti,ab. 1832911
69 RCT.ti,ab. 48577
70 67 or 68 or 69 1952480
71 25 and 70 32
72 71 not 29 25

WORLDSymposium, 2021

https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/132/issue/2

Searched used CTRL+F: Niemann. All highlighted records relate to Niemann-Pick C. No additional records retrieved.

WORLDSymposium, 2022

https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/135/issue/2

Searched used CTRL+F: Niemann. All highlighted records relate to Niemann-Pick C. No additional records retrieved.

European Society of Human Genetics-2021

https://www.abstractsonline.com/pp8/#!/10372

Searched using search box: Niemann. No additional relevant records retrieved.

Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2021

https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12458

Searched PDF with CTRL+F: sphingomyelinase. Kapetanakis (P-173) retrieved by EAG's additional searches in Ovid Embase. No additional records identified.

Appendix B: Results based on undiscounted QALYs

The following section presents the EAG scenario analyses and EAG preferred base case results based on undiscounted QALYs.

EAG scenario analyses using undiscounted QALYs

Table 42: Deterministic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	42.68	[redacted]	
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	37.21	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	39.03	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	17.64	[redacted]	[redacted]
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	42.45	[redacted]	[redacted]
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	38.79	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	32.77	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	37.12	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	33.85	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	41.55	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	42.68	[redacted]	[redacted]
Starting age					
Reduced to 2 years	6.2.6	[redacted]	44.75	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	42.43	[redacted]	[redacted]
Modelled patient weight				[redacted]	
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	42.68	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 43: Probabilistic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	16.1	[redacted]	40.69	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	35.50	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	37.55	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	16.77	[redacted]	[redacted]
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	40.69	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	37.30	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	30.65	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	35.14	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	32.95	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	39.73	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	40.55	[redacted]	[redacted]
Starting age					
Reduced to 2 years	6.2.6	[redacted]	43.45	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	40.76	[redacted]	[redacted]
Modelled patient weight				[redacted]	
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	41.08	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 44: Deterministic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	24.03	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	19.25	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	20.11	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	13.84	[redacted]	[redacted]
Mortality					
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	21.92	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.92	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.05	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	18.50	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	24.03	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	27.78	[redacted]	[redacted]
Liver complication rate					

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	23.90	[redacted]	[redacted]
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	24.03	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	24.03	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 45: Probabilistic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	22.21	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	17.47	[redacted]	[redacted]
b. Observed benefit continues: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	18.44	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	12.36	[redacted]	[redacted]
Mortality					
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	20.41	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	17.21	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	18.96	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	17.87	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	22.19	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	25.56	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	22.40	[redacted]	[redacted]
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	22.53	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	22.09	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

EAG's preferred assumptions (undiscounted QALYs)

The EAG preferred deterministic and probabilistic base case ICERs are provided in Table 46 to Table 49.

Table 46: EAG's deterministic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	40.72	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	42.68	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					[redacted]
Removed carer disutility associated with death of patient	6.2.3	[redacted]	33.85	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	37.21	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	32.77	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	37.12	[redacted]	[redacted]
c. Assume 1 carer in each health state	6.2.3	[redacted]	41.55	[redacted]	[redacted]
Removed disease-related mortality (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	42.45	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	42.68	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	21.78	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 47: EAG's probabilistic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	38.79	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	40.69	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					[redacted]
Removed carer disutility associated with death of patient	6.2.3	[redacted]	32.95	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	35.50	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	30.65	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	35.14	[redacted]	[redacted]
c. Assume 1 carer in each health state	6.2.3	[redacted]	39.73	[redacted]	[redacted]
Disease related mortality removed (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	40.69	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	40.53	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	20.83	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 48: EAG's deterministic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	22.44	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	24.03	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually) 6.2.1					[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	18.50	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2-years		[redacted]	19.25	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.92	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.05	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	24.03	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	10.44	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 49: EAG's probabilistic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	20.74	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	22.21	[redacted]	[redacted]

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
EAG Preferred base case assumptions (applied individually)					[redacted]
Removed carer disutility associated with death of patient	6.2.3	[redacted]	17.86	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.36.2.1	[redacted]	17.81	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	16.97	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	18.85	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	22.37	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	9.24	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann Pick disease type B and AB) [ID3913]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with acid sphingomyelinase deficiency or caring for a patient with acid sphingomyelinase deficiency. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 29 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with acid sphingomyelinase deficiency

Table 1 About you, acid sphingomyelinase deficiency, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with acid sphingomyelinase deficiency? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with acid sphingomyelinase deficiency? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Niemann-Pick UK (NPUK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with acid sphingomyelinase deficiency? **If you are a carer (for someone with acid sphingomyelinase deficiency) please share your experience of caring for them**	I have held the position of CEO for Niemann-Pick UK (NPUK) since 2005 and have gained experience of providing the patient perspective in over 20 years as a patient advocate, and as the mother of three children affected by Niemann-Pick type C disease. Since my earliest interactions with the ASMD community, I have come to understand the impact of this progressive and life-limiting disease which significantly reduces life expectancy. Representing the views of our patient community is a huge responsibility and one that I take very seriously. Patients and their family members know what is most important to them and what change will have the most impact on their daily lives. I take every opportunity to meet and talk with patients and their families, and I recognise their valuable contribution in shaping the services we provide at NPUK. The following statement is based on my experience, my interactions with ASMD patients and their families and the patient experience data gathered by NPUK throughout the year.
7a. What do you think of the current treatments and care available for acid sphingomyelinase deficiency) on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	One patient explained: “I was diagnosed when I was three years old, and from an early age I knew that I was different, that I was special. Unlike the other kids I was always going into hospital for tests. I had to have blood tests, flu jabs, x-rays, overnight stays at the hospital for monitoring. But the biggest hint was my large tummy that was noticeable from being a toddler.”

	Multiple medical appointments and screening tests often limit a patient and carers ability to go about their daily lives, with time away from school or work impacting on their ability to achieve educational goals or financial stability. In addition, appointments with expert clinicians are limited, usually twice per year, and patients and carers report much lower levels of satisfaction with locally based care. This is related to a lack of knowledge and understanding of their condition, the progressive nature of symptoms and their inability to access suitable symptomatic treatments, supportive aids and/or adaptations in a timely manner. Despite this, patients and their carers report high levels of satisfaction with the care they receive from specialist centres feeling confident and supported by their clinical teams' knowledge and expertise in this rare condition. This confidence is not often shared in relation to care in local centres, which can be challenging due to the rare nature and limited knowledge / experience of treating of ASMD. A caregiver reported: "Bruising was very noticeable at a very early stage, I dreaded putting our son in short trousers as he looked as though he had been beaten, his legs and arms pickled with bruises from normal play, On one occasion after surgery to remove a cyst from his cheek, on returning to the hospital to have his stitches removed, he was whisked off and my husband and I questioned, as they really could not believe that the amount of bruising he had on his face was a result of the surgery, eventually a call to our specialist consultant confirmed that bruising due to low platelets does take place. The nosebleeds happened a lot later, probably when he was 13, alarming at first but we all soon learnt how to cope with them, he had his nose cauterised a couple of times, again though this was due to his low platelets, as a side effect of his enlarged spleen" My reported view on current treatments aligns with the thoughts and experiences of our patient and caregiver community and is reflected within patient experience surveys and case studies collected over many years.

8. If there are disadvantages for patients of current NHS treatments for acid sphingomyelinase deficiency) (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Patients and carers report dissatisfaction with their diagnostic journey, which in some cases is stretched over many years, leading to delays in accessing expert care, practical support, and symptomatic treatments, as well as impacting family planning decisions. Most patients in England receive care at one of the eight designated NHS Specialist Centres providing Highly Specialised Services for patients affected by Lysosomal Storage Disorders. Patients and carers report difficulties in travelling to specialist centres, which are often located far from their home. This is especially so when the disease is more progressed and their burden of disease greater, or when there are family and/or financial constraints. Despite this, patients and their carers report high levels of satisfaction with the care they receive, feeling confident and supported by their clinical teams' knowledge and expertise in this rare condition. However, there are currently no treatment options for ASMD except supportive care. Best supportive care is complex and costly, due to the progressive and multisystemic nature of ASMD and involvement of many different specialities. Treatments, involve symptomatic relief of the disease, including pain relief for musculoskeletal pain, the management of the complications of the disease, (e.g., blood transfusion following bleeding episodes, significantly elevated cholesterol levels and the consequential cardiovascular disease, dietary /digestive aids and invasive surgeries). For patients, this means years of frequent and multiple medical appointments, with regular monitoring and often invasive tests through involving several different clinical teams, including Cardio/respiratory, Endocrinology, Haematology, Hepatology, Physiotherapy, Dietetics. With these clinical teams often located in different locations around the country, the coordination of these appointments can be challenging. In addition, appointments with highly specialised teams are limited, usually twice per year, and patients and carers report much lower levels of satisfaction with locally based GP and hospital care.

	This is related to a lack of knowledge and understanding of their condition, the progressive nature of symptoms and their inability to access suitable symptomatic treatments, supportive aids and/or adaptations in a timely manner.
9a. If there are advantages of olipudase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does olipudase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Following treatment with olipudase alfa, families and carers observed life-changing effects, reporting that their child was no longer exhausted, could attend school for a full day (and parents could resume work), eat normal size meals, walk greater distances without breathlessness and have the energy to enjoy social activities. Furthermore, they could expect to have a far greater life expectancy, with less dependence on healthcare and clinical interventions. Most importantly in my experience of supporting treated patients (ten plus years'), I have observed that treatment with olipudase alfa is transformative and can, over time, reverse (not just stabilise or improve) the effects of ASMD, significantly improving patient and carers' lives and enabling patients to reach and maintain full or near-full health for an extended period of time. Without treatment, parents and carers report feelings of anxiety, stress and depression, linked to their thoughts about keeping their child safe, their health, guilt and feelings of being 'at fault' (for passing on a genetic disease, not spending enough time with siblings, their child's quality of life, what their child is missing out on). Anxieties are exacerbated by constant fatigue and isolation associated with being a caregiver. In addition, sadness that their child was not able to do what they wanted to do and extreme stress in not knowing how the disease would progress, whilst knowing that the outcome was death if it was left untreated. Parents and carers also reported impacts on their work and social life, with many having to give up work entirely or go part time, to care for their child and attend medical appointments, often with severe consequences on family finances. "We questioned and felt a lot of guilt - did we do the right thing to have kids? Should we have done more genetic testing? Were we selfish to think that we didn't have these mutated genes in our cells? There was a lot of stress for us as parents just

	knowing that we brought kids into this world who were going to have an uphill battle." "It is heart-breaking to watch your child go through everything. Really, it puts a lot of stress on us as parents, but also me and my husband's relationship, and it affects all aspects of our lives. Before his infusions and stuff, he required so much care." "You wake up thinking about it. That takes over your life, how am I going to normalize my child's life? How is she going to be able to live normal and not be constantly sick and in the hospital?" "There were times when my wife would go in her bedroom and cry." Sibling speakers at the NPUK Family Conference spoke with great emotion about how they felt growing up - with feelings of guilt (not being affected, not having health issues), how they felt left out, isolated, not knowing what was going on, how they could at times be resentful of the attention that their affected sibling was receiving and their embarrassment when friends came to their homes. They talked of becoming 'young carers' and how they experienced a range of practical, emotional and psychological issues, leading to problems at school, social isolation, feeling neglected and being bullied. They also talked of anxiety for their affected sibling, not feeling able to talk to their parents and worrying about death and dying and what will happen to their sibling as ASMD progresses.
10. If there are disadvantages of olipudase alfa over current treatments on the NHS please describe these. For example, are there any risks with olipudase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	In a recent global survey, "The impacts of olipudase alfa on paediatric patients with ASMD and their families" disadvantages mentioned by patients and families included the treatment not crossing the blood-brain barrier, missing school or work to receive treatment, and the demands and challenges of the clinical trial. All those participating in the survey and those consulted outside of the survey reported that the benefits of the treatment against best supportive care outweighed the risks and disadvantages of olipudase alfa, with most saying: • There were no adverse impacts - benefits outweigh the risks • Side effects were minor issues compared to the effects of ASMD

	• Any concerns about the treatment were addressed by the clinician and vanished once results were apparent • Patients and families adapted easily to the two weekly infusions, at home or in clinic, with homecare the preferred option
11. Are there any groups of patients who might benefit more from olipudase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Clinical data is very strong and published evidence shows clearance of storage and reversal of disease. As it is currently not possible to accurately identify where a patient sits on the spectrum of ASMD disease, outside of very small numbers of classical type A homozygous mutations, treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment. I do not agree with the EAG's assumption that the target population for olipudase alfa would be clearly recognisable to clinicians. In my understanding, it is not easy to determine the clinical distinctions of disease type A/B / disease type B early in the disease course. These distinctions often can't be determined for years, even by the world's experts. The only group that may declare itself in the first year 16 months of life is the most severe cases acute neurovisceral or classical type A mentioned above. In addition, and in relation to the EAG's question regarding clarification that trials of olipudase alfa included participants with ASMD type A/B – I am aware of two paediatric patients with type A/B who were included in the clinical trial, and who have experienced increased physical and mental health benefits. Working in partnership with the National Niemann-Pick Disease Foundation (USA) and the International Niemann-Pick Disease Registry, NPUK commissioned a survey "The impacts of olipudase alfa on paediatric patients with ASMD and their families" to highlight the patient experience and perspective regarding the burden of disease, burden of therapy, benefits of therapy, risks, and tolerance of risk. Four of the patients surveyed had neurological symptoms associated with type A/B. NPUK has provided a copy of the survey report as part of their submission. Phase two of this survey "The impacts of olipudase alfa on adult ASMD patients and their families" has recently been completed. Preliminary results were presented at

	the National Niemann-Pick Disease Foundation (USA) annual conference in July 2023, a copy of this presentation is provided as an appendix to this form.
12. Are there any potential equality issues that should be taken into account when considering acid sphingomyelinase deficiency) and olipudase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	All ASMD patients are disadvantaged by the severe and progressive nature of this condition, and the complex and diverse symptoms and multi-system impacts that prevent them living full lives.
13. Are there any other issues that you would like the committee to consider?	The impact of this technology goes beyond direct health benefits for patients and the cost saving for health systems and includes societal economic benefits such as maintenance of earning potential for the patient and carers. Early diagnosis and treatment for patients with clinically detectable disease will prevent significant and irreversible burden of disease, reduce comorbidity and mortality. The introduction of this technology requires no new specialised equipment or services, IV infusions can be managed in existing clinical centres through current service specifications, or preferably by a home-based infusion service or if appropriate, self-infusion.

	Whilst this technology may be viewed as a 'high-cost treatment' there will be a significant and long-term downstream reduction in healthcare and societal costs over the lifetime of a treated patient. The cost of not treating – patients receiving only best supportive care / symptomatic management, i.e., antibiotics and hospitalisations for respiratory infections, home oxygen needs, medications and treatments to manage bleeding or low platelets, liver transplants, medications to address high cholesterol, portal hypertension and other consequences of a chronic condition - will be much greater. The development of this technology has benefitted from 20plus years of investment from the patient community, including surveys, PROMs, natural history studies, an invasive and burdensome trial protocol – nevertheless, patients and their families have been actively engaged, as this presents the only potential option for patients and evidence shows it can make a huge difference to their quality of life with long term implications. It is important to state the small numbers of patients affected by ASMD and therefore potentially eligible for treatment. In our experience over 30+ years of working with the ASMD community, the number of patients supported in any given year has not exceeded 40. It must be noted that this is a life-limiting and life-shortening disease, and that patients don't have a normal lifespan, and that there will be some who have milder disease and therefore have not yet been diagnosed or may have been misdiagnosed. NPUK currently support 37 ASMD patients 34 with ASMD Niemann-Pick disease type B (16 Children, 18 Adults) and 3 with ASMD Niemann-Pick disease type A. For newly diagnosed patients, genetic counselling should be provided prior to and following diagnosis to assist patient and family understanding and enable informed decisions regarding treatment and family planning, including carrier status and potential impact on future offspring and siblings. This should be included within the service provision and provided in a timely manner. Currently there is no routine screening for ASMD as part of the UK's newborn screening programme. Whilst we understand the Committee or any decision they

	make will not influence or change this, it must be noted that to enable the full benefit of this treatment, inclusion in the NBS programme is highly recommended. In addition, I would ask the Committee to give appropriate and careful consideration to the management of patients currently receiving olipudase alfa post-trial and in any period leading up to and post their decision-making process, to avoid additional and unnecessary anxiety and stress.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case	Based on my long-term experience of supporting ASMD patients and their families, and in consideration of the variable nature and severe impact of this progressive, life-limiting and significantly debilitating condition, I believe that ASMD causes severe impairment. Whilst the lack of data on long-term effectiveness is acknowledged, my experience of supporting treated patients (ten plus years') has shown that olipudase alfa is transformative and can, over time, reverse (not just stabilise or improve) the effects of ASMD, with expert clinical opinion and published evidence supporting our view. With treatment, health is significantly improved and continues to improve, enabling patients to reach and maintain full or near-full health for an extended period of time.
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	Once again, the lack of long-term treatment effectiveness data is acknowledged, however, the clinical advice to the EAG seems to ignore published evidence and expert clinical opinion (it must be noted that the availability of clinical expertise and clinical experience in treating ASMD patients.is severely limited). There is published evidence including data showing sustained benefit and

	continuing improvement following treatment of 6.5 years+ including to liver and lung function, and greatly reduced spleen size and continued improvements to health with long term use: *Lachmann RH, Diaz GA, Wasserstein MP, Armstrong NM, Yarramaneni A, Kim Y, Kumar M. Olipudase alfa enzyme replacement therapy for acid sphingomyelinase deficiency (ASMD): sustained improvements in clinical outcomes after 6.5 years of treatment in adults. Orphanet J Rare Dis. 2023 Apr 25;18(1):94. doi: 10.1186/s13023-023-02700-x. PMID: 37098529; PMCID: PMC10131350.* Whilst longer term, robust data may not be available for many years, patient experience reported to us over a ten-year period speaks volumes and provides meaningful evidence of significant benefit, with severely impacted children and adults now in near or near-full health, able to fully function, live independently, attend and achieve in education or work, and have the energy to participate in social activities.
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL • *How does acid sphingomyelinase deficiency affect the quality of life of carers?* • *On average, how many people are involved in caring for someone with acid sphingomyelinase deficiency? Does this differ by age?* • *Would you expect carer quality of life to improve in people whose disease responded to treatment? If so, how?*	I support the EAG view in regard to the application of carer disutility regardless of treatment arm. I agree that carer disutility is greater for patients in more severe health states, and whilst this will still apply following treatment, we can expect it to be less marked over time. I understand and acknowledge the issues in collecting carer disutility data in ASMD. Whilst I agree that Pompe disease is not a good comparison with ASMD, I disagree that Pompe disease has an overall greater carer burden. ASMD has very different symptoms and challenges, with patients having variable abilities and disabilities, some requiring constant support into adulthood with significant carer burden. Whilst the assumption of 1.78 carers for children could be reduced slightly, I strongly feel it should be above the EAG proposed number of 1 As symptoms are variable and severe, and dependent on disease progression, carer involvement is necessary and can be all-consuming, and emotionally exhausting, considering the frequent and multiple medical appointments, regular monitoring and several different clinical teams, often located in different locations plus the challenges of coordinating appointments at any age / point of progression. Add to this assistance with self-care, including personal care, help to prepare meals and eat, assistance with mobility and daily tasks, which applies to both child and adult patients. I feel 1.5 carers for children and adults would be more appropriate.

	Whilst I agree in part with the EAG view on carer disutility associated with patient death, I do not believe that this should be dismissed completely. Undoubtedly, the death of a patient has an impact for a significant period, with carer disutility reducing over time.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	ASMD is a spectrum of disease, with variable presentation and progression. Whilst most ASMD patients are diagnosed in childhood, and experience increasingly severe health issues, there are those (usually (A/B) that experience severe issues and pass away in childhood.
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	ASMD patients are most often under normal weight and shorter in stature than their peers. With treatment, we have seen the normalisation of height and weight over time.
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations	I am not aware of an agreed international classification of severe disease, and I would like to stress that ASMD is multi-systemic and severely life limiting. The inclusion criteria for both the paediatric and adult trials excluded the most ill patients in the patient community, so the severe "subgroups" in the study are actually now healthier than many of the patients in the community. Patients describe reaching a point 'of no return' in their disease progression, where the disease 'creeps up' without early indicators, explaining that they often don't realise how clinically unwell they are, as feeling unwell is their 'normal'. To further assist the EAG with their questions regarding the reliability of mortality data, another source that provides a different approach, looking at causes of death rather than incidence, may be helpful:

	David Cassiman, Seymour Packman, Bruno Bembi, Hadhami Ben Turkia, Moeenaldeen Al-Sayed, Manuel Schiff, Jackie Imrie, Paulina Mabe, Tsutomu Takahashi, Karl Eugen Mengel, Roberto Giugliani, Gerald F. Cox, Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases, Molecular Genetics and Metabolism, Volume 118, Issue 3, 2016, Pages 206-213, ISSN 1096-7192. Olipudase alfa not only appears to halt progression but reverses many aspects of this debilitating and life limiting disease. With evidence that treatment benefits can overcome disease severity and, in some cases, reverse disease impact, we would expect to see the health of treated children continue to improve, to the extent that symptoms in adulthood are significantly or fully reduced. Based on my experience of working with the patient community, it is my understanding that the benefits of treatment for patients with severe disease are significant and may increase over time. Clinical data is very strong and shows clearance of storage and reversal of disease. As it is currently not possible to accurately identify where a patient sits on the spectrum of ASMD disease, outside of very small numbers of classical type A homozygous mutations, I believe that treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment.
Are there any important issues that have been missed in EAR?	Improvements to lung and liver function and the reduction in spleen size following treatment with olipudase alfa have a total body effect and bring multiple benefits for patients, which cannot be overstated. Considering only the statistics of DLCO and spleen volume does not accurately convey the reduction of disease burden and real-life impacts experienced and reported by patients and their carers..

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann Pick disease type B and AB) [ID3913]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with acid sphingomyelinase deficiency or caring for a patient with acid sphingomyelinase deficiency. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 29 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with acid sphingomyelinase deficiency

Table 1 About you, acid sphingomyelinase deficiency, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with acid sphingomyelinase deficiency? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with acid sphingomyelinase deficiency? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	NPUK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with acid sphingomyelinase deficiency? **If you are a carer (for someone with acid sphingomyelinase deficiency) please share your experience of caring for them**	At 3yrs our son was hospitalised from a severe tonsillitis infection. He was found to have a very enlarged liver and spleen which eventually led to his diagnosis of ASMD. The genetic counselling (whilst we were still trying to cope with the diagnosis and so much unknown about how ill he would be, with no cure nor treatment) resulted in us deciding not to have another child. There was a 1 in 4 chance of having an affected baby and I would not have terminated a pregnancy – I felt it would have been like choosing not to have our son. Following diagnosis, I totally withdrew from my friends and family and found it difficult to function. My husband threw himself into his work. Over the following year, our son had frequent infections, fits (fits only until 7years), hospitalisation, and difficulties eating. I had a very successful and well-paid career, which I clearly could no longer commit to. So, I gave it up when he was 4yrs, to work in the showroom for my husband's small business. That allowed me to be flexible to stay in hospital and be home whenever needed. At that time, I couldn't and didn't consider the big loss in income and loss of a career I had built and enjoyed. Retrospectively though, it was the right decision, as his infections and neutropenia meant that he missed a lot of school and was in hospital a great deal (with me) often 3-14 days, and sometimes 4 times a year. Up to the age of 15yrs old, he had over 25 emergency (unscheduled) hospital admissions to the children's ward, often needing IV antibiotics (needing a stay of at least 3 days) for febrile neutropenia. We were trying to give him as normal life as possible, but it was obvious that visiting crowded places indoors (e.g., cinemas in the winter and seeing family over Christmas), was causing the infections and the resulting hospitalisation. To avoid being admitted to hospital (due to the febrile neutropenia protocol), we never flew abroad and avoided UK holidays where we would

	mix with other children (every holiday he would catch something and end up in a hospital). He would miss school if there was an obvious infection going round the class and not play with peers if their siblings were ill. He was put on prophylactic antibiotics in the winter months and always had lots of mouth ulcers. The severely enlarged spleen also caused low platelets. Through primary school he was covered in bruises and took ages to heal, and the school was always calling me. A knock into him, during play with a friend (not roughly), caused a bleed on his liver. Following this, he became very scared of being knocked in the abdomen. The 'no contact sports' rule (due to his enlarged spleen and liver) had already been very isolating as dodgeball, football and kick-post were the playground games. Following this incident, the school reported that he would isolate himself; "*back into corners"*, *"cover his hands over his belly"* and be "*scared of the more boisterous, unpredictable children"*. He would constantly *"assess risk"* and developed "*tactics like going to the toilet or hiding under the table so he could avoid playground breaks unnoticed"*. We were so worried about this anxiety, but also because he was becoming isolated due to his slow physical development and very tiny size (0.4-2nd centile growth). He became very self-conscious and embarrassed of not being able to reach his feet (I would put his shoes and socks on, wash his feet), not wear normal trousers, not play normal games, couldn't even reach the primary school urinal so would wet himself if the cubicles were full (the Head had a new low one put in especially). Aged 5yrs onwards, we also had to manage; bowel problems (pain, constipation, diarrhoea), eating difficulties (little and often - always feeling weak, sick and full), fatigue (unable to do any after school activities), breathlessness, Vit D and iron deficiency, shin pain (he would drop down and clutch them during a walk), dropped inwards ankles, hamstring and joint pain (advised no anti-inflammatory medication because of his liver), headaches, swelling and burning of hands and feet (which *"really annoyed"* him and interrupted sleep and lessons), discomfort in abdomen (cramps, tenderness, uncomfortable in bed).

	We managed all the clinical appointments as positively as we could for our son. There were usually 8-12 a yr, in 4 different hospitals, including; metabolic, heart, respiratory, liver, gastroenterology, haematology, dietician, physio and the local paediatrician (whose ward we had open-access to for neutropenia). In addition, there were scans (dexa, MRI, CT, Ultrasounds), heart monitors and respiratory and blood tests. On top of that, there was the rushing into hospital with fever admissions and day to day challenges at school. He loved to draw, loved cars, play table tennis, bowls with old people and badminton. Our focus was to make his life as fun as it could be. However, we were finding it very difficult to cope with the emotional stress of his illness during primary school. My husband would say that every time I called him, he would have a sinking feeling and think *"what now?"*. We would solve one challenge then be confronted with the next. We found it so difficult coping with a progressive illness that started from 'normal'. Not just the frustration he had - in not keeping up with peers or being able to do what he used to do. But also, understanding and managing his symptoms. For example, we thought he was a fussy eater so we were always trying to get him to eat when he just couldn't. Also, fatigue was so hard to manage – he would go downhill so rapidly if he didn't eat often enough or over did it (which he did because he wouldn't accept what he couldn't do). This slowly got worse, and each stage crept up on us. I felt confused about how best to manage him and hadn't realised how the disease was progressing until I looked back months later. This made me feel guilty and that I was failing him by not realising. I had pains in my chest that wouldn't go away, panic attacks and whenever I was alone in the car I'd cry. We had attended the annual NPUK conference since diagnosis for education and support. There, I had spoken to other older ASMD patients who described very negative experiences at school, so I fought for a named Senior school on his EHCP (age 11). This was a very small school, in the next road to home, had nurses on site and he'd have a one to one in small classes. This was private so had to be funded by the council. I did this because the local state school was further from home (he would need an ambulance if febrile, as I couldn't get there in time for the protocol), and their risk assessment of his enlarged spleen and liver meant they would be constantly removing him from the

	other children and offering poor access to the curriculum when ill or fatigued. This was a stressful process, as at the same time his disease was progressing, and he was always exhausted. I knew he would need to be at school near home to rest in the day if needed. He couldn't carry his bag any more due to back pain or eat enough calories (was feeling too full and sick all the time), had to rush to the toilet 3 or 4 times a day (would need to be very close or would have an accident), headaches, dizzy and faint with fatigue after walking. I would have home-schooled him, but he was absolutely determined to go to school. He was always trying to be seen as 'normal' even though he was so tiny in comparison to his developing pubescent peers (he was half the size of some). He had to run to keep up with their walking and was unable to join in with their activities because of fatigue, no muscle development and bone pain, as well as the severely enlarged spleen and liver. At that time, he loved lessons, as then he felt a bit normal, sitting down and working the same as them. By 14-16yrs it was very sad because his fatigue meant he had no real 'out-of-school' life as when home, he was just recovering from the effort of school. There was no sign of puberty or growth, whilst his friends were changing; going out, interested in girls, summer jobs, etc. I would often have to feed him on the sofa and help him to function really (like he would be too tired to wash). Fatigue was also affecting his academic work which upset him as he was so determined. He had previously been in top sets but was really struggling with his immediate memory, *"1st centile for recall - working memory"*. This was assessed by a neurologist and Education psychologist and found to be due to *"severe fatigue"*. He was spending more time off school at home resting which also made him more isolated from the other children. At this point, the pressure on us as a family felt much worse. I was struggling to ever do any work, get him to all the appointments, as well as care for him daily. He was waking up exhausted every day, with a list of things that hurt, and anxieties about school and peers. I constantly felt worried and tense. By 16, his bowel difficulties, feeling sick and hunger were often stopping him leaving the house until the afternoon, but then bone pain and fatigue would limit his activity. When he went out, he would walk with his camera as he loved photography. But a walk on one day would mean he'd be exhausted on the sofa the next, with hardly the energy to eat, which he needed to do

	little and often or he would get worse. This was a difficult cycle for me to manage. He had become even more dependent on me and panicked if I left him if we were somewhere he didn't know well. In hospital I couldn't go to the toilet without him wanting to come and drag his IV pump with him. Another source of stress was talking to professionals like councils and DWP. Trying to explain ASMD and his needs/symptoms to non-medical strangers was time consuming, emotionally draining and rarely successful. I think this was because their interpretation of *'fatigue'*, '*hunger'* and *'feeling sick'* was nothing like the severe, life-affecting symptoms that he was experiencing. We kept positive when with him, but as parents, found coping with his illness, anxiety and the obvious degradation (lung function was now 49%) stressful and very lonely. The time caring meant we didn't really have a social life and didn't have a support network either (my Mum and Dad got so distressed so I stopped telling them things, and extended family and friends couldn't really understand and had naturally moved on with their busy lives). I developed auto-immune health problems: Psoriasis patches, Lichen Planus and Atrophic Gastritis. Ironically, Covid came as the break we needed. Our son was shielded – which he said didn't feel much different to his normal winter months really. School closed, his GCSEs were cancelled, and we closed our business temporarily to protect him. He wasn't pushing himself in the same way and could manage his bowels (as always at home), slept and rested more. People said they could *"relate to your life better, having been through lockdowns".* We spent Covid and the next years (16-18yrs) with him studying only at home on photography and art A-levels. He contributed ideas, art and a voice to *'Invisible Manners'* a 5min animation by NPUK (https://www.youtube.com/watch?v=A1QmA_HK7e4) which showed the difficulties of having ASMD. This inspired him to apply to Norwich Arts University (as had always been his ambition) to study animation. His photography work got him an unconditional place. Determined to attend Uni and start getting back into the world, he asked a local business for a job, sitting serving ice-cream. However, he couldn't keep up. It was horrible to see that he had

	forgotten how limited he was by fatigue, after being at home all the time during and after Covid. Frustrated, he wrote to the company with a mind map of his symptoms asking to be considered for compassionate use of Olipudase Alfa. They were not able to consider his letter, as his consultant had to apply with clinical data only. However, I attach the mind map as an appendix, as it shows a useful snapshot of his symptoms and quality of life issues at 18yrs. His consultant encouraged him to do the Uni foundation year 0, even if not to the best of his ability, to occupy him whilst waiting to hear back from the compassionate use program. He worked at home and attended short lectures. He was offered DSA paid taxi trips, but declined, as he was too anxious about toilet accidents to go in a taxi. So, I drove him to the Uni door and back around his bowel movements and waited for him in Norwich. It was really hard to manage his health, as after a day out, he'd need a rest day. It was stimulating for him to have creative projects to work on in the afternoons when he was able, and meet people his own age, if only in the classroom. I was exhausted, struggling to get up in the morning, laying there thinking about future disease progression if we didn't get compassionate use. Would he be able to continue Uni, need oxygen, a liver transplant? I knew this was a possible outcome and it haunted me that a young lady I had met with ASMD had sadly passed away at just 21 from liver disease. This was very unlike me to allow these thoughts in. I tried to shake it off for my husband's sake, as his attitude was, *"we've just got to get on with it".* At 19 years old, he met the clinical criteria for compassionate use, with Hepatosplenomegaly, Interstitial lung disease, Osteoporosis, Neutropenia and all the symptoms I have described. Before it sunk in, the first thing he said was, *"So if I get hit, I won't die now."* I asked him why he said that, and he explained that it was because he had been told by the consultant that the enlarged spleen should be protected and couldn't be fully removed, as without it, storage would increase in the other organs like the lungs. Next was, *"I won't need to go to hospital when I'm ill now*".

	I thought his daily exhaustion, bone pain, bowel problems and isolation seemed to me to be the biggest difficulties I was helping him to manage, but obviously deep down he had these worries about his safety and going to hospital. However, once it sunk in, he was very excited. He began treatment in April 2023 at the Royal Free. At the time of writing, he has finished the 14-week dose escalation and has had 2 further full doses.
7a. What do you think of the current treatments and care available for acid sphingomyelinase deficiency) on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	There is no treatment for ASMD on the NHS. Care has been best in specialised centres (but travelling to appointments is costly in time and money). The only available care is to support the diverse range of symptoms, requiring many different professionals, in different departments and hospitals (lungs, blood, gastro, skin, liver, physio, diet, eyes, heart, orthotics, mental health). Often, they haven't seen a ASMD patient before, so ask a lot of questions which makes us feel insecure. Sometimes appointments have felt *"pointless"* as the consultants can't offer much help. The GP system has caused slow (and sometimes no) responses, immediate redirection, so a lot of chasing and going round in circles, which is very stressful for him and me. Sadly, these comments and experiences are very similar to what I've heard from other ASMD patients and their families.
8. If there are disadvantages for patients of current NHS treatments for acid sphingomyelinase deficiency) (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Often consultants are trying their best to relieve symptoms with medications that *"might help*" yet have side effects, rather than be able to treat the disease at source to prevent the progression. An example of this was for his bowel difficulties. The gastroenterologist prescribed a low dose of Domperidone. After only a week this caused such severe heart palpitations, our son was admitted to hospital which set off a chain of heart monitoring. He said he'd rather feel sick and stay home until he'd been in the toilet long enough for it all to pass, usually after lunch. A big impact on QoL. Another example of treatment affecting QoL was for his infections. The enlarged spleen had caused low neutrophils so febrile neutropenia protocol meant hospitalisation instead of getting better at home. We were anxious and limited our lifestyle to avoid infections. Last Autumn, the 2 hospitals where he has 'open-access' via Haematology, told us to avoid infection, *"as at this time we had no beds"*. I found this very stressful after 15yrs of Paediatricians saying he must go in within an hour.

9a. If there are advantages of olipudase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does olipudase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Only 4.5 months into treatment with Olipudase Alfa, He and we feel so much better emotionally – it feels like there is hope for a better life. He has started doing short walks most days – recently without pain! but still gets breathless if too far. I've noticed he is having less sofa days and has started pacing round the house, like he used to when he was young. Also, he doesn't keep saying he feels sick anymore – and he is eating larger portions. He asked me to show him how to cook eggs and make turkey burgers. He asked to go out to try Indian food. He isn't in the toilet as long and can leave the house earlier. Last week, he took photos of a local pub to give to them as a gift, so can introduce himself for a lunchtime job next summer. He is doing his digital artwork every day to prepare for Uni Yr 1 and starting work before lunch. He's emailed them for the timetable so he can arrange for his infusion to be on a free day. He has contacted the Uni badminton club. He has been to Norwich to check he can walk from Uni to the bus stop and told me he thinks that soon we can *"give the Blue Badge back!"*. He has been to the cinema and says he isn't worried about catching things because he has noticed his neutrophils have steadily gone up to the highest ever seen, *"I'm not neutropenic now Mum"*. He hit his leg hard on the car door 2 weeks ago – we were all surprised that there were no bruises (normally would be big and black) and his many Petechiae spots have all gone. It is too early to do the scans but already his abdomen appears different, it is flatter, instead of curving out. His pallor is rosier and eyes brighter. He is able to put his own shoes on now and has started wearing jeans (button fly instead of elastic). He has some energy in the evening now, so we three have started going out to dinner together regularly, have been making plans and are laughing together again. I honestly feel like *"we are recovering as a family."* I told him I was proud of his determination and positive attitude after all he has been through, and he looked confused and said, *"but if the spleen and liver go down most of it all goes away Mum"*. I see why he would think like that, on his mind map of symptoms most of the QoL issues are due to; the enlarged spleen, the low immunity (caused by the enlarged spleen), the fatigue (caused in part by the large spleen causing anaemia and difficulty sleeping) and other symptoms like sickness/bowel problems (also caused by the large spleen).

	In coming months, we hope his organ storage will reduce and energy levels will increase, as seen in the clinical trials so he can (as he said in his letter to the company), *"stop wasting my life, exhausted on the sofa and be able to live a better life starting with attending Uni and producing cool animation work I'll be proud of!"* If our son continues to respond to this treatment i.e., reduced spleen and liver volume, resulting in higher platelets, and neutrophils (seen already) less fatigue, bowel difficulties/sickness and anxiety about being knocked into, then I predict these outcomes for my QoL as his carer (in order of my importance, best one first): 1.Freedom/Independence: as he gains daily independence from needing care and support (e.g. from constant fatigue, needing food) and anxiety (e.g. from feeling unwell, from worry that enlarged, so vulnerable, organs being knocked, etc). I too would gain independence again (feeling able to leave him) allowing; some time with my husband - doing as we choose, enjoy exercise, have hobbies and spend time with my elderly Mum (which I regret not being able to do with my Dad). Really, to have some life of my own without constant considerations, limitations and anxiety. 2.Reduction in anxiety and stress: nearly all of my stress is caused by his daily difficulties (pain/feeling unwell, limitations and frustrations) and trying to enable him to study, be a little independent and manage what he considers risk. A reduced spleen volume and less fatigue and easier eating would reduce that and as a result my stress related conditions: panic attacks, psoriasis and other auto immune conditions (even in this short time since beginning the enzyme replacement treatment my psoriasis has already improved and my days feel much calmer). 3.Be able to have goals, refresh skills and return to some sort of career: not feel any more like my education, and previous career success has been wasted. I feel this would be possible if I did not feel constantly 'needed' and stressed, so had the ability to plan my time and focus once more. 4.Social relationships/activities: Both me and my husband were very sporty and social people so I think our physical and mental health would dramatically improve if we had time to get back to even a small social life. It would also be great to feel that I was 'good company' for friends again. Note: It would feel fine still helping our son -if he wanted me to! (Being there for his medical appointments and fortnightly infusions) as they are planned and not everyday care.

	So, disease modifying Olipudase Alfa, absolutely addresses the disadvantages of trying to care for diverse symptoms (symptoms which are a consequence of storage enlarging and damaging organs).
10. If there are disadvantages of olipudase alfa over current treatments on the NHS please describe these. For example, are there any risks with olipudase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No because the treatment is a regular and straightforward routine and doesn't feel stressful. Initially, during dose escalation in hospital, he had slightly raised temperatures and headaches a day after infusion which went away with paracetamol and one loratadine tablet. He didn't need to slow down or reduce the dose. He finds having the infusion no problem and happily does his photo editing during the infusion (he is very used to cannulas). We have all said it is nice to have medical interventions which feel positive.
11. Are there any groups of patients who might benefit more from olipudase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Infusions at home feel very easy. People with mobility and cognitive issues may need support to attend hospital for the initial 14-week escalation. Although they must already have some support in place to attend the many medical appointments anyway. Children and adults will both benefit greatly for different reasons. Children won't have to go through the unpredictable, stressful childhood of constant infections, low platelets, possible neutropenia, anxiety and isolation, ruining their (and their family's) quality of life. Adults will get back some of the health and quality of life they have lost, at a time when they are likely to be much more unwell, with greater and more complex health needs than the children (as progressive).
12. Are there any potential equality issues that should be taken into account when considering acid sphingomyelinase deficiency) and olipudase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged	None that I can see.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case	No comment
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	I know its difficult with such a small sample size, but this data should continuously improve over time. The people I have known involved in trials since they first started have shown startling improvement, both in the initial 2-3 years (reduced spleen & liver size, normalising of bloods, bowels, less bone pain, anxiety, fatigue and more muscle development and energy) but longer term (5 years +) seeing much more improvement in lung function, muscle development and energy.
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL	The company's assumption that QoL improves on treatment is linked to how many of the QoL issues are a result of an enlarged spleen and storage. I think more data will be collected to validate this assumption on 'carer quality of life after treatment' as treatment is given. Caring for an ASMD patient has a daily, severely negative effect on carers' quality of life in order of most difficult:

Patient expert statement

• *How does acid sphingomyelinase deficiency affect the quality of life of carers?* • *On average, how many people are involved in caring for someone with acid sphingomyelinase deficiency? Does this differ by age?* • *Would you expect carer quality of life to improve in people whose disease responded to treatment? If so, how?*	1.Stress/anxiety: Watching my son get more unwell, suffer symptoms (I can't help with) and feel his embarrassment, humiliation and frustration, know it is progressive and life limiting, having to explain it is life limiting and all the diverse symptoms to family and professionals (schools, councils, disability allowance, employers, medics), fear of the future, managing appointments, financial pressures, not getting out of the house nor exercise, being isolated, not being relatable to friends and family, being in hospital, all cause stress. 2.Career/ Self-fulfilment: The stress, demands on time and unpredictability of his health prevented me having my career. Caring for our son's ASMD symptoms has not allowed me to have personal goals. 3.Relationship with partner: We have managed to pull through all the stress together, with the focus on our son. We don't have time 'as a couple' as others do with children over 18yrs. I think if we'd had had another child or I had a part-time job with an employer (rather than our own business), we would really have struggled to stay together as a unit. Divorce seems really common. 4.Social Isolation: I've felt physically isolated, without the time to mix, and the care is home-based on the sofa as he is too tired (so can't mix as carer and patient). I've felt emotionally isolated as others don't understand our situation and can sometimes unintentionally make you feel worse! 5.Self-care: I don't feel able to leave my son, pursue hobbies, sports or exercise. Some days in the morning I don't have time to wash or eat properly through the day, as my day is led by him. You don't have room for other difficulties: eg I was distraught that I wasn't able to spend as much time as I wanted with father when he was end of life. 6.Family planning: I would have loved more children, but I dare not feeling it would compromise my ability to look after my son (not knowing how ill he would be) and I didn't want 1 in 4 chance of having another ill child (I would not have been able to terminate a pregnancy). In childhood, me and my husband cared for our son (husband needed, but to a lesser extent in terms of time). I would say without Olipudase Alfa, it would be the same at 18yrs but over time getting worse (with him needing more care) in adulthood. This is because as a child he had the energy to attend school giving me a break. From 16yrs, as he was getting so much more fatigued school was at

	home, so going forward, if he didn't have the energy to work and always needed me there, I would need breaks. Reference to how carers QoL improves with response to Olipudase Alfa, in a relatively short time period, mine and my husband's QoL has improved significantly both emotionally and physically. For example, already I have not got to spend all morning; preparing food, encouraging him to eat little amounts very often (to pick up his energy) and help him with self-care. This is because he doesn't feel sick anymore, not in the toilet so much and can eat more giving him more energy and time to do things himself. I do not have the stress of listening to a list of painful ailments or anxiety about what he can and can't manage (as the headaches, bruising and bone pain are already reduced and he feels more positive about his day). Please may I draw the committee's attention to **my response to all of question 9 above (a list of changes and QoL improvements)**.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	No comment.
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	For your information, I think the enlarged spleen and liver contributed to my son's weight. He was always on the 0.4-2 centile for height, yet around 25 centile for weight, even though very little muscle development with extremely thin arms and legs, no visible fat at all and a protruding rib cage. He had an enlarged abdomen. At 19yrs he was 53kg.
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations	No comment
Are there any important issues that have been missed in EAR?	No comment

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Untreated by Olipudase Alfa (a disease modifying therapy), ASMD is an increasingly multi-symptomatic, painful, and psychologically damaging disease, which reduces length and quality-of-life.
- For both the patient and the carers, it is stressful, isolating, distressingly progressive and severely impacts their ability to work, have relationships and self-care.
- The spleen enlargement causes other complex physiological and psychological symptoms, which have a debilitating effect on the patient's health and quality-of-life, (and as a direct consequence, that of the carers).
- Treatment by enzyme replacement is proven to prevent and even reverse storage in the affected vital organs; spleen, liver and lungs. This not only stops the disease progression that causes early morbidity but removes most of the quality-of-life issues, enabling a life with the energy, health and state of mind to make choices, achieve goals and plan for the future.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement

Olipudase alfa for treating Niemann-Pick disease types A and B [ID3913]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Niemann Pick Disease UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	There are so many facets to living with this life limiting disease ASMD Type B that it is difficult to summarise. As a child my development was affected in so many ways, regular abstraction from school to attend hospital appointments, ill health due to infections that were always very difficult to fight off, constant fatigue, upset stomach, hunger and constant fear. Fear from being physically hurt, excluded from everything, fear of being included and not being able to cope, to list just a few. Being susceptible to so many illnesses in a social environment resulted in lots of time in semi or total isolation, which meant I was always trying to catch up and spend a lot of time learning from books, parents, or carers because I missed important lessons. Often, I was prohibited from participating in activities with my friends in case I was hurt. This social isolation at a time of key social development is difficult as a child and has lead to minimal friends as an adult. Regularly being told you are different and that you needed to be treated differently affects your long-term mental health. As a child with ASMD type B, there were so many activities I wanted to do and be apart of but was denied the opportunity due to

	either my health or the risks associated with doing it. Instead, I spent a lot of time in and out of hospital having an array of tests and procedures and getting to know clinicians on first name terms or learning handwriting or playing ping pong on my own because no one knew what to do with me. At the age of 11 I was so badly affected with the condition that I was regularly in discussions with paediatricians about how ill I was and that I needed lifesaving surgery. At this young age, having these discussions with doctors and my parents about my own mortality was terrifying especially given the risks associated with the procedure, (Partial Splenectomy) all of which I didn't truly understand at the time. I was even sent on the trip of a lifetime with Dreamflight to Florida as I think few expected me to survive. In fact as a child I was aware that my life expectancy may only be another 5 or 10 years and I was regularly reminded of this as at this time there was very limited information about the disease. As an adolescent, my physical development was delayed, the small group of friends I did have were going through puberty and showing interests in partners. I was still 4'10" and looked about 11 years old even when I was 16 and 17. At this stage in my life my abdomen was significantly distended and I looked like I was pregnant, however my extremities were tiny and malnourished. I used to get pushed around at school and was prone to bullying because of my size. On several occasions I ended up in A+E being monitored for hours to make sure I hadn't ruptured anything after being assaulted by other students. Desperate to fit in and look my age, I would regularly have growth hormone injections to help induce puberty and allow me to grow. This took years and was slow to see any changes, while my friends seemed to be changing in front of my eyes. I didn't realise how much this phase in my life affected me until I was older and looked back. As the disease develops you become more and more tired. You can eat 10 meals a day and never gain any weight because the storage affects the absorption of food through the gut. Your lungs deteriorate and you become out of breath more easily, as well as developing 4 or more chest infections over the winter, no sooner do you recover from one but develop another. There were more requirements for increasing hospital intervention and because of the rarity of the disease and the fact that I was no longer a child, I had no choice but to travel to either London or Manchester from Devon for my care as there were no local specialists or even doctors that could help me. This meant these regular appointments, which would sometimes take 18 or so hours to complete or often required an overnight stay which sounds simple but for my parents trying to juggle work commitments and trying to pay for these visits was very stressful and expensive.

	After leaving school, I had several jobs before joining the NHS ambulance service as a trainee paramedic. This was something I was extremely passionate about and I felt I had a lot to offer with all my own medical experience. I had to work so hard to achieve this. Training at the gym for 3 hours a day after work to build up my strength. Running and cycling for miles even though I was exhausted. All of which was very difficult when you don't retain nutrients. On a few occasions I was really ill from overdoing it because my body couldn't take anymore, but I was determined that I was not going to be a victim of this disease and I would have a life. After qualifying to be Paramedic at the age of 23 a new set of challenges began. With the demands of shift work, which any normal 23-year-old would have no issues, I used to find myself falling asleep in between jobs, because I was constantly exhausted. Suffering from thrombocytopenia I was always covered in bruises and my weakened immune system meant I was always ill as I worked around poorly people, but I loved my job and refused to be defeated by my disease. I struggled with relationships as a young adult because I lacked complete confidence in this area, and I dreaded having to tell people about my condition and would be regularly reminded at home that I buried my head in the sand. I met [redacted], my wife around the time I joined the ambulance service. A time that was full of excitement and firsts but also clouded by the thought of having difficult discussions surrounding my health, my reduced life expectancy and what the disease involved and what the future looked like. [redacted] was fantastic about all of this and continues to be a huge support to me. I have two wonderful stepchildren who we have also had to discuss these topics with. They received the information well but [redacted] who was only 6 yrs at the time did not fully understand the extent of the disease. As she has grown and understood my condition fully, she has spent many hours on the internet looking up how to check organ compatibility in case I needed a transplant in the near future. Physically there are many well-known effects this condition has on your body, but there is less emphasis on the long-term effects on your mental health and that of those around you. Prior to treatment my close friends and family were constantly worried about my health and what the future would if any, look like. All year long I would develop one illness after another, every hospital visit showed a further decline in my health and my family were aware that many people with my condition don't survive beyond middle age if they are "lucky". In my adult life I never committed to anything that didn't help or add fulfilment to my personal wellbeing because I refused to waste precious time on it, as my life was limited. I have never planned for the long-

	term future, I never knew how to. Even now I struggle with this, because it has been drummed into me all my life that I might not be around to enjoy it, a privilege many take for granted. I have worked extremely hard to prove to others that I can do something even at my own detriment because I will not be told that I'm not capable. I have been fighting all of my life for a chance of 'a life'. The ERT has given me that life. It has changed my world completely. Medically it has reversed all the damage the disease has done to my body. I no longer feel weak, tired, hungry, sick, constant pain in some form, but most of all I haven't been frightened. Medically it has achieved much more than we all hoped for in the very beginning of the trial 10yrs ago. With this treatment for the first time in my life I have the chance of a future.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There are no treatments for this condition, except the ERT. Treatment or care only limits the effects of the disease or buying the effected individual more time. I was extremely fortunate within my lifetime to have experienced some groundbreaking procedures executed by some extremely clever and pioneering individuals and their care brought me time I wouldn't have had otherwise. I have tried many medications and procedures to varying effects, but none have ever improved my health, but merely slowed my deterioration. The last conversation I had with my consultant before starting the trial was that we needed to discuss the possibility of a liver transplant as there were few other options available to me, certainly nothing less than more lifesaving surgery.
10. Is there an unmet need for patients with this condition?	Yes, absolutely, prior to the development of this enzyme replacement therapy, there was a total unmet need for patients with this condition. In my lifetime, I have lost several friends to this disease who despite all the best attempts to save them including, liver transplants have died. There is nothing the NHS currently offers that even successfully slows down the disease let alone reverses the existing damage.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This drug has changed my life in an unquantifiable way. It has given me excellent health! Not just slightly improved but a life changing difference. For the first time I have a future with my family and loved one's. Since starting the treatment 10 years ago I have only been ill a few times with minor winter colds. I have had COVID 19 three times but on all of these occasions have had very minor or no symptoms and have recovered quicker than healthier people I know. Before the enzyme I would have surely died catching COVID19. I eat less, as all food stays in my system long enough now to be absorbed and my health and strength improve accordingly. I am no longer tired all the time, I noticed this significant change after approximately 10 months on the trial, resulting, with being able to easily work full time while simultaneously attending college part time in the evenings for 3 years to achieve a diploma in engineering and still travelling to London every 2 weeks for the enzyme. [476-mile round trip]. My health has continued to improve so much year on year that 12 months ago I ran a half marathon one Sunday with no training just because I wanted to see how far I could run in one morning. I now have a hugely responsible job, overseeing and managing the Southwest of England's ambulance fleet of NHS emergency vehicles. I regularly experience huge levels of stress and work 65 – 70 hours a week, yet I am never poorly and continue to have brilliant health. My abdomen is no longer painful and does not wake me three or more times a night, and I rarely bruise. My hospital attendances are now solely due to check ups and never last long as everything is either continuing to improve or is as 'normal'. I no longer make rushed decisions in the fear that I am wasting my life and instead look forward to what the future may hold. My liver function is now normal, and I don't have to face another life-threatening surgery. All the medications I took regularly have now stopped with the exception of calcium. I love my life now and make the most of everyday as this treatment has given me the ability to live it and not just exist. I see a future that doesn't involve hospital operations and premature death and the only thing that terrifies me now is the thought that this treatment will stop. Something that everyone who cares for me also shares.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	There are no disadvantages to this technology, only huge gains.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No, because the gains are subjective. A young person affected will see a less dramatic improvement in their health due to reduced amount of time they have been exposed to the disease, but indirectly will benefit massively from the lack of mental health associated with the disease. Similarly, the severely affected patient will see huge changes in their physical health but slower changes in their mental health due to trauma they have already experienced. In my opinion any ASMD Type B patient who is given this technology will experience a vast improvement in their health in one form or another.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that I can think of.

Other issues	
15. Are there any other issues that you would like the committee to consider?	I would like them to look at the not only the overwhelming physical data but the also the psychoemotional effect associated with the huge changes in someone's health. This treatment hasn't suspended deterioration or showed minor to moderate improvement in the quality of someone's life, but reversed decades of increasing ill health and improved my health from imminent liver transplant to 25% healthier than the average male of my age. My mental health and that of those around me has also improved with the hope of a positive future.

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- This treatment has reversed decades of extreme ill health.
- Changed my life from, life limited to a normal prognosis.
- Prevention from imminent liver transplant to 25% healthier than the average male of my age in the time I have been on the treatment.
- Improvement of my mental health and that of my families, with the hope of a positive future.
- This treatment has worked so well it has removed the lifelong fear I have always had to live with.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann Pick disease type B and AB) [ID3913]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Monday 18th September 2023** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating acid sphingomyelinase deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	University College London Hospitals
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acid sphingomyelinase deficiency? ☐ A specialist in the clinical evidence base for acid sphingomyelinase deficiency or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for acid sphingomyelinase deficiency?	To clear sphingomyelin from visceral tissues, improve the clinical features of the disease and stop future progression.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reductions in visceromegaly and improvements in pulmonary gas exchange
10. In your view, is there an unmet need for patients and healthcare professionals in acid sphingomyelinase deficiency?	Yes. No disease modifying therapy is currently available.
11. How is acid sphingomyelinase deficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients should be seen in highly specialised LSD services. Treatment is supportive. There are some recently published consensus clinical guidelines (Orphanet J Rare Dis. 2023 Apr 17;18(1):85). Olipudase alfa would transform the life of patients with non-neuronopathic ASMD in terms of both quality of life and survival.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology would be use as other enzyme replacement therapies for lysosomal storage disorders. The need for dose escalation might mean that patients would have to receive their infusions in a hospital setting for longer, but I think with experience it would be possible to move much of this phase of care to homecare for many adult patients. In the long-term, infusions would be provided at home.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Olipudase alfa will have dramatic effects on quality of life and survival.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology will have less effect for those with neuronopathic disease. However, for these patients the visceral disease is still a significant cause of morbidity which would respond to treatment with olipudase.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology requires fortnightly intravenous infusions. Similar therapies have proven to be acceptable to patients. We have a well established homecare system for delivering enzyme replacement therapies in the UK and olipudase alfa would be added to that framework.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that the HSS LSD services would be asked to develop rules for starting and stopping treatment. These would be based on clinical features of the disease which are routinely measured anyway. It might be useful for laboratories to offer testing for lyso-sphingomyelin, a biomarker of disease. However, as it is easy to monitor response clinically and with routine investigations this would not be essential.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This is a transformational treatment. Our experience is that many ASMD patients do not realise how their quality of life is affected by their disease until they have been treated. Symptoms which they regarded as normal (limited exercise capacity, pain, fatigue) disappear with treatment and they develop a

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	new understanding of what 'normal' life is. I do not think QALY calculations can fully capture this.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Until now there has been no disease modifying treatment available for ASMD and treatment has essentially be palliative. With olipudase alfa we can now not only prevent progression of visceral ASMD, we can reverse all the clinical features of the disease.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Olipudase alfa has been safe and well tolerated. Infusion related reactions have been easy to manage and self limiting.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials do reflect current UK practice. From the point of view of patient mortality, the effects on liver and lung disease are the most important. We now have almost 10 years experience from the firt patients treated in the phase 1 studies and they continue to show improvements in spleen volume with normalisation of many other parameters including liver volume and pulmonary gas exchange. In adult patients there have been no emergent adverse effects.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I don't think the trials capture the effect the treatment has on patients everyday lives. It would be important to get the experience of patients who have received olipudase alfa.

23. How do data on real-world experience compare with the trial data?	We have not been able to use olipudase alfa outside of clinical trials in the UK
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	The NHS should be able to offer all affected patients access to the treatment.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case • *Is olipudase alfa expected to restore people with acid sphingomyelinase deficiency to full or near-full health?*	Yes, olipudase alfa can restore ASMD patients to full health. The only proviso to this is that if disease is advanced, with organ fibrosis, at the time treatment starts, that can not be reversed by treatment and patients may be left with some residual impairment.
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data. • *Would olipudase alfa's treatment effect be expected to wane over time?*	The patients in the phase 1b study have now been treated for almost 10 years and there is no evidence of any decline in treatment effect.

EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL • *How does acid sphingomyelinase deficiency affect the quality of life of carers?* • *On average, how many carers would you expect for a) adults and b) children with acid sphingomyelinase deficiency?*	I can only comment on adults. This is a slowly progressive disease and adult patients are mostly able to function independently until the very late stages of the disease.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality • *Would you expect disease-specific mortality to be apparent in paediatric population?* • *Are clinical experts aware of any credible mortality data for acid sphingomyelinase deficiency?*	ASMD undoubtedly causes death in children and adults as per the below reference: Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, Imrie J, Mabe P, Takahashi T, Mengel KE, Giugliani R, Cox GF. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases. Mol Genet Metab. 2016 Jul;118(3):206-213. doi: 10.1016/j.ymgme.2016.05.001
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	ASMD causes growth restriction I children, but they do show catch up growth and in my experience adults have a similar weight distribution to the general public.

• *Would you expect the average weight of the population with acid sphingomyelinase deficiency (both adults and paediatrics) to differ from that of the general public? If so, how?*	
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations • *Would you expect response to olipudase alfa to vary by severity of acid sphingomyelinase deficiency?* • *How many people have severe disease in clinical practice and how are these people identified?*	Patients with ASMD show a response to olipudase alfa across the spectrum of disease with clearance of sphingomyelin form then liver and lungs. However, advanced disease is characterised by fibrosis (cirrhosis of the liver and pulmonary fibrosis) and this is not amenable to enzyme replacement therapy. These patients do however still show remarkable clinical benefit from therapy, and personal experience suggest that organ fibrosis does not progress once storage is cleared. As no disease modifying therapy has been available to date, there are currently some patients in our population who have advanced disease. If olipudase alfa were to be made available, then we would no longer expect to se ASMD patients progress to this point of the disease.
Are there any important issues that have been missed in EAR?	I have not seen the EAR so can't comment on this

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Olipudase alfa for treating Niemann-Pick disease types A and B [ID3913]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Niemann-Pick UK (NPUK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Niemann-Pick UK was established in 1991. We are the only patient organisation providing information, support and advocacy services to patients affected by ASMD Niemann-Pick disease and Niemann-Pick disease type C, plus their families and the professionals involved in their care. Our charitable objectives are to relieve sickness and any distress which may arise there from, and to advance the education and awareness of families, professionals and the general public in all matters concerning the disease. Our vision is a world where the burden of Niemann-Pick disease is minimised, those affected have access to effective therapies, can meaningfully participate in society, reach their full potential and achieve the best quality of life possible. Our organisation has the widest experience of supporting Niemann-Pick patients and their families in the UK, developed over 31 years. We aim to make a positive difference to the lives of those affected, from diagnosis to bereavement and beyond, through the provision of individualised support and advocacy services, delivered by our expert team. Since 1999, we have funded the post of a full time Clinical Nurse Specialist (CNS), currently based at Salford Royal Hospital, and working in conjunction with the designated NHS specialist centres in England to provide expert care and practical advice in clinic and at home. We also provide non-clinical advice and advocacy, mental health and wellbeing support via a 24-hour helpline, website and social media activities, plus a range of educational resources and mutual support opportunities. We collaborate nationally and internationally with other patient organisations and relevant institutions. International links are vital in providing support and information to patients and families affected by ultra-rare conditions such as ours. In 2009, we cofounded the International Niemann-Pick-Disease Alliance, a network of 24 patient organisations working to support those affected by NPD across 17 countries. In 2012, we played a leading role in the development of the International Niemann-Pick Disease Registry (INPDR). This disease-specific registry collects clinical and patient-reported data, documenting the patient experience and supporting clinical and epidemiological research. Currently, we support approx. 90% of known UK patients (149) affected by Niemann-Pick diseases, both ASMD Niemann-Pick disease (37) and Niemann-Pick disease type C (112). In addition, we support immediate and extended family members, families that have been bereaved, and we offer information for health, social care and research professionals. For example, “A Guide to ASMD Niemann-Pick Disease Types A and B for Healthcare Professionals” is included as part

	this submission. We share our newsletter and disease updates to more than a thousand people worldwide and we do not charge a membership fee. We are entirely supported by grants, voluntary donations and fundraising. Currently, our work is funded by the Charities Aid Foundation (CAF), the Pears Foundation, the Joan Ainslie Charitable Trust, BBC Children in Need, the Hollie Foundation, the Tesco Community Foundation and unrestricted educational grants from industry.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the evaluation stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	In the last 12 months, we have not received funding from the company bringing the treatment to NICE for evaluation and there are no comparator treatment companies. We have received unrestricted educational grants from two companies working in the Niemann-Pick type C field, amounting to £60k and equivalent to 25% of our total grant funding income.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have very strong links with the community we serve. This is built upon the quality of services that we provide, and how we are viewed by those we support: honest, trustworthy and working with integrity. The work of our Care and Support team enables direct and regular communication and conversation about the needs of those within our community and how they change over time. These strong relationships ensure we can reach all relevant patients and carers and to ensure they have equal opportunity to share their thoughts and experiences with us. We recognise the value of the patient voice and experience in shaping the services we provide. Therefore, patient experience data is gathered throughout the year, not just for specific purposes. We employ different methods to capture

	this experience, including hosting focus groups and workshops, providing one to one interview sessions (in person and virtually), direct feedback to staff team members and the use of self-completion surveys. Utilising the strength of two national patient organisations and our own registry (Niemann-Pick UK, the National Niemann-Pick Disease Foundation (NNPDF) and the International Niemann-Pick Disease Registry (INPDR)), we commissioned an organisation called Rare Disease Research Partners (RDRP) to conduct a survey *"The impacts of olipudase alfa on paediatric patients with ASMD and their families"* to highlight the patient experience and perspective regarding the burden of disease, burden of therapy, benefits of therapy, risks, and tolerance of risk. The study aims were to: (1) increase the understanding of the impacts of ASMD on paediatric patients and their families, (2) explore the effects of olipudase alfa on paediatric patients and their families and (3) gain insights from patients and their families into the unmet need for treatment of ASMD. We engaged with RDRP as a professional third-party research organisation to reduce bias and maintain scientific rigor. The purpose of this study was to collect additional evidence, from the patient and caregiver perspective, on the impact of olipudase alfa therapy on paediatric patients with acid sphingomyelinase deficiency (ASMD). This supplements clinical trial results and provides additional information to support our submissions to regulatory agencies. The final survey report is included as an appendix to this form. Patients and carers have also contributed to the development of informative publications, including "Acid Sphingomyelinase Deficiency Niemann-Pick disease type B: A practical guide for individuals, parents and carers", a copy of which has been included with this submission. First produced in 2011, this publication is currently being updated with the support of the ASMD patient community with the revised version available in print later this year

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	ASMD is a progressive and life-limiting disease which significantly reduces life expectancy. Clinical features of the disease result in significantly debilitating symptoms and multiple long-term healthcare needs, resulting in significant health service input involving frequent hospital appointments with multiple clinical specialties, and frequent monitoring tests and investigations. Natural history studies have shown that patients die of lung and or liver disease at an early age, this is reflected by our experience during the past 30 years of supporting those affected. The severity of symptoms often prevents patients from fully participating in daily activities, affecting their ability to attend school, to work and take part in activities they wish. This places great psychological and financial strain on patients and their families. Being an ultra-rare condition, with knowledge and understanding limited to a handful of expert centres, patients can feel bewildered and isolated due to conflicting advice or a lack of information specific to their condition. The psychosocial impact of ASMD for both patients (body image, bullying, unable to socialise, standing out as being different) and their carers (anxiety, guilt, relationship breakdown, loss of earnings, genetic implications for family planning) is significant. Patients describe reaching a point 'of no return' in their disease progression, where the disease 'creeps up' without early indicators, suddenly taking over. Patients often don't realise how clinically unwell they are, as feeling unwell is their 'normal'. This was highlighted during the clinical trial of this technology, with those participating reporting significant changes in their energy and wellbeing, with the realisation of how limiting their condition was on daily life prior to the trial. Patients and carers have reported the following disease manifestations and impacts of living with ASMD: increased and significant fatigue, shortness of breath, enlarged organs and increased abdominal girth, early satiety, risk of spleen rupture, liver disease and cardiac issues. In addition, the psychosocial impact for patients is a major factor and includes negative body image, a sense of 'feeling different', a consequent of the abdominal swelling, due to significantly enlarged abdominal organs. <u>Bone issues</u> ASMD affects bones, with patients more likely to be affected by bone thinning (osteopenia/osteoporosis). Patients report bone pain, muscular pains, back pain (due to the weight and size of the enlarged spleen / liver), and due to bone thinning, an increased risk of fracture. <u>Enlarged organs</u> An enlarged spleen and/or liver is common in ASMD patients, causing considerable discomfort and pain. Furthermore, the enlarged organs restrict lung capacity, causing breathing problems, puts pressure on the stomach, affecting one's ability to eat usual sized meals, impacting digestion, causing nausea and frequent vomiting. An enlarged spleen is susceptible to injury, consequently patients are prevented from usual play / sports activities due to this risk, reducing social opportunities and reinforcing the sense they are different. A further consequence of the enlarged spleen is hypersplenism, with associated anaemia, thrombocytopenia, and risk of bruising or bleeding, and a low white blood cell count, with an increased risk of infection.

	"I was diagnosed when I was three years old, and from an early age I knew that I was different, that I was special. Unlike the other kids I was always going into hospital for tests. I had to have blood tests, flu jabs, x-rays, overnight stays at the hospital for monitoring. But the biggest hint was my large tummy that was noticeable from being a toddler." "As I progressed into my teens, that's when I started to take more notice of what was wrong with me. I was and still am noticeably shorter than the other boys and due to my over-sized, liver and spleen I had to sit out of PE lessons whenever we did full contact sports such as rugby. I had to quit playing football in my team as I was in danger of getting hurt as the other teams didn't know what was wrong and I was an easy target due to my size." "He is still a very happy boy, but no child wants to be throwing up five times a day. And he'd wake up first thing in the morning throwing up, and it was just uncomfortable for him to sit for really short periods of time. You could just tell it was uncomfortable in his belly. So, it affected really all areas of his development." (Interview, before treatment, started treatment at 2 years of age) <u>Bruising and Nosebleeds</u> ASMD patients can experience frequent nosebleeds, which can be challenging to manage and, in some cases, requires medical intervention. Many also report difficulties in stopping bleeding, if injured. Bruising easily and frequently is also reported "And then really hard to stop his bleeding, he didn't have nosebleeds, but if he got a cut or a scrape… You could see the effect of the disease on the spleen, like that part was hard, it was very to get his bleeding to stop, although he never really had nosebleeds, which was interesting with him." "Bruising was very noticeable at a very early stage, I dreaded putting our son in short trousers as he looked as though he had been beaten, his legs and arms pickled with bruises from normal play, On one occasion after surgery to remove a cyst from his cheek, on returning to the hospital to have his stitches removed, he was whisked off and my husband and I questioned, as they really could not believe that the amount of bruising he had on his face was a result of the surgery, eventually a call to our consultant confirmed that bruising due to low platelets does take place. The nosebleeds happened a lot later, probably when he was 13, alarming at first but we all soon learnt how to cope with them, he had his nose cauterised a couple of times, again though this was due to his low platelets, as a side effect of his enlarged spleen" <u>Slow growth and delayed puberty</u> Delayed growth and puberty due to ASMD is a source of significant anxiety and distress for patients. Children feel 'different' and this often leads to increased insecurity and negative body image, as they watch their peers 'growing up' whilst they remain 'a child'. In some cases, puberty does not happen until late twenties, with patients remaining shorter in stature "At 23 my son is still showing very few signs of puberty, his voice is slightly deeper, and he gets an occasional spot, but he had no body hair, so appearance wise looks about 15. We have been told he may not reach puberty until his late twenties. The effects of this are that he has friends who are girls, but no girlfriend; he is constantly being evicted from pubs, as they think he is underage, although his driving licence now helps, shops refuse to sell him certain items, and when starting his own business no one took him seriously."

	Body image Patients experiencing delayed growth and puberty, plus enlarged organs resulting in a swollen stomach often leads them to feel self-conscious and 'different'. This changes the way they see themselves, especially when they compare themselves to their peers. This results in a negative body image and low self-esteem and with slow growth and delayed puberty, with feelings developing into psychological issues and often continuing into adulthood. "I remember that sometimes she cried, and when I tried to explain that her belly was somewhat different from the belly of other children, and that we had to be careful with it, sometimes she really started to cry and she was very sad. Sometimes she really got sad, and she said, I don't want to have another belly than other children." Tiredness & Fatigue Tiredness and fatigue is a common symptom for people living with ASMD and results in patients having to make adjustments in their daily work/school and social lives to compensate. As patients have an enlarged spleen, this affects the level of red blood cells, leading to anaemia and less oxygen being transported around the body, causing fatigue. An enlarged spleen uses up a lot of energy from calories consumed and patients find it difficult to take in additional calories due to pressure this causes on the stomach, limiting intake of food and requiring patients to eat little and often. "Tiredness and fatigue is the most noticeable effect of the disease. My endurance is quite limited and my concentration has suffered as a result, though careful planning helps to counteract this. I began noticing the tiredness much more after a serious stay in hospital when I was 17. It was quite jarring to suddenly have to be carted about by my parents in the car all the time at that age.", "…And as time passed by, we noticed that her energy level decreased, and when she got home from school, she asked us to go to bed.[…] And we also noticed that if she had to walk a certain distance, that it was difficult for her to catch up with the other children because she was always tired." Shortness of breath ASMD patients can experience breathing difficulties and shortness of breath in completing everyday tasks such as climbing stairs, getting dressed or walking short distances. Patients report an extremely unpleasant feeling of finding it more difficult or uncomfortable to breathe, to a greater degree than you would normally expect during exercise. Storage in the lungs reduces the flow of oxygen to the body's cells, with most ASMD patients showing evidence of interstitial lung disease. And being more prone to respiratory infections. "It was her favourite thing to do is play tag. […] And when she'd run and she'd be holding her stomach to get away, she'd get to the safe spot, and you could see her just always out of breath." Disruption to family and social life Multiple medical appointments and screening tests often limit a patient and carers ability to go about their daily lives, with time away from school or work impacting on their ability to achieve educational goals or financial stability. This impacts heavily on family life and disrupts routines for the patient and other members of the family. For patients, extreme fatigue is also a factor that prevents full participation in usual daily and social activities. Adaptations to the home, or supportive measures at school or work may also be required.

	"Our son was diagnosed prior to starting Primary School, so before he started, I met with the Headmaster and explained my fears about his safety. Being so rare, ASMD doesn't fit into any of the 'tick boxes' or follow any standard procedures. By getting the school on side by communicating on a personal level; working with the school nurse on a care plan; giving a little informal talk to all the teachers and by sharing my fears and emotions with his main teacher each year; my son's care at school has been absolutely excellent. From little things like making sure he is always at the front of a queue so his spleen and liver won't get knocked, to putting in a lower urinal because he was shorter than the other boys and couldn't reach!" Bullying In ASMD, bullying is reported all too often, due to a lack of understanding the condition or the fact that patients may be regarded as 'different' due to their physical appearance, for example if they have a shorter than average stature or an enlarged spleen. It can also happen if they are seen to be receiving special allowances or additional support at school, or they get to sit down whilst their peers must stand. Bullying can make the difference between a child's life being tolerable or miserable. Research suggests that children with disabilities or long-term conditions are three times more likely to be bullied than their peers. "Everyone was taller than our son; this caused him problems at school with name-calling, bullying and lack of female interest. Although it sounds unkind we would light heartedly tease him, long before he went to school, he got used to being teased, so when the children at school started it didn't seem to hurt so much. He picked big friends, who were really great and protected him." "When I first started my new school people made up a rumour that I was pregnant because of the size of my belly; but no-one says it now because everyone knows me." Mental Health – Patients Living with ASMD is challenging and results in numerous psychological stresses including extensive medical testing and uncertainty of disease course, coping daily with the effects of a chronic illness, and grief and bereavement surrounding this progressively debilitating, and ultimately, fatal disease. Patients develop a different perspective on life to their peers. Five major findings emerged from a study conducted by the University of California: (1) limited physical activity, social isolation, and peer rejection were identified as significant stressors; (2) stressors had a specific impact during the age span of 10–16 years; (3) parents and adult patients expressed frustration regarding the lack of available information and treatment; (4) patients described close family relationships as a way of coping with illness; and (5) adult patients identified early medical experiences as having a considerable psychological impact. "And it was very obvious through her leotard that her stomach was somewhat extended for a certain reason. Kids would ask her why is your stomach so big, blah, blah. So, it was noticeable, not to us, but just to other people, as well. […] I think she was just a little bit distracted, to a degree, and thinking about other issues within her body that were uncomfortable. […] I think it was more of a psychological impact, possibly, because she was so much smaller than everyone, and her stomach was bigger."

	"Every day she told us that she was having pain in the belly, and of course, yes, she didn't like it. So, from that point of view, it had an impact on her wellbeing, of course." Effects on Parents/caregivers Parents and carers reported feelings of anxiety, stress and depression. These feelings were linked to their thoughts about: keeping their child safe, the child's health, guilt and feelings of being 'at fault' (for passing on a genetic disease, not spending enough time with siblings, their child's quality of life, what their child is missing out on: "It was dark times. We questioned and felt a lot of guilt and questioned did we do the right thing looking to have kids? Should we have done more genetic testing? Were we selfish to think that we thought we didn't have these mutated genes in our cells? There was a lot of stress for us as parents just knowing that we brought kids into this world who were going to have an uphill battle." These are exacerbated by a lack of sleep and constant fatigue from the child waking up at night, and isolation associated with being a caregiver. Sadness was also an issue for parents/caregivers who saw their child not being able to do what they wanted to do. A recurring theme was being under extreme stress not knowing how the disease was going to progress and waiting for the child to die knowing that this was the outcome if the disease was left untreated. Parents and carers also reported impacts on their work and social life, with many having to give up work entirely or go part time, to care for their child and attend medical appointments, often with severe consequences on family finances. "It is heart-breaking to watch your child go through everything that he's been going through. Really, it puts a lot of stress on us as parents, but also me and my husband's relationship, and it affects all aspects of our lives. Before his infusions and stuff, he required so much care." "I think you think of them every day and you think of them every night. You wake up thinking about it. That takes over your life, how am I going to normalize my child's life? How is she going to be able to live normal and not be constantly sick and in the hospital?" "Extreme anxiety, extreme depression on my end, a lot of frustration. My husband and I, you go from living this typical life essentially to being thrown with a potentially life-threatening diagnosis of your child." "In terms of stress. There were times when my wife would go in her bedroom and cry." Effect on siblings Parents and carers often have little time to spend with healthy siblings and find it difficult to answer questions and give information about ASMD. Other siblings don't understand why their affected sibling receives more attention and the children of affected adults, who are often 'young carers' experience a range of practical, emotional and psychological issues, which can lead to problems at school, social isolation, feeling neglected and being bullied. Teenage siblings have more complex needs; they cannot explain what is wrong with their affected sibling and can feel embarrassed about bringing friends into their home. They have questions about ASMD inheritance and relationships that they feel can't be discussed with their

	parents – leading to a breakdown in communication. They worry about death and dying and what will happen to their siblings as ASMD progresses. Sibling speakers at our 2019 Family Conference spoke with great emotion about how they felt growing up -with feelings of guilt (not being affected, not having health issues), how they felt left out, isolated, not knowing what was going on, how they could at times be resentful of the attention that their affected sibling was receiving and their embarrassment when friends came to their homes. They also talked of bullying and anxiety for their affected sibling.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers reported dissatisfaction with their diagnostic journey, which in some cases is stretched over many years, leading to delays in accessing expert care, practical support, and symptomatic treatments, as well as impacting family planning decisions. Most patients in England receive care at one of the eight designated NHS Specialist Centres providing Highly Specialised Services for patients affected by Lysosomal Storage Disorders. Patients and carers report difficulties in travelling to specialist centres, which are often located far from their home. This is especially so when the disease is more progressed and their burden of disease greater, or when there are family and/or financial constraints. Despite this, patients and their carers report high levels of satisfaction with the care they receive, feeling confident and supported by their clinical teams' knowledge and expertise in this rare condition. However, there are currently no treatment options for ASMD except supportive care. Best supportive care is complex and costly, due to the progressive and multisystemic nature of ASMD and involvement of many different specialities. Treatments, involve symptomatic relief of the disease, including pain relief for musculoskeletal pain, the management of the complications of the disease, (e.g., blood transfusion following bleeding episodes, significantly elevated cholesterol levels and the consequential cardiovascular disease, dietary /digestive aids and invasive surgeries). For patients, this means years of frequent and multiple medical appointments, with regular monitoring and often invasive tests through involving several different clinical teams, including: Cardio/respiratory, Endocrinology, Haematology, Hepatology, Physiotherapy, Dietetics. With these clinical teams often located in different locations around the country, the coordination of these appointments can be challenging. In addition, appointments with highly specialised teams are limited, usually twice per year, and patients and carers report much lower levels of satisfaction with locally based GP and hospital care. This is related to a lack of knowledge and understanding of their condition, the progressive nature of symptoms and their inability to access suitable symptomatic treatments, supportive aids and/or adaptations in a timely manner.
8. Is there an unmet need for patients with this condition?	There is a significant unmet need for patients and family living with ASMD. The scale of issues is enormous, with patients experiencing substantial challenges in both their emotional and physical health. They experience difficulties in attending school/work, participating in recreational activities, and in their social and economic wellbeing. The emotional burden of a complex and debilitating disease with symptoms that are constantly changing but always progressing is huge. As the disease relentlessly progresses patients need for multi-specialist clinical care and interventions increases. Their health and care needs also increase, with a greater impact on the wider family, including parents carers/ siblings and the children of affected adults. The impact of not funding this treatment includes early death, irreversible damage and disability, families taking drastic action to access treatment outside of the UK, an increasing burden on the public purse, plus long-term mental health issues within affected families. Despite the overwhelming benefits of olipudase alfa, there remains unmet need in managing the neurological manifestations of ASMD, particularly associated with classical type A homozygous mutations, and this remains a high priority for many patients and families.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Olipudase alfa is the only disease modifying treatment option for ASMD patients and has the potential to make a significant impact on their health outcomes. Patients and families observed life-changing effects with olipudase alfa, based on their experience. They consistently reported the view that all patients with ASMD should have access to olipudase alfa. Olipudase alfa not only appears to halt progression but reverses many aspects of this debilitating and life limiting disease. With early treatment that prevents irreversible disease, patients are no longer exhausted, can attend school /work for a full day, eat normal size meals, walk greater distances without breathlessness, contribute to society and have the energy to enjoy family or social life. Furthermore, they should expect to have a far greater life expectancy, with less dependence on healthcare and clinical interventions. When surveyed, participants reported the advantages of the technology as significant improvements in many symptoms, leading to improved quality of life: "Also, the energy, she is really full of energy now. It's amazing. She's very active and she likes to do sports, […] Now she's really an early bird, she's awake very early, and it's not a problem for her to handle these long schooldays anymore." They reported the benefits of this treatment being so obvious and life changing that in some cases there were no symptoms or signs of ASMD at all, they felt that treatment must continue and be accessible to everyone with ASMD. "The drug has drastically improved our son's life. He looks and acts like any other kid his age. He is much more confident now that his belly is small, and he is similar in size to his peers. […] You would never know that he has ASMD." Although this survey focussed on paediatric patients, similar outcomes have been reported by adult patients: "My abdomen is vastly different. I was recently told by a sonographer that an ultrasound of my abdomen showed that my spleen was now normal size as was my liver. My lungs have continued to improve, so much so, I now cycle to work and back every day, something I could have never have done before. I no longer feel hungry all the time and for the first time in my life have normal bowel habits, it sounds a small detail, but when you have had an upset stomach all your life, it's a huge change." We expect to be able to further demonstrate the experience of adult patients following phase 2 of the survey, which is currently in development.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Disadvantages mentioned in our survey included the treatment not crossing the blood-brain barrier, missing school or work to receive treatment, and the demands and challenges of the clinical trial. In our survey, all parents/caregivers reported that the benefits of the treatment outweighed the risks and disadvantages, with most saying that there were no adverse impacts on their child. Adult patients have also reported no disadvantage: • Benefits outweigh the risks • Side effects were minor issues compared to the effects of ASMD • Any concerns about the treatment were addressed by the clinician and vanished once results were apparent • Patients and families adapted easily to the two weekly infusions, at home or in clinic, with homecare the preferred option

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Clinical data is very strong and shows clearance of storage and reversal of disease. As it is currently not possible to accurately identify where a patient sits on the spectrum of ASMD disease, outside of very small numbers of classical type A homozygous mutations, treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None identified.

Other issues

13. Are there any other issues that you would like the committee to consider?	Early diagnosis and treatment for patients with clinically detectable disease will prevent significant and irreversible burden of disease, reduce comorbidity and mortality. The introduction of this technology requires no new specialised equipment or services, IV infusions can be managed in existing clinical centres through current service specifications, or preferably by a home-based infusion service or if appropriate, self-infusion. Whilst this technology may be viewed as a 'high-cost treatment' there will be a significant and long-term downstream reduction in healthcare and societal costs over the lifetime of a treated patient. For untreated patients, with only symptomatic management, i.e., antibiotics and hospitalisations for respiratory infections, home oxygen needs, medications and treatments to manage bleeding or low platelets, medications to address high cholesterol, portal hypertension and other consequences of a chronic condition, the cost will be much greater. The impact of this technology beyond direct health benefits and the cost saving for health systems, include societal economic benefits such as maintenance of earning potential for the patient and carers. The development of this technology has benefitted from 20plus years of investment from the patient community, including surveys, PROMs, natural history studies, invasive and burdensome trial protocol – nevertheless, patients and their families have been actively engaged, as this presents the only potential option for patients and evidence shows it can make a huge difference to their quality of life with long term implications. It is important to state the small numbers of patients affected by ASMD and therefore potentially eligible for treatment. In our experience over 30 years of working with the ASMD community, the number of patients supported in any given year has not exceeded 40. It must be noted that this is a life-limiting and life-shortening disease, and that patients don't have a normal lifespan, and that there will be some who have milder disease and therefore have not yet been diagnosed or misdiagnosed. NPUK currently support 37 ASMD patients 34 with ASMD Niemann-Pick disease type B (16 Children, 18 Adults) and 3 with ASMD Niemann-Pick disease type A. For newly diagnosed patients, Genetic counselling should be provided prior to and following diagnosis to assist patient and family understanding and enable informed decisions regarding family planning, including carrier status and potential impact on future offspring and siblings. This should be included within the service provision and provided in a timely manner. Currently there is no routine screening for ASMD as part of the UK's newborn screening programme. Whilst we understand the Committee or any decision they make will not influence or change this, it must be noted that to enable the full benefit of this treatment, inclusion in the NBS programme is highly recommended. In addition, we ask the Committee to give appropriate and careful consideration to the management of patients currently receiving olipudase alfa post trial and in any period leading up to and post their decision-making process, to avoid additional and unnecessary anxiety and stress.

14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every evaluation.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• ASMD is a systemic disease with a wide array of manifestations causing high physical and psychological burden (for patients, carers and siblings) and significantly impacting quality of life • There are no treatment options for ASMD except best supportive care, which is complex and costly, due to the progressive and multisystemic nature of ASMD and involvement of many different specialities. • There is a high level of unmet medical need in the patient community • Olipudase alfa is the only potential treatment option for patients; evidence has shown significant and long-term impact on quality of life and psychosocial status for patients and their families • Patients and families observed life-changing effects with olipudase alfa based on their experience, consistently reporting the view that all patients with ASMD need access to olipudase alfa

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Rare Disease Research Partners

The impacts of olipudase alfa on paediatric patients with ASMD and their families

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Samantha Wiseman, Coordinator

SUMMARY OF FINDINGS

Rare Disease Research Partners (RDRP) conducted an international study on behalf of the National Niemann-Pick Disease Foundation (NNPDF), Niemann-Pick UK (NPUK) and the International Niemann-Pick Disease Registry (INPDR) with the aim of collecting additional evidence, from the patient and caregiver perspective, on the impact of olipudase alfa therapy on patients with acid sphingomyelinase deficiency (ASMD). This evidence was collected to supplement clinical trial results and submissions to the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and other regulatory agencies.

Results are based on parents of paediatric patients with ASMD from four different countries.

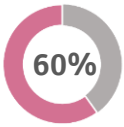
Online survey

10 patients. Median age 8.5 years (mean 9.8 ±4.5, range 3.3–19.0). 50% female

Interviews

8 patients. Median age 8.0 years (mean 8.7 ±3.6, range 3.3–14.3)

First symptoms



(n=10) appeared between 2 months and less than 2 years of age

Median age of **confirmed diagnosis**

1 year of age

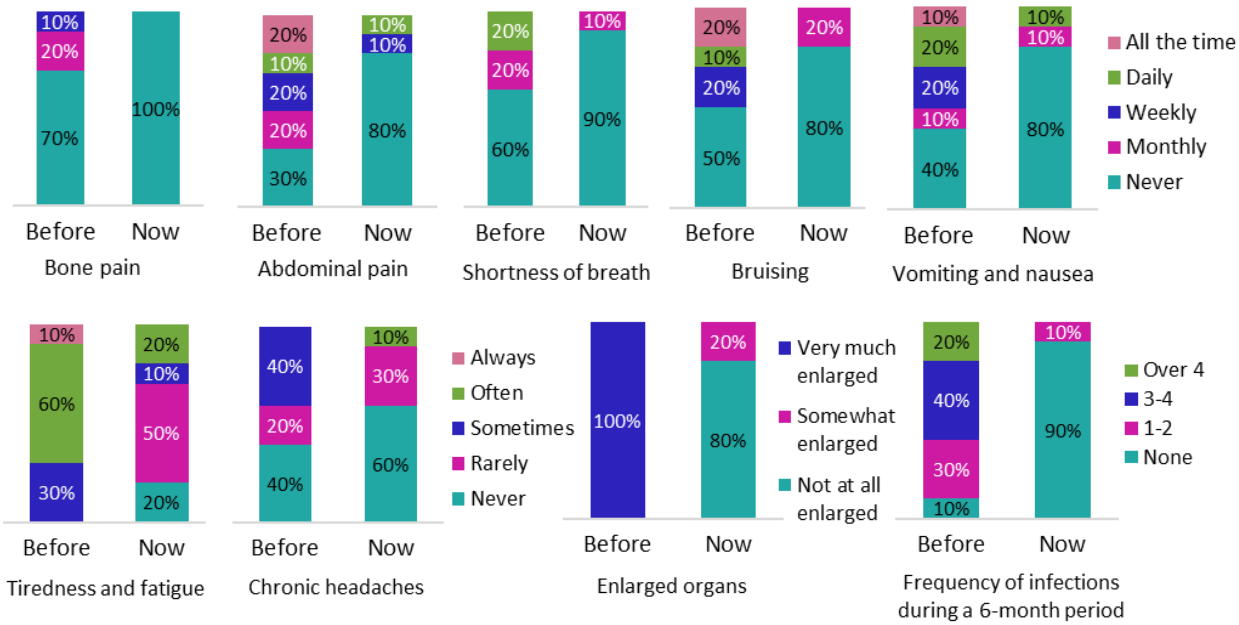
(mean 1.7 ±1.4, range 0–5.0)

Treatment with olipudase alfa **started** at a median age of

3.5 years

(mean 5.0 ±3.8, range 1.5–14.0)

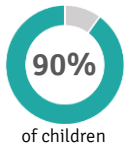
How often were symptoms experienced before (n=10) and after (n=10) treatment with olipudase alfa



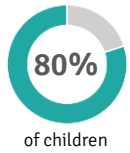
Overall change in symptoms and activities since starting treatment with olipudase alfa

Percentage of children whose symptoms were very much better since starting treatment

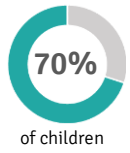
- Abdominal problems (10/10)
- Pain under ribs/ abdominal discomfort (10/10)
- Satisfaction with abdominal body image (10/10)



- Filling up early when eating (9/10; moderately better 1/10)
- Difficulty bending over (9/10; moderately better 1/10)

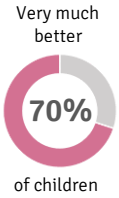


- Bodily pain (8/10; no change 2/10)

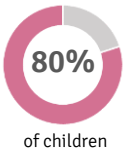


- Fatigue (7/10; moderately better 2/10; a little better 1/10)
- Shortness of breath at rest and with activity (7/10; moderately better 2/10; no change 2/10)

Percentage of children whose ability to perform activities was very much better since starting treatment



- Ability to go to school (7/10; moderately better 1/10, a little better 1/10; no change 1/10)
- Perform self-care activities (7/10; a little better 1/10; no change 2/10)



- Ability to participate in exercise (8/10; moderately better 1/10; a little better 1/10)

All symptoms evaluated in the survey were more likely to have no impact on a child after olipudase alfa therapy compared to before olipudase therapy

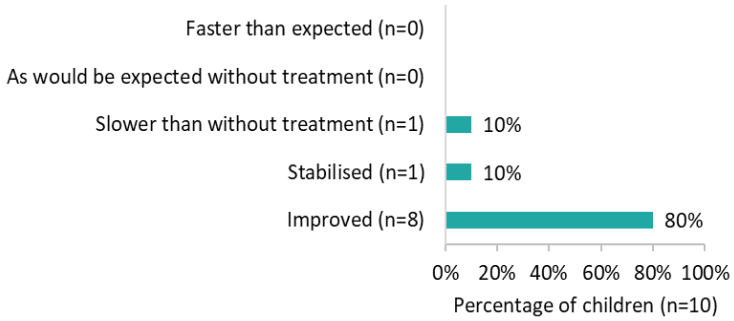
Impact of treatment on day-to-day life with ASMD

Before treatment, 90% (9/10) of parents/caregivers were concerned about the harm **physical activity** or sport could cause to their child's enlarged organs but all parents reported these concerns were much better (8/9) or somewhat better (1/9) after treatment.

60% (6/10) of parents/caregivers reported changes in their child's **mental health** after treatment, including: better self-image and confidence, the child is physically more comfortable, the child has no limitations.

Satisfaction with olipudase alfa

of parents/caregivers (9/10) were **extremely satisfied** with olipudase alfa



Progression of ASMD while on treatment

Parents/caregivers confirmed in the interviews that this was **a life-saving treatment**, and that in some of these children there were no symptoms or signs of ASMD at all, as children could now lead a normal life.

80% (8/10) of parents/caregivers described the overall progression of ASMD while receiving treatment with olipudase alfa as 'condition improved'.

Concerns about treatment

Most parents/caregivers said in the survey that there were no disadvantages or adverse impacts on their child.

- Benefits outweigh the risks
- Side effects were minor issues compared to the effects of ASMD
- Any concerns about the treatment were addressed by the clinician

Concerns about the treatment vanished once parents saw the results.

Views on current and new treatment options available for ASMD

Respondents explained that although olipudase alfa had been effective in reducing symptoms of ASMD, new therapies may be needed for people with neurological symptoms.

Access to treatment

Parents/caregivers believed that the benefits of this treatment on their children were so obvious and life changing, and that their children are the living proof this treatment works, that it must continue and be accessible to everyone with ASMD.

CONTENTS

BACKGROUND

Acid sphingomyelinase deficiency (ASMD) is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *SMPD1* gene, which codes for ASM.[1] Deficient ASM activity results in the accumulation of sphingomyelin and other lipids in cells and tissues.[2] ASMD is classified as Niemann-Pick disease type A (acute neurovisceral) and Niemann-Pick disease type B (chronic visceral) or A/B (chronic neurovisceral).[2,3] Type A is characterised by severe progressive neurodegeneration in their first year followed by early death.[2,4] Types B and A/B have a broad spectrum of disease severity, with type B associated with no central nervous system involvement, and A/B presenting with some neurological involvement but not as severe as type A.[3] Symptoms of types B and A/B usually start in childhood.[2,4]

Olipudase alfa is an enzyme replacement therapy (ERT) under investigation to treat ASMD. It does not cross the blood brain barrier, therefore is unable to treat central nervous system (CNS) manifestations.[3] Early trials have included patients with ASMD Types B and A/B.

The National Niemann-Pick Disease Foundation (NNPDF), Niemann-Pick UK (NPUK) and the International Niemann-Pick Disease Registry (INPDR) wished to collect additional evidence, from the patient and caregiver perspective, on the impact of olipudase alfa therapy on patients with ASMD. This evidence is used to supplement clinical trial results and submissions to the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and other regulatory agencies.

Rare Disease Research Partners (RDRP) conducted an international study on behalf of NNPDF, NPUK and INPDR, involving an online survey and semi-structured interviews with patients or their caregivers. In this report, we summarise the responses of patients with ASMD and their caregivers.

STUDY AIMS

The study aims were to:

- increase the understanding of the impacts of ASMD on paediatric patients and their families
- explore the effects of olipudase alfa on paediatric patients and their families
- gain insights from patients and their families into the unmet need for treatment of ASMD

METHODS

The study consisted of an international online survey in English followed by semi-structured interviews.

The survey was open to adults aged 18 years and over (or their parent/caregiver) who:

- were fluent in English (including non-native English speakers) and
- were able to give informed consent and
- had a confirmed diagnosis of ASMD and
- had used the experimental drug olipudase alfa for more than 12 months and
- had commenced treatment with olipudase alfa under the age of 18 years (paediatric age)

Caregivers with more than one child with ASMD receiving olipudase alfa were asked to complete a separate survey for each child.

The semi-structured interviews were available to respondents who had consented to be contacted by NNPDF about the interviews and had completed the online survey. Those who wished to participate in an interview were required to complete an additional consent form prior to the interview.

Recruitment

Recruitment to participate in the on-line survey was conducted through NNPDF & NPUK. Communications were sent to their membership via email.

Participants who also wished to take part in an interview (as indicated on the on-line survey) were identified by RDRP and NNPDF made direct contact with the participant.

Consent

A Participation Information Sheet and Informed Consent were displayed at the start of the on-line survey. Only those that provided consent were able to proceed with the survey. Separate consent was obtained for the interviews.

Survey

The online survey was designed with input from NNPDF, NPUK & INPDR to cover demographics, first symptoms, treatment with olipudase alfa, symptoms before and after treatment, overall change in symptoms & activities since treatment, current treatment for ASMD, experience with olipudase alfa and satisfaction with olipudase alfa. The survey included multiple choice, matrix and open text questions to provide both quantitative and qualitative data.

The survey was hosted on the on-line Qualtrics^{XM} platform and distributed via a link. The survey was open from 19 January to 15 February 2022.

Interviews

A semi-structured interview guide was developed that covered questions from the survey in more depth and to further understand the impacts of olipudase alfa on patients and their families.

Interviews were conducted via Zoom by Connect Research and by one researcher to ensure a consistent approach. Ten interviews took place between 4th Feb 2022 and 21st Feb 2022 and were audio recorded and transcribed for analysis.

Analysis

A qualitative and quantitative analysis of the survey results was undertaken. Interview transcripts were analysed using an inductive thematic approach using NVivo software.

RESULTS

Respondents

Twenty-six respondents attempted the survey between 19 January–14 February 2022, from which 16 passed the screening questions. Four respondents did not continue with the survey. Two respondents were adult patients and have been excluded from this report. Responses included a total of ten paediatric patients who have been included in this analysis (Figure 1).

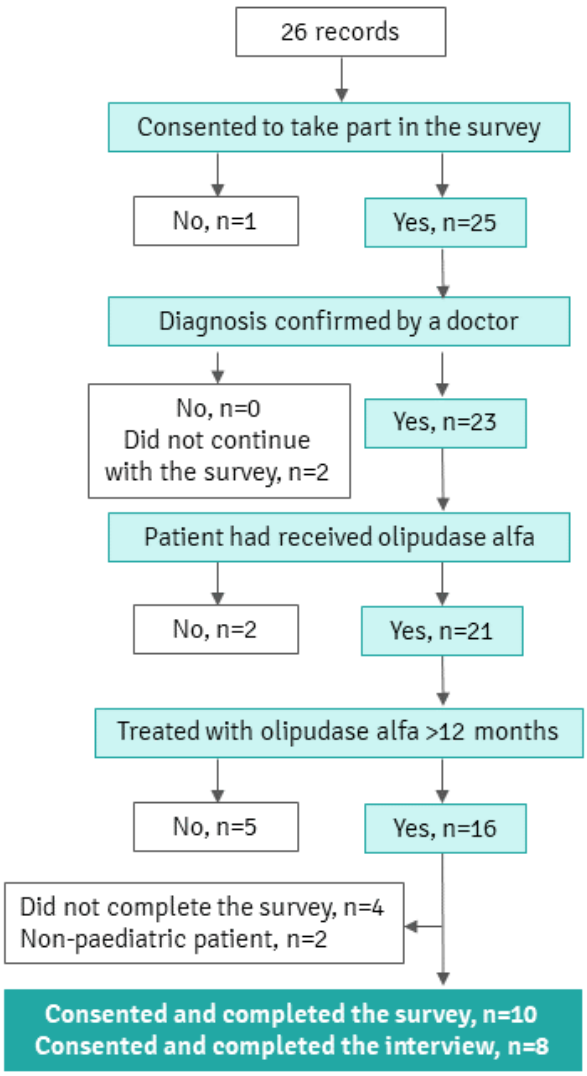


Figure 1. Flow diagram of paediatric patients from the survey and interviews included in the analysis.

Survey respondents were born and resided in four different countries: Belgium, Brazil, USA and the UK (Figure 2). Parents/caregivers from USA and Belgium undertook interviews (Figure 2).

All respondents included in this report were parents/caregivers of a patient with ASMD and included one parent/caregiver who completed separate surveys for two children. Interviews were undertaken for eight patients whose parents/caregivers were available at the time (Figure 1), with one parent/caregiver completing separate interviews for two children. Responses from this parent/caregiver were different for each of the two children and have been analysed separately. Where data referred to parents/caregivers only, analysis has been performed on nine parents/caregivers and this has been indicated.

Figure 2. Country of birth and residence of participants in the survey (n=10) and interviews (n=8). All respondents were born in the same country where they resided.

Patient demographics

Survey **10** patients

Median age of the ten patients with ASMD at the time of the survey was 8.5 years (mean 9.8 ±4.5, range 3.3–19.0).

Median age of males: 8.2 years (mean 8.0 ±3.7, range 3.3–11.7)

Median age of females: 8.8 years (mean 11.5 ±5.0, range 7.7–19.0)

The ten patients included in the survey were born between 2003 and 2018, with 80% (8/10) being born between 2010–2018 (Figure 3a).

Interviews **8** patients

Parents/caregivers of two female patients did not participate in the interviews (Figure 3b). Median age of the eight patients whose parent/caregiver participated in the interviews was 8.0 years (mean 8.7 ±3.6, range 3.3–14.3) and were born between 2007 and 2018.

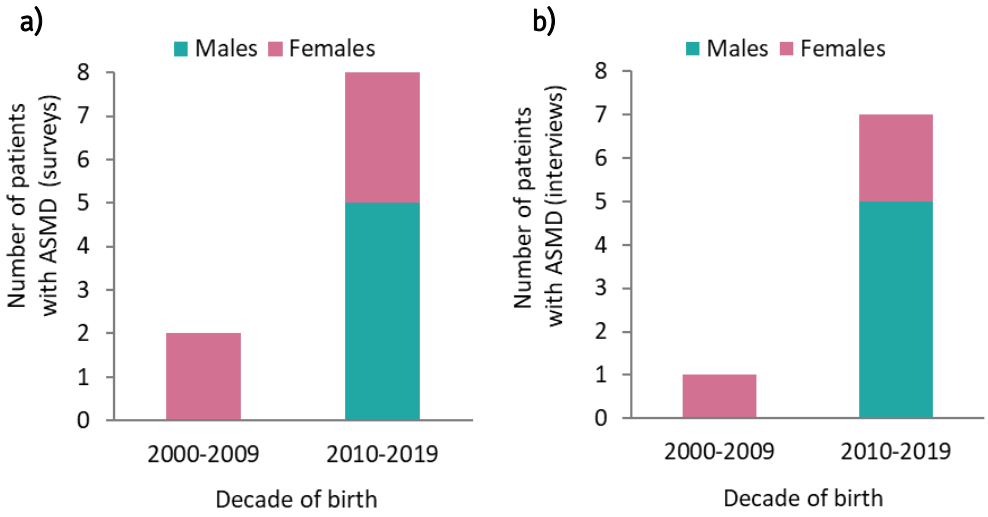


Figure 3. Distribution of patients by decade of birth: a) survey (n=10) and b) interviews (n=8).

First symptoms

Respondents were asked when the first symptoms of ASMD appeared. First symptoms of ASMD were reported to appear between 2 months and less than 2 years of age for sixty percent of patients (6/10) (Figure 4). All patients in the study had experienced symptoms of ASMD before 6 years of age (Table 1).

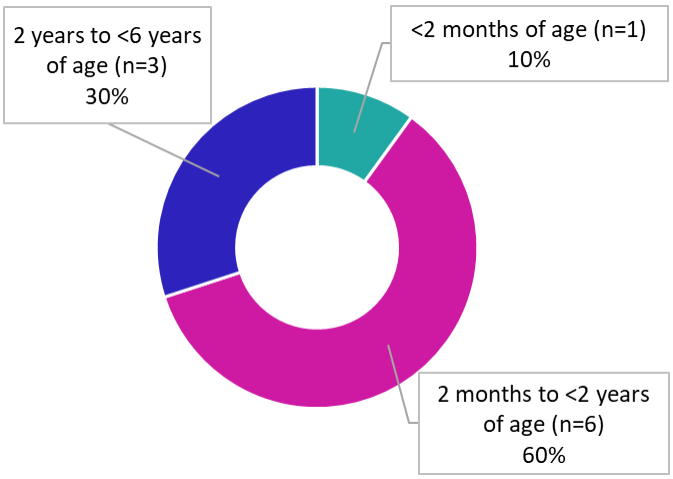


Figure 4. Age of first symptoms of ASMD (n=10)

Table 1. Age at which first symptoms of ASMD were experienced.

Age at which first symptoms of ASMD were experienced	All (n=10)		Males (n=5)		Females (n=5)	
	n	%	n	%	n	%
Less than 2 months of age	1	10	—	—	1	20
From 2 months—less than 2 years of age	6	60	4	80	2	40
From 2 years—less than 6 years of age	3	30	1	20	2	40
From 6 years—less than 18 years of age	—	—	—	—	—	—
I have never experienced symptoms	—	—	—	—	—	—

> "When she was born, she had a little bit of, what I would call, buddha belly. And over time, as she grew, the buddha belly grew with her. So, a lot of folks told us that it was just baby fat, and she would grow out of it, but she just never seemed to grow out of it. She developed a stomach that looked like she was pregnant, a little bit, and we raised concerns with doctors when she was two, when she was three. And then, by the time she was five, it was there's something going on here, can you take a look."
> *Interview, first symptoms <2 years of age*

Diagnosis

Only one patient was tested for ASMD because of a previous confirmed diagnosis in a sibling.

None of the ten patients had a diagnosis made before birth. The median age at which diagnosis was confirmed was 1.0 years of age (mean 1.7 ±1.4, range 0–5.0). Sixty percent (6/10) of patients were diagnosed after symptoms of ASMD appeared (Figure 5). Only one patient was tested for ASMD because of a previous confirmed diagnosis in a brother, being the only patient with a diagnosis made before the age of one.

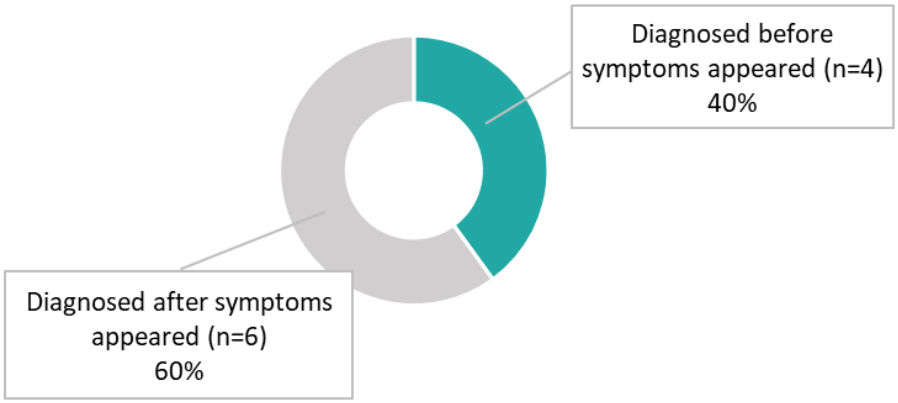


Figure 5. Percentage of patients (n=10) for whom a diagnosis of ASMD was made before or after symptoms appeared.

Parents/caregivers explained during the interviews what their journey to diagnosis was. The journey had been diverse:

- For some children, diagnosis happened by chance

> "Her diagnosis was actually caught by accident, I would say. So, her normal paediatrician wasn't in the office. She saw another paediatrician. That paediatrician felt her stomach and said, oh, my God, I feel her liver. I feel her spleen, you need to go to the hospital immediately, get x-rays and CAT scans, and all sorts of things done to figure out what's going on." *Interview, diagnosed at 5 years of age*

> "When he turned a year old, he still was not walking. His paediatrician still was not concerned. And then, when he was exactly 13 months old, he went in for a routine surgery. And that's when the doctors discovered the enlarged liver and spleen." *Interview, diagnosed at 1 year of age*

- For some parents/caregivers, the journey to diagnosis had been frustrating as they knew the signs their child was presenting were not normal, and took a long time to feel listened to by clinicians

> “We finally got frustrated with that paediatrician and then went and saw another paediatrician and he immediately saw her and her belly stood out to him and he said that that wasn’t normal.” *Interview, diagnosed at 2 years of age*

> “There were all sorts of red flags popping up here and there, but the doctors kept telling us she was fine.” *Interview, diagnosed at 5 years of age*

- After many tests on the child, one parent/caregiver did their own research in Google and asked the clinician to test their child for ASMD

> “For the next six months, they tested her every week. They took her blood and did tests on her, and they couldn't figure out what was wrong with her. I, actually, just doing Google research, came across Niemann-Pick and I asked them to test for that because they had tested for everything else.” *Interview, diagnosed at 5 years of age*

- For one child, diagnosis happened very rapidly

> “It was about a month, it was a very quick, relatively quick diagnostic journey for us and for him. So it was the initial CT scan that showed the spleen and the liver involvement, and then the initial testing came back for the negative Gaucher. And then the very next panel that the metabolic doctor sent off, found the Niemann-Pick.”
> *Interview, diagnosed at 1 year of age*

In the interviews, parents/caregivers also explained that some children had been misdiagnosed. Misdiagnoses named by parents/caregivers included leukaemia, Gaucher and childhood mononucleosis but they explained many other diagnoses had been named during tests.

> “They wanted to put her on statins. We said that's ridiculous, she’s five years old, we’re not going to do that. We got all sorts of other potential diagnoses, that we were like, that seems a little extreme.” *Interview, diagnosed at 5 years of age*

Diagnosis of ASMD was mostly made by:

Parents/caregivers were asked if their children had experienced one or more neurological symptoms of ASMD. Sixty percent of children (6/10) had not experienced neurological symptoms

at the time of the study, 40% (4/10) had experienced hypotonia (an abnormally low level of muscle tone), 30% (3/10) ataxia (impaired balance or co-ordination of movement), 10% (1/10) neuropathy (dysfunction causing numbness or weakness, usually in the hands or feet) and 10% (1/10) seizures (Figure 6).

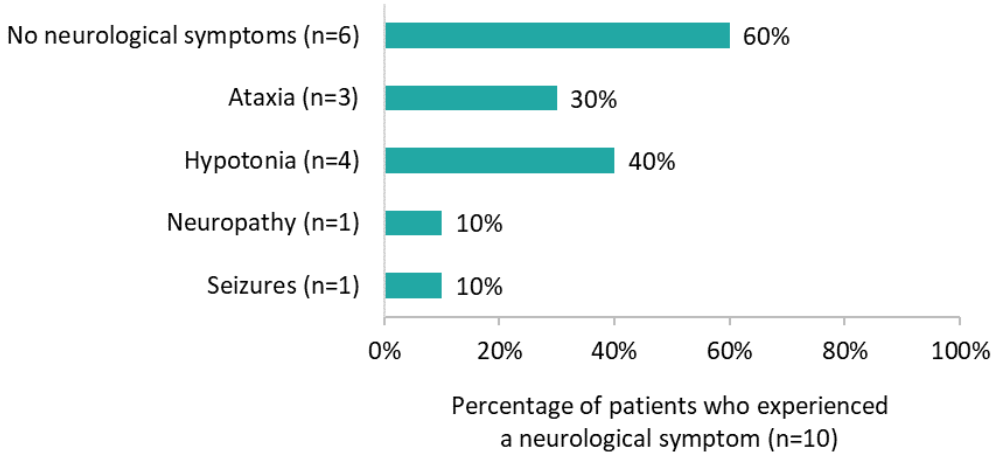


Figure 6. Percentage of patients (n=10) who experienced a neurological symptom. Values add up to more than 100% as patients could report multiple symptoms.

Treatment

Children **received olipudase alfa at a median age of 3.5 years** (mean 5.0 ±3.8, range 1.5–14.0, n=10).

All patients were still on treatment at the time of the survey and had been **on treatment for a median of 5 years** (mean 4.6 ±1.5, range 1.3–6.1. n=10).

How often were symptoms experienced before and after treatment with olipudase alfa

Respondents were asked to rate how often various ASMD symptoms had been experienced by the patient before treatment with olipudase alfa and now, after having been on treatment. Table 2 shows a summary of the responses.

Table 2. How often were symptoms experienced by patients (n=10) before treatment with olipudase alfa and how often symptoms are experienced now.

	Never				Monthly				Weekly				Daily*				All the time‡			
	Before		Now		Before		Now		Before		Now		Before		Now		Before		Now	
Symptom	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bone pain	7	70	10	100	2	20	—	—	1	10	—	—	—	—	—	—	—	—	—	—
Abdominal pain	3	30	8	80	2	20	—	—	2	20	1	10	1	10	1	10	2	20	—	—
Shortness of breath	6	60	9	90	2	20	1	10	—	—	—	—	2	20	—	—	—	—	—	—
Nosebleeds	8	80	9	90	1	10	1	10	—	—	—	—	1	10	—	—	—	—	—	—
Bruising	5	50	8	80	—	—	2	20	2	20	—	—	1	10	—	—	2	20	—	—
Vomiting/Nausea	4	40	8	80	1	10	1	10	2	20	—	—	2	20	1	10	1	10	—	—
	Never				**Rarely**				**Sometimes**				**Often**				**Always**			
	Before		**Now**		**Before**		**Now**		**Before**		**Now**		**Before**		**Now**		**Before**		**Now**	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Tiredness/ fatigue	—	—	2	20	—	—	5	50	3	30	1	10	6	60	2	20	1	10	—	—
Chronic headaches	4	40	6	60	2	20	3	30	4	40	—	—	—	—	1	10	—	—	—	—

* At least 1-2 episodes each day.
‡ Ongoing through each day.

Bone pain

Before treatment with olipudase alfa, 70% (7/10) of patients had never experienced bone pain, one patient experienced bone pain weekly, and two patients monthly. Now, whilst on treatment with olipudase alfa 100% (10/10) of patients do not experience bone pain (Figure 7).

> "The bone pain was something that he would complain about. And we figured it was growing pains, maybe he was growing, and that's what the doctor said. […] He would do things, was always able to walk and able to do things but he would mention that his legs hurt." *Interview, before treatment, started treatment at 7 years of age*

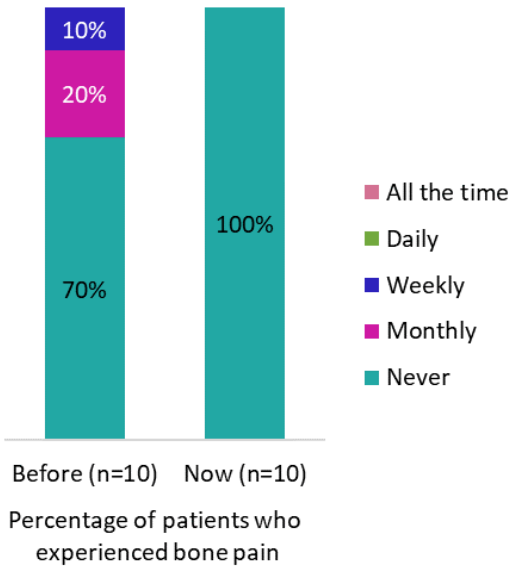


Figure 7. Percentage of patients (n=10) who experienced bone pain before and after treatment with olipudase alfa.

Abdominal pain

Before treatment with olipudase alfa, two patients had experienced abdominal pain monthly, two weekly, one daily and two all the time. Since starting treatment, no patients experience abdominal pain all the time. Thirty percent (3/10) of patients had never experienced pain before treatment, while 80% (8/10) of patients reported not experiencing abdominal pain now (Figure 8).

> "At the same time, she always seemed to have a lot of stomach pains. I think as she got older, the stomach pains were coming up more and more often. And I could see when she was running, she'd be holding her stomach. We thought she may have a gluten intolerance, so we tested her for gluten intolerance." *Interview, before treatment, started treatment at 7 years of age*

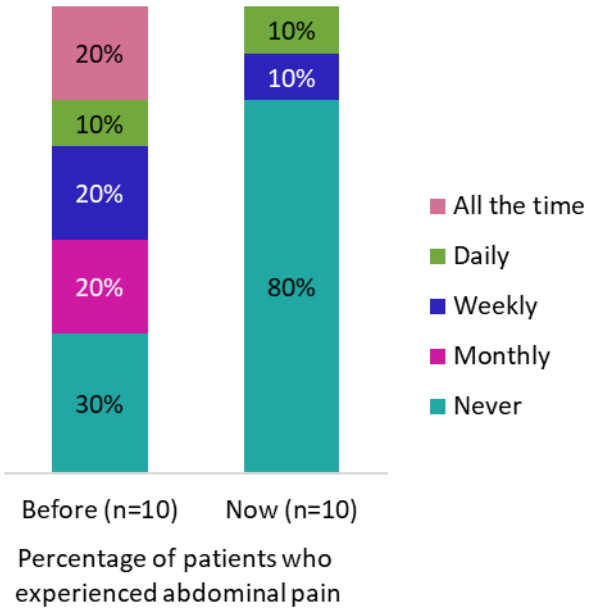


Figure 8. Percentage of patients (n=10) who experienced abdominal pain before and after treatment with olipudase alfa.

During the interviews, most parents/caregivers reinforced the fact that there was a reduction in abdominal pain after treatment:

> *Before treatment:*
> "…she complained about pain in the belly. So, that's very difficult for us to exactly understand what it is that she feels, but I remember that every day she said, yes, my belly hurts, I have pain. Maybe it was the organs that were very dense. I don't know. It was also difficult for her to exactly indicate where it was, but every day she told us that she was having pain in the belly."
> *After treatment:*
> "Also, the pain in the belly is completely gone, I think it's due to the organs that went to normal size again, and that is also supported by what the doctors tell us."
> *Interview, diagnosed at 2 years of age, started treatment at 4 years of age, 3 years and 6 months on treatment*

Enlarged organs

The children's organs (liver and spleen) were very much enlarged in 100% (10/10) of the patients before treatment with olipudase alfa whilst none of the children had their organs very much enlarged now (Figure 9).

Eighty percent (8/10) of children did not have their organs enlarged at all now and 20% (2/10) somewhat enlarged (Figure 9). In the interviews, parents/caregivers explained that their children's spleen had gone from being large and noticeable to be normal size after treatment:

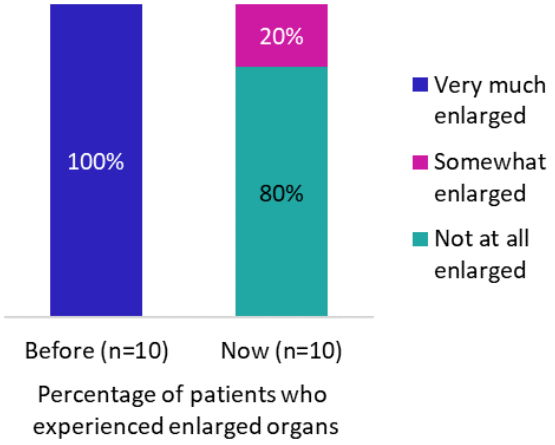


Figure 9. Percentage of children (n=10) whose organs were enlarged before treatment with olipudase alfa and now.

> "You're not supposed to feel the spleen coming underneath the ribs. And before, they could clearly notice that. Now they don't notice that anymore. Also, the liver, before, it was really dense. […]So, they say, okay, the size of the liver and the spleen, it's just normal now."
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

> *Before treatment:*
> "I don't remember the age but he started having the enlarged spleen."
> *After treatment:*
> "Because he was young and he had less build-up, I feel like his spleen got small fast."
> *Interview, started treatment at 2 years of age, 6 years and 1 month on treatment*

> "He, just looking at him himself, physically the belly's gone. He's working on getting a six pack now."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

Parents/caregivers explained during the interviews, that children were constantly hungry but struggled to eat normal amounts of food, due to the enlarged organs. This and the vomiting (see Vomiting and nausea section) affected their ability to gain weight.

> "We were noticing that she was having a very challenging time eating. She would say I'm hungry, I'm hungry, I'm hungry, then we'd feed her, she'd take one bite and say I'm full, and get up and walk away from the table."
> *Interview, before treatment, started treatment at 7 years of age*

> “I would say before the neurological symptoms set in for him, it was mostly just the size of his belly that made moving difficult. It was more a logistic thing than a neurological thing because his liver and his spleen were into his pelvis.”
> *Interview, before treatment, started treatment at 6 years of age*

> “But his organs, his belly was becoming increasingly more distended before the ERT […]. He was hooked up to feeding pumps, because the pressure that was being put on his stomach, he was only able to tolerate small volumes at a time. He was on continuous feed, so he had a feeding pump hooked up to him all the time, and oxygen hooked up to him. It’s just a lot of stuff for a little kid to deal with.”
> *Interview, before treatment, started treatment at 2 years of age*

During the interviews, one parent/caregiver explained how their child’s enlarged abdomen had impacted their balance, causing the child to fall a few times, and having to miss school, but after treatment, the belly is completely gone.

> *Before treatment:*
> “She fell a lot. So, due to the bigger belly, she had some stability problems and she really fell a lot.[…] The only times when she missed school was when she fell. That happened I think two times or something, yes, and she got an impact, a trauma on her head.”
> *After treatment:*
> “…the belly is completely gone.”
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

Vomiting and nausea

Before treatment 40% (4/10) of patients never experienced vomiting and nausea. This doubled to 80% (8/10) of patients never experiencing vomiting and nausea after starting treatment with olipudase alfa (Figure 10). One patient experienced vomiting and nausea all the time before treatment, now after starting treatment this has reduced to monthly. The frequency of vomiting and nausea did not change for one patient who experienced vomiting and nausea daily before and after starting treatment.

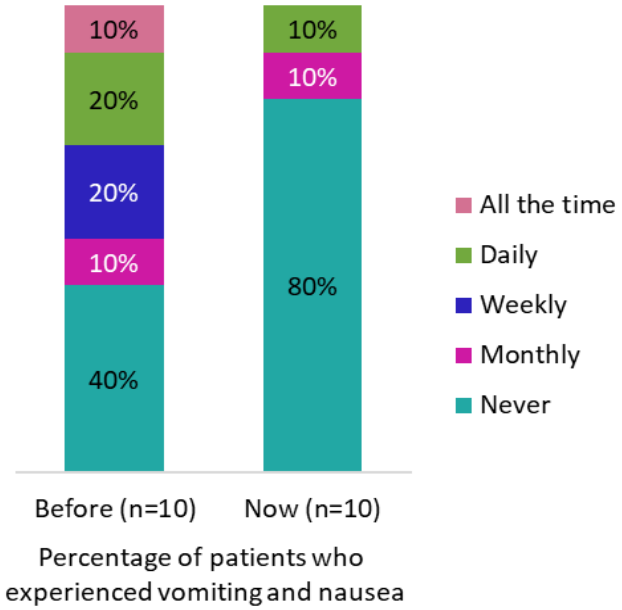


Figure 10. Percentage of patients (n=10) who experienced vomiting and nausea before and after treatment with olipudase alfa.

In the interviews, parents/caregivers explained vomiting before treatment had become severe, with one child vomiting more than five times per day. Parents/caregivers could not understand why their children would be constantly hungry but would then vomit their food. Vomiting could continue over night and did not allow children to gain a full night sleep however, after treatment, children started to sleep through the night.

> *Before treatment:*
> "So when he was first born, he was a pretty typical developing baby. He did have a lot of vomiting issues, which we had been told numerous times that it was just reflux, but we felt like this seems a little more severe than reflux. But we were first-time parents, so we didn't know, really. So, that, the vomiting got progressively worse before he started on olipudase. There were days he would vomit upwards of five times a day."
> *After treatment:*
> "He went from throwing up five times a day to now maybe he vomits once every four, five days. So, he still does have occasional vomiting, but it's immensely better than what it was, and it's manageable now."
> *Interview, started treatment at 2 years of age*

> "He would eat a full meal and he would eat a lot. And then after he was finished eating, he would throw up, which it makes sense now, with everything being so enlarged. But yes, so he would eat. And that's why I didn't understand why he wasn't gaining weight. Because he would eat a lot and then he would throw up, not at the end of every meal, but enough to make you wonder, why is this happening?"
> *Interview, before treatment, started treatment at 1.5 years of age*

Some children had to take meal supplements to be able to gain the calories before treatment because their nausea and gag-reflexes would not allow them to eat enough solid food, but after treatment these issues resolved.

> *Before treatment:*
> "It would be every third or fourth day he could have a vomiting episode, it just seemed like he would get backed up or too big a bite, something would cause the gag reflex in him. He didn't have any problems swallowing, […] 90% of his calories came from a PaediaSure or like a very thick liquid that he drank with a little bit of food on the side of that."
> *After treatment:*
> "About six months into treatment he… We'd started watching him wolf down food and we were just ready for him to gag, because you just… All of a sudden he's just taking orange slices like nothing. And I think I just remember looking up at each other like holy cow, he's just like downing food. And so all of a sudden he could eat no problem, everything and anything. We slowly phased out the fortified drink, it was probably decrease, decrease, decrease, it took a year."
> *Interview, started treatment at 6 years of age*

Shortness of breath

Before treatment 60% (6/10) of patients never experienced shortness of breath. Two patients experienced shortness of breath monthly and two patients experienced this daily. Since starting treatment with olipudase alfa, 90% (9/10) of patients now never experience shortness of breath, and only one experiences this monthly (Figure 11).

> "It was her favourite thing to do is play tag. […] And when she'd run and she'd be holding her stomach to get away, she'd get to the safe spot, and you could see her just always out of breath." *Interview, before treatment, started treatment at 7 years of age*

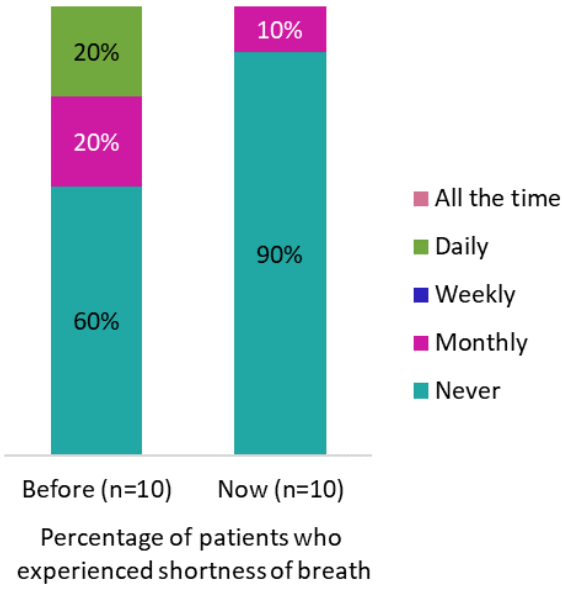


Figure 11. Percentage of patients (n=10) who experienced shortness of breath before and after treatment with olipudase alfa.

Nosebleeds

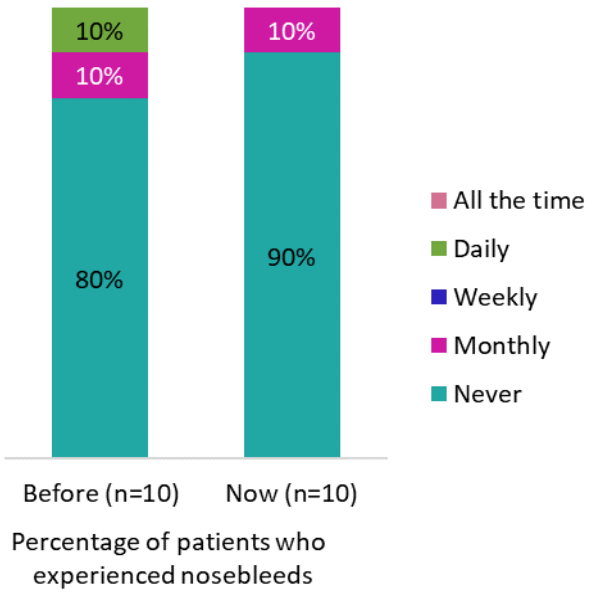


Figure 12. Percentage of patients (n=10) who experienced nosebleeds before and after treatment with olipudase alfa.

One patient (10%) experienced nosebleeds monthly before treatment with olipudase alfa, this reduced to never experiencing nosebleeds after starting treatment. Eighty percent of patients (8/10) never experienced nosebleeds prior to treatment, this increased to 90% (9/10) of patients never experiencing a nosebleed since starting treatment (Figure 12).

Another patient (10%) experienced nosebleeds daily before treatment with olipudase alfa, this reduced to monthly after starting treatment.

> "The nosebleeds. That was one thing that [name] had that [name] did not have, a lot of nosebleeds. Probably started at one years old, one or two maybe. I'll never forget, he fell and his face hit the grass outside and he was gushing blood. And since that fall is when we feel like the nosebleeds started. They would happen on occasion. He still gets them regularly. He thinks nothing of it, it's just his life."
> *Interview, started treatment at 2 years of age, 6 years and 1 month on treatment*

Other bleeding

One parent/caregiver reflected over the interviews that although their child had no nosebleeds, it was difficult to stop bleeding if the child had, for example, suffered a cut.

> "And then really hard to stop his bleeding, he didn't have nosebleeds, but if he got a cut or a scrape like the… You could see the effect of the disease on the spleen, like that part was hard, it was very to get his bleeding to stop, although he never really had nosebleeds, which was interesting with him."
> *Interview, before treatment, started treatment at 6 years of age*

Bruising

Before treatment 50% (5/10) of patients never experienced bruising but this increased to 80% (8/10) after treatment. Two patients experienced bruising weekly before treatment and were never experiencing bruising now. Two children experienced bruising all the time before treatment, but now, one was never bruising and the other experienced it monthly (Figure 13). The child experiencing daily bruises before treatment was now experiencing them monthly.

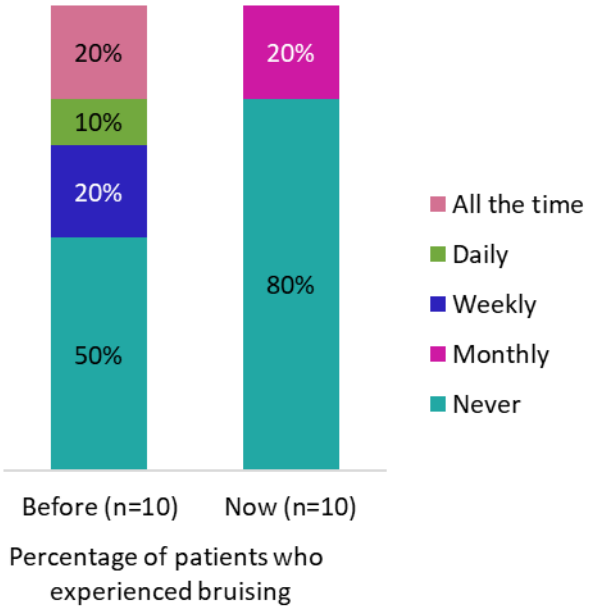


Figure 13. Percentage of patients (n=10) who experienced bruising before and after treatment with olipudase alfa.

> "It was her favourite thing to do is play tag. But every time she fell, she would have these massive bruises. Her legs were just covered in bruises. Her arms were just covered in bruises." *Interview, before treatment, started treatment at 7 years of age*
>
> *Before treatment:*
> "She was always having bruises and these things. And we could really notice that"
> *After treatment:*
> "The bruises are less. She's still sensitive to it, so she's always having these small bruises more than most other children, but it's better than before."
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

Tiredness and fatigue

Ninety percent (90%) of patients experienced tiredness and fatigue often 60% (6/10) and sometimes 30% (3/10) before treatment with olipudase alfa. This reduced to 30% (3/10) patients after starting treatment (sometimes 10% and often 20%) (Figure 14).

> "He would play for a little bit and then he'd want to take a nap. And then that goes back to, too, why are you so tired? You're not running around like other kids. You're not playing. So it makes you just wonder." *Interview, before treatment, started treatment at 1.5 years of age*

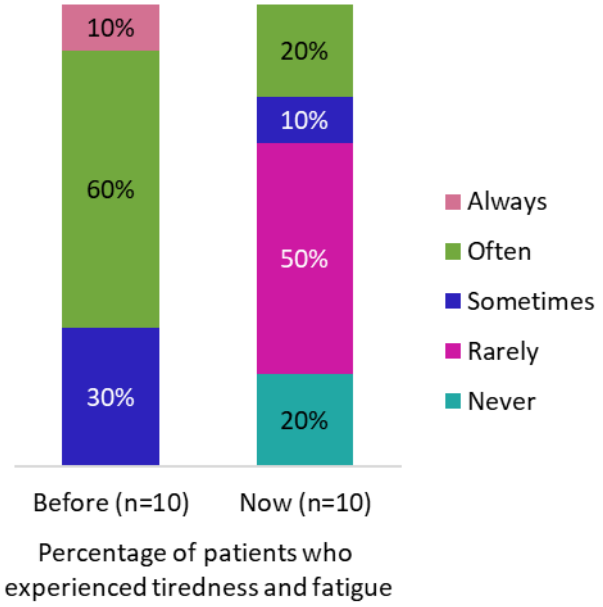


Figure 14. Percentage of patients (n=10) who experienced tiredness and fatigue before and after treatment with olipudase alfa.

Eight out of ten patients experienced an improvement in their tiredness and fatigue symptoms after stating treatment. One patients' tiredness and fatigue remained the same (often) before and after treatment. One patients' tiredness and fatigue symptoms worsened after treatment, reporting sometimes before treatment and often after treatment.

> *Before treatment:*
> "Yes, often tired. Didn't want to do anything."
> *After treatment:*
> "He's able to be active. He's doing push-ups."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*
>
> *Before treatment:*
> "…when she was really young, she never wanted to sleep. She was always very happy, very joyful. And as time passed by, we noticed that her energy level decreased, and when she got home from school, she asked us to go to bed.[…] And we also noticed that if she had to walk a certain distance, that it was difficult for her to catch up with the other children because she was always tired."
> *After treatment:*
> "Also, the energy, she is really full of energy now. It's amazing. She's very active and she likes to do sports, […] Now she's really an early bird, she's awake very early, and it's not a problem for her to handle these long schooldays anymore."
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

Chronic headaches

Forty percent (4/10) of patients never experienced chronic headaches before treatment. This increased to 60% (6/10) of patients never experiencing chronic headaches after starting treatment (Figure 15).

Two patients reported an increase in their chronic headaches after starting treatment. One patient reported 'never' before treatment and 'rarely' after treatment. Another patient reported 'sometimes' before treatment and 'often' after treatment.

> "It's hard to know exactly what he's feeling, because he can't communicate with us, but based off of how he would act when I would lay him down, the second I would lay his head down, he'd whine." *Interview, before treatment, started treatment at 2 years of age*

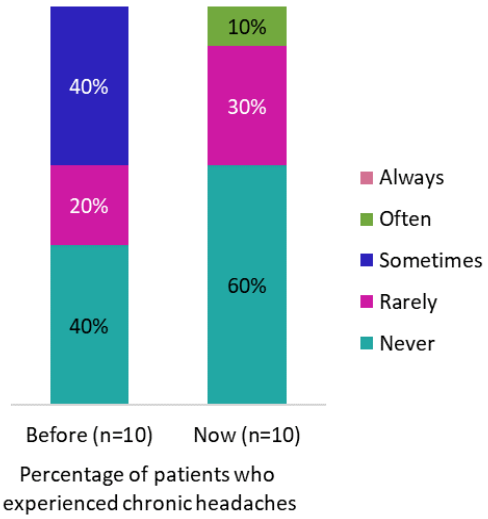


Figure 15. Percentage of patients (n=10) who experienced chronic headaches before and after treatment with olipudase alfa.

Growth delay

Parents/caregivers were asked if patients had experienced growth delay before treatment, with 70% (7/10) responding that the child had presented with 'very much' growth delay and 30% (3/10) answering that growth delay was only experienced 'somewhat' (Figure 16a).

> "She was the smallest kid in her class." *Interview, before treatment, started treatment at 7 years of age*

> "You know before his tonsils and adenoids came out, he was… That helped him gain more weight, so he was able to swallow more I think easier when he got that out and he was able to put on weight. So there would be like a little growth spurt that would give him some relief temporarily, and then it would just increase again, the size of his belly, and it would take all of… Whatever little bit he gained, would go away again. And then just it did get harder to get the calories on him at the end, like if you look back at pictures and stuff, he just looked a little more malnourished." *Interview, before treatment, started treatment at 6 years of age*

> "His growth started to fall off the curve. He was never on the curve since birth, but his paediatrician was like, he's following his own little curve just underneath the charts, so she wasn't too concerned with it until we got to his six-month check-up, when she felt like his liver was enlarged, felt enlarged, and that's what spiralled everything." *Interview, before treatment, started treatment at 2 years of age*

Parents/caregivers were also asked if there had been any changes in the child's growth delay now after treatment, with 80% (8/10) responding that their child's growth was now 'much better' (Figure 16b).

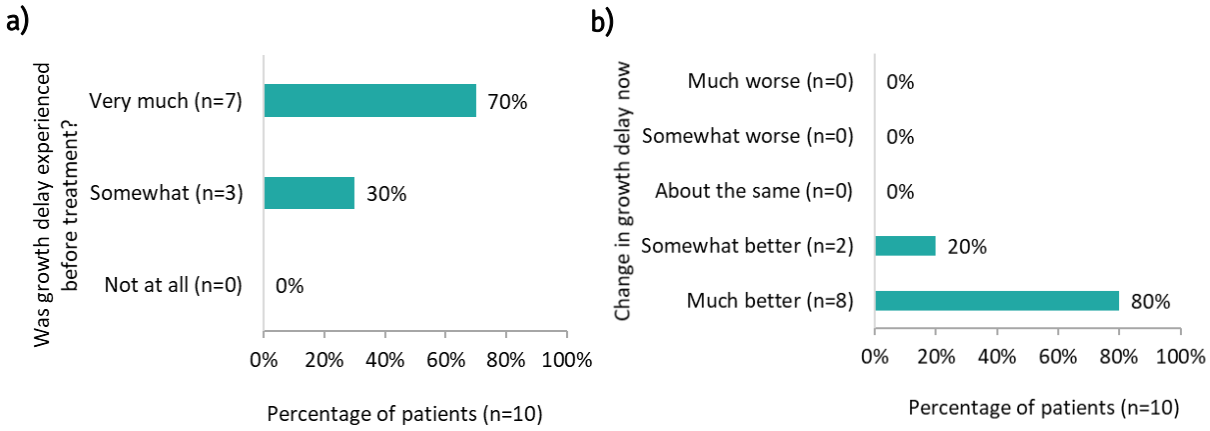


Figure 16. a) Growth delay experienced by children before treatment with olipudase alfa (percentage) (n=10) and b) changes in the child's growth delay now (percentage) (n=10).

> "You wouldn't think it, if you saw her today you would not think that that child could not walk, that she was a bag of bones, that she was nine months old and in three month old clothes because she was so small. You wouldn't think it."
> *Interview, after treatment, started treatment at 3 years of age, 4 years and 11 months on treatment*

> "Before beginning the drug, he was I think in the 15th percentile of his age for height and weight. He is now, I believe, in the 85th to… I think it's the 85th percentile. But he has a head full of hair. He is over three feet tall. He is weighing about 40 lbs. He's a little skinny but he's tall."
> *Interview, started treatment at 1.5 years of age, 3 years and 10 months on treatment*

> "He has grown a ton. He went from not being on the growth chart at all, to he's now at the 50th percentile for weight and height. So, he grew a lot, put on a lot of weight, and he's a healthy size now.[…] His body is just absorbing nutrients a lot better now."
> *Interview, started treatment at 2 years of age, 1 year and 3 months on treatment*

> "He was always on that 3% growth curve, he's up in the 30%, 40% growth curve now. So, he's still, I wouldn't say small at all, but he's not the tallest in his grade. But he's not the shortest. So, he's grown quite a bit. We've seen a huge impact on growth."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

> "But we had the impression that before, she was really small, and it was also confirmed when they measured her, that she is somewhat small. But now, if you compare her to other people from school, of the same age, it's rather normal now."
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

Infections

Parents/caregivers were asked how many infections the child generally had during a 6-month period before treatment with olipudase alfa and now. Infections could include ear infections, upper respiratory tract infections, pneumonia, etc.

Before treatment with olipudase alfa, 40% (4/10) of children used to have 3–4 infections over a 6-month period and 20% (2/10) experienced more than four infections. Now, 90% (9/10) of children were not experiencing any infections in the last 6-month period (Figure 17).

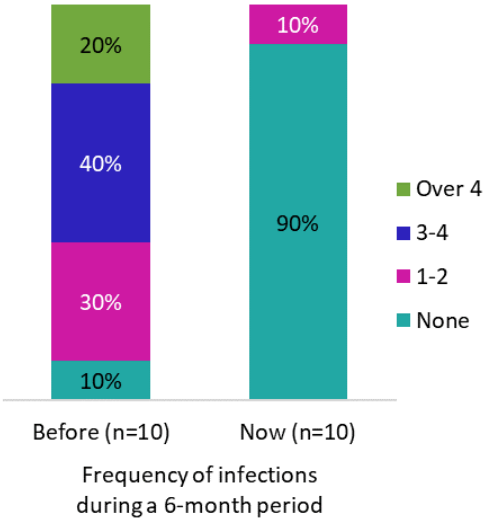


Figure 17. Frequency of infections experienced over a 6-month period before treatment with olipudase alfa and now.

Respiratory and ear infections were frequent before treatment with some parents/caregivers explaining that it seemed like their child's infection would never go away, with one child being diagnosed with allergies due to the chronic congestion suffered due to the infections.

> "She would get ear infections a lot. And they would give her a ten-day supply of medication, and it would never heal her. She would have to go through two ten-day cycles. But it was on a monthly basis that she was getting ear infections."
> *Interview, before treatment, started treatment at 7 years of age*

> "Yes, over four [over 6 months]. [Name] got a lot of ear infections... It was so bad to the point where we got the tubes put in his ears at a young age, just because that's how bad. It was constantly ear infections, it was constantly colds, everything.[…] And a fever always comes along with it, so it was tough."
> *Interview, before treatment, started treatment at 2 years of age*

> "So for his first year, we noticed that [Name] developed RSV when he was a few months old. He always seemed congested. But we were always met with it's allergies. But he's so young. You really can't diagnose a child with allergies this young. So we just noticed he always had some type of respiratory something going on that just never seemed… It would clear up and then it would come back."
> *Interview, before treatment, started treatment at 1.5 years of age*

> "He had to be on CPAP briefly with some oxygen, and what started that was a bad virus and we had to cure him of that virus and then get the tonsils and adenoids out. And then the other infections, it was basically just… The one hospitalisation came from the flu that turned into pneumonia and he was on BiPAP for a while. And then other infections might have been just a regular cold…"
> *Interview, before treatment, started treatment at 6 years of age*

The number of ear infections were dramatically reduced after starting treatment.

> *Before treatment:*
> "He would constantly have an ear infection. He's had two sets of tubes in his ears."
> *After treatment:*
> "Before the fall, he had not had an ear infection in probably at least two years. It has been a long time."
> *Interview, started treatment at 1.5 years of age*

Some parents/caregivers explained that before treatment, infections such as the common cold would imply a stay in hospital, but this changed after receiving treatment.

> "… whenever he got sick before ERT, he would nine times out of ten end up in the hospital, even if it was a common cold, just because his lungs weren't in the greatest shape […]. Actually, the first time he got a cold after being on the infusions was the only time he didn't end up in the hospital…."
> *Interview, before treatment, started treatment at 2 years of age*

In the interviews, one parent/caregiver explained that even a toe infection implied a visit to the hospital, as it will not go away.

> "We went to the hospital because she had a massively infected toe, and it did not disappear, even though we tried to treat with a cream that was prescribed by our general practitioner." *Interview, before treatment, started treatment at 4 years of age*

Bone fractures

Parents/caregivers reported 90% (9/10) of children had no bone fractures before treatment, and one child had 1–3 fractures. Now, 80% (8/10) reported not having had any fractures since starting treatment, while two children had 1–3 fractures (Figure 18). In the interviews, one parent/caregiver said the fracture was a in the tibia because of the child losing his balance. None of the children had more than three fractures before or after treatment.

> "The one fracture was before treatment, the femur, it was the spiral fracture [unclear]. The x-rays said his bones looked fine, but I mean there's no way, I don't think you can see the damage the disease does."
> *Interview, before treatment, started treatment at 6 years of age*

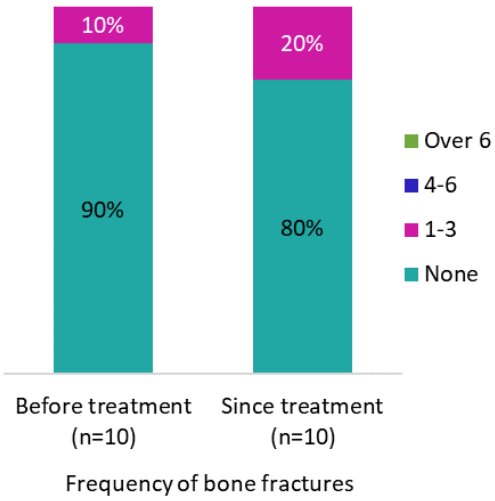


Figure 18. Frequency of bone fractures before and since treatment with olipudase alfa.

Please note that during an interview with one parent/caregiver, they noted that their child did suffer a skull fracture two years ago. This was not initially reported in the survey only in the interview.

Cognitive abilities

Parents/caregivers were asked if they thought their child's cognitive abilities were affected before treatment with olipudase alfa, i.e. learning new skills, making decisions, following instructions and/or focusing their attention. Sixty percent (6/10) of children did not have any cognitive abilities affected, and one child and two children had their cognitive abilities 'somewhat' affected and 'a little bit' affected, respectively (Figure 19).

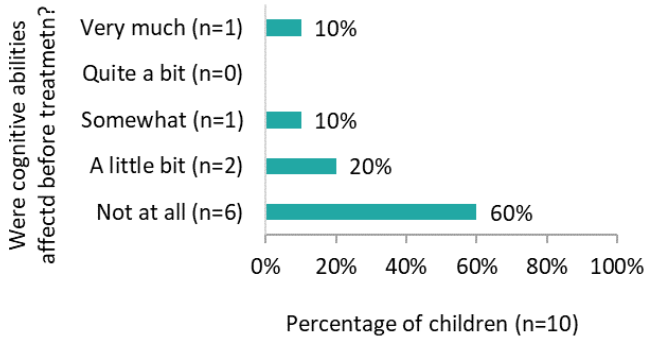


Figure 19. Effect of ASMD in cognitive abilities before treatment.

Parents/caregivers were asked if there were any changes in the child's cognitive abilities now, after starting treatment. Fifty percent (5/10) responded that their child's cognitive abilities were 'about the same' now than before, but cognitive abilities were 'much better' for one child and 'somewhat worse' for three children (Figure 20).

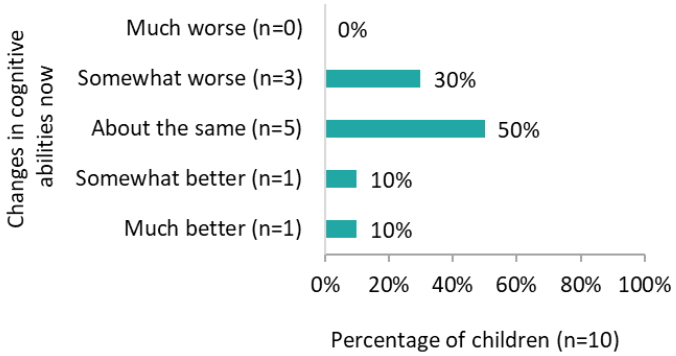


Figure 20. Changes in cognitive abilities now.

> "I think it was harder to see because he was closer to his age group as far as his knowledge and where he was at, like he was just a little below the norm. And then as he got older, you could see that gap just get bigger and bigger and bigger. So that was the cognitive, neurological portion that you could barely see. Delay in talking, he did speak though when he was two, it just took longer, he did get there and he was pretty communicative after that and almost to the point you didn't notice it, he did fairly well in school." *Interview, before treatment, started treatment at 6 years of age*

> "He was regressing pretty quickly. Like I said, he used to be able to sit up on his own, play with his toys, just way more alert, and he started getting pretty lethargic very fast. He got to the point where he wasn't able to do too much, and this was all pre-olipudase." *Interview, before treatment, started treatment at 2 years of age*

Other symptoms

Large appetite but not gaining weight

In most interviews, parents/caregivers mentioned that their child was constantly eating before treatment started. Parents/caregivers linked this large appetite to the enlarged organs and the vomiting. One parent/caregiver had to provide their child with protein drinks so the child would be satiated.

> “Prior to treatment she had a very large appetite and so that would be the thing, we could never fill her up enough. And it’s like you have to cut it off because it’s like where is this food going. So we implemented obviously as much food as we could but we also had her on children protein drinks to help her fill up because we were just constantly eating.” *Interview, before treatment, started treatment at 3 years of age*

> “And then we noticed he wasn’t gaining weight. I saw how much he was eating, and he was not gaining weight. His paediatrician said, well, it’s because he probably has a high metabolism. But at this point, [Name] still was not walking so that didn’t make sense to me.” *Interview, before treatment, started treatment at 1.5 years of age*

Hair

One parent/caregiver noticed their child had no hair before treatment with olipudase alfa but the child gained a full-head of hair after starting treatment.

> “I noticed too his hair. He had no hair. And then we later found out that your hair is also a sign of your health, which makes sense. Because once he began the trial drug, he started gaining weight, he was getting taller, he’s got a head full of hair.” *Interview, started treatment at 1.5 years of age*

Seizures

One of the children was diagnosed with seizures at the age of two and these have recently become less frequent and shorter.

> “We feel like we’re in a good spot with his seizures right now. He does still have them daily. Probably right now it’s I’d say on average two a day, but they’re relatively short and they’re not too disruptive to his life right now, but that definitely wasn’t always the case. There were periods of time where he was having five a day, and that definitely settled down now and gotten better. It’s manageable now for everyone.” *Interview, started treatment at 2 years of age, 1 year and 3 months on treatment*

Apnoea

One of the children required oxygen before treatment because of their apnoea but after treatment the child stopped needing oxygen while sleeping.

> *Before treatment:*
> “And he required oxygen because he had non-apneic hypoxemia. He was diagnosed with that before we started ERT, so his oxygen was dropping when he was sleeping, just because of the build-up that was happening in his lungs.”
> *After treatment:*
> “Gosh, it’s changed in a lot of ways. He doesn’t need oxygen anymore, so he is able to go to sleep now without being hooked up to tubes and stuff, which was alone a big deal for us.”
> *Interview, started treatment at 2 years of age*

Muscle tone and milestones

Before treatment, parents/caregivers said their child was growing weaker and was not able to reach their milestones, like sitting, walking.

> "His muscle tone was growing weaker. His core was very weak. He used to be able to do things like sit up on his own and stand while holding on to things, and just had a lot more strength, and then the bigger his belly got, the more distended it got because of his large organs." *Interview, before treatment, started treatment at 2 years of age*

> "And then just the lack of not wanting to stand or not wanting to walk. She would try but she couldn't grasp it."
> *Interview, before treatment, started treatment at 3 years of age*

Difficulty in overcoming 'episodes'

> "It almost seemed like he would have a bad episode and then he would kind of recover from that and then have another bad episode. And the episodes sort of were worse each time although he was able to recover from them. And by episode I mean it was different things, when he was two he had his tonsils and adenoids out, but it was more difficult surgery than it would have been for a normal kid. Broke his leg at age five and then that was a more difficult recovery. And then flu and pneumonia right before he started was really difficult recovery. So I would say his fragility maybe was increasing with his age, he was definitely becoming more malnourished, you could see more just his weight and his belly and his limbs just looked skinnier."
> *Interview, before treatment, started treatment at 6 years of age*

Managing symptoms of ASMD before treatment with olipudase alfa

Three survey respondents indicated that their children never used any treatments or therapies to manage symptoms of ASMD before treatment with olipudase alfa.

> "There was a lot of stuff that was out of our control, so we just did the best we could." *Interview, before treatment, started treatment at 6 years of age*

However, most parents/caregivers stated in the survey and the interviews that they had tried to manage symptoms through eating a healthy diet, vitamin supplements, ibuprofen, nasal drips, acid reflux and nausea medications, supplemental oxygen feeding pumps. Therapies included physiotherapy, speech therapy and occupational therapy.

> "Everything that we looked at in her food changed, we changed our entire how we ate, how we slept, what activities we did. Anything that I could think of that could potentially help her be healthy or be safer we changed everything in our home. All the junk food, all the good stuff went out, it was just pure vegetables and lean meats and me reading about cholesterol, like what could I do to potentially help her diet, right. It just became really all that we focussed on to make sure that we were doing anything that we could in the time being until there was a way to access treatment." *Interview, before treatment, started treatment at 3 years of age*

Impact of ASMD symptoms on the child's day to day life before and after treatment with olipudase alfa

Parents/caregivers were asked about the impacts of ASMD symptoms experienced before treatment with olipudase alfa and now, after treatment.

Table 3. Impact of symptoms on day-to-day life of children (n=10) before treatment with olipudase alfa and now.

	None at all				Very little				Some				Quite a lot				Very much			
	Before		Now		Before		Now		Before		Now		Before		Now		Before		Now	
Symptom	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bone pain	6	60	9	90	2	20	1	10	1	10	—	—	1	10	—	—	—	—	—	—
Abdominal pain	3	30	7	70	—	—	2	20	4	40	—	—	1	10	—	—	2	20	1	10
Shortness of breath	5	50	8	80	—	—	2	20	3	30	—	—	2	20	—	—	—	—	—	—
Nosebleeds	7	70	9	90	2	20	1	10	—	—	—	—	1	10	—	—	—	—	—	—
Bruising	5	50	10	100	3	30	—	—	1	10	—	—	—	—	—	—	1	10	—	—
Vomiting/Nausea	3	30	7	70	—	—	2	20	3	30	—	—	2	20	—	—	2	20	1	10
Tiredness/ fatigue	—	—	4	40	1	10	3	30	4	40	2	20	2	20	—	—	3	30	1	10
Chronic headaches	4	40	6	60	2	20	3	30	3	30	—	—	—	—	—	—	1	10	1	10

Impacts before and after treatment reported in the surveys can be seen in Figure 21. Parents/caregivers reported an overall positive impact on their child's day-to-day life with all symptoms. All symptoms showed an increase in parents/caregivers reporting an impact of 'none at all'.

Bone pain

Sixty percent (6/10) reported bone pain had no impact (none at all) on their child's day-to-day life before treatment, this increased to 90% (9/10) reporting no impact after starting treatment. One (1/10) reported 'quite a lot' before treatment and now 'very little' impact after starting treatment.

Abdominal pain

Thirty percent (3/10) reported abdominal pain had no impact (none at all) on their child's day-to-day life before treatment, this increased to 70% (7/10) reporting no impact after starting treatment. One (1/10) reported 'very much' before and after treatment with olipudase alfa.

Shortness of breath

Half of parents/caregivers reported that their child's shortness of breath had no impact (none at all) on their child's day-to-day life before treatment, this increased to 80% (8/10) of parents/caregivers. Two reported 'very little' impact on their child's day-to-day life after starting treatment with olipudase alfa.

Nosebleeds

Seventy percent (7/10) reported that nosebleeds had no impact (none at all) on their child's day-to-day life before treatment, this increased to 90% (9/10). One parent/caregiver reported

nosebleeds had 'quite a lot' of impact before treatment, but now has 'very little' impact on their child's day-to-day life after starting treatment.

Bruising

Fifty percent (5/10) reported that bruising had no impact (none at all) on their child's day-to-day life before treatment. Since starting treatment with olipudase alfa, all 10 parents/caregivers (100%) reported that bruising now had no impact on their child's day-to-day life.

Vomiting & Nausea

Thirty percent (3/10) reported that vomiting and nausea had no impact (none at all) on their child's day-to-day life before treatment. Another 30% reported 'some' impact on their child's day-to-day life. Twenty percent (2/10) reported that nausea and vomiting had 'quite a lot' and 'very much' impact before treatment. Now 70% (7/10) report that nausea and vomiting have no impact on their child's day-to-day life. Twenty percent (2/10) report 'very little' impact now and one (1/10) reported 'very much' before and after treatment with olipudase alfa.

Tiredness & Fatigue

Tiredness and fatigue impacted all patients' day-to-day lives before treatment with olipudase alfa. No parents/caregivers reported no impact (none at all) before treatment, however this increased to 40% (4/10) after starting treatment. Before treatment 10% (1/10) reported 'very little', 40% (4/10) reported 'some', 20% (2/10) reported 'quite a lot' and 30% (3/10) reported 'very much'. After starting treatment with olipudase alfa, 30% (3/10) reported 'very little', 20% (2/10) reported 'some' and 10% (1/10) reported 'very much'.

Chronic headaches

Forty percent (4/10) reported that chronic headaches had no impact (none at all) on their child's day-to-day life before treatment, this increased to 60% (6/10) since starting treatment with olipudase alfa. Twenty percent (2/10) reported 'very little' impact before treatment, this increased to 30% (3/10) after starting treatment. Thirty percent (3/10) reported 'some' impact before treatment. One (1/10) parent/caregiver reported 'very much' before and after treatment with olipudase alfa.

Enlarged organs

Eighty percent (8/10) reported that enlarged organs had a large (very much) impact on their child's day-to-day life before treatment. One parent/caregiver (10%) reported 'quite a lot' and one reported 'some' impact before treatment. After starting treatment, 80% 8/10 reported that their child's organs were no longer enlarged, therefore the impact question was not applicable to them, and they were therefore not able to answer the question. Two respondents reported that their child's organs were still 'somewhat' enlarged after starting treatment and they were able to answer the question to rate the impact on their child's day-to-day life. One reported 'quite a lot' and one reported 'none at all'.

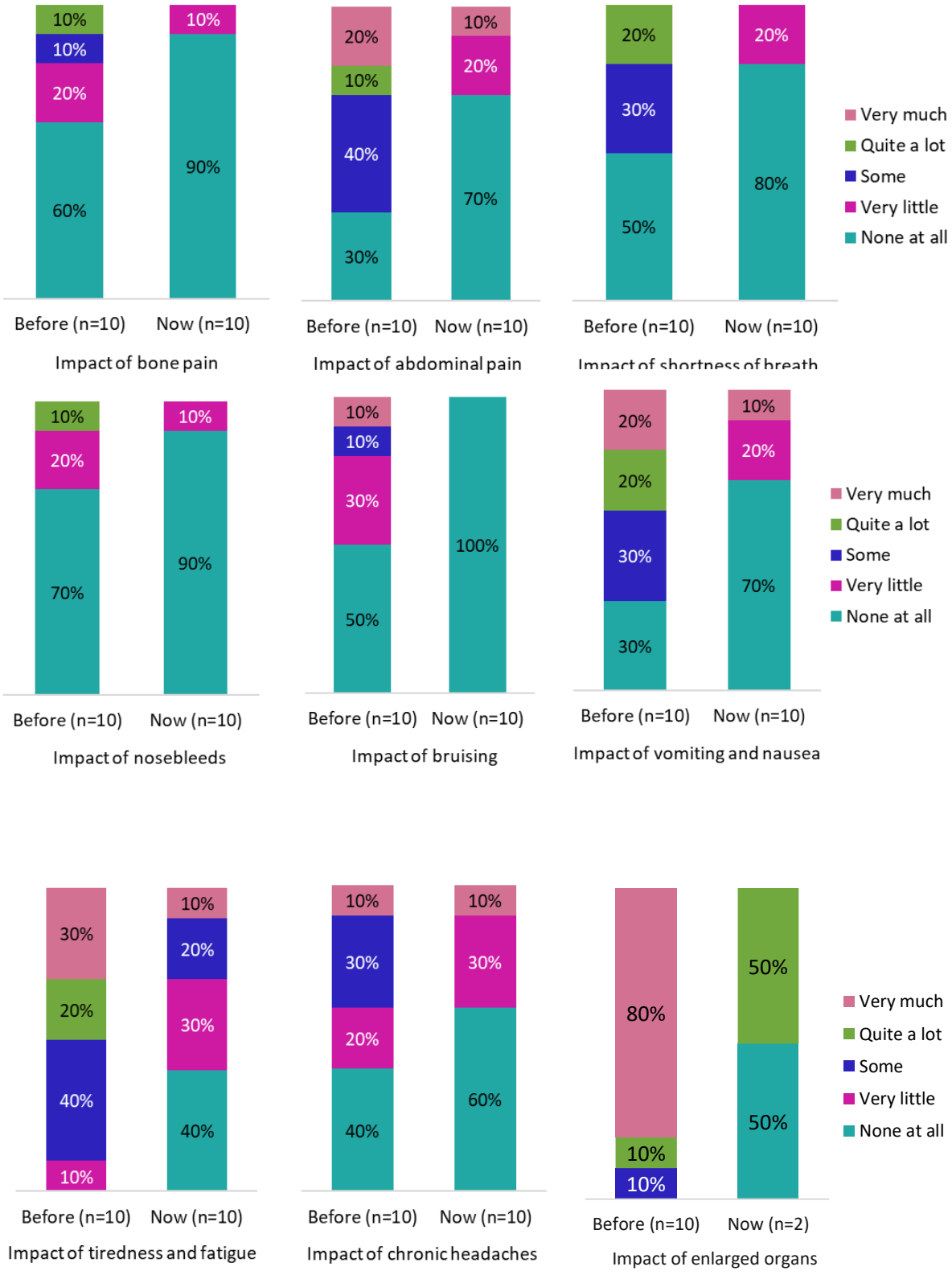


Figure 21. Impact of symptoms on child's day-to-day life before and since starting treatment with olipudase alfa

Overall change in symptoms and activities since treatment with olipudase alfa

Abdominal problems

Parents/caregivers were asked about the overall change in abdominal problems (e.g. filling up early when eating, pain under the ribs on the left side, abdominal discomfort, difficulty bending over, satisfaction with abdominal body image) since starting treatment with olipudase alfa. Parents/caregivers indicated abdominal problems were much better in 100% (10/10) of children since starting treatment (Figure 22).

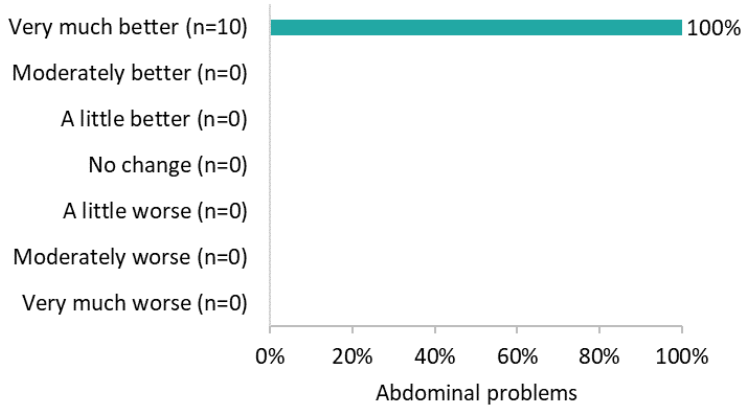


Figure 22. Overall change in abdominal problems since starting treatment with olipudase alfa (n=10).

The overall change in specific abdominal symptoms followed a similar result, with pain under the ribs on the left side and abdominal discomfort being 'very much better' since treatment in 100% (10/10) of children (Figures 23b & c) and filling up early when eating and difficulty bending over being 'very much better' in 90% (9/10) of children and 'moderately better' in 10% (1/10) for both symptoms (Figure 23a & d). In addition, satisfaction with their abdominal body image was also 'very much better' in 100% (10/10) of children (Figure 23e).

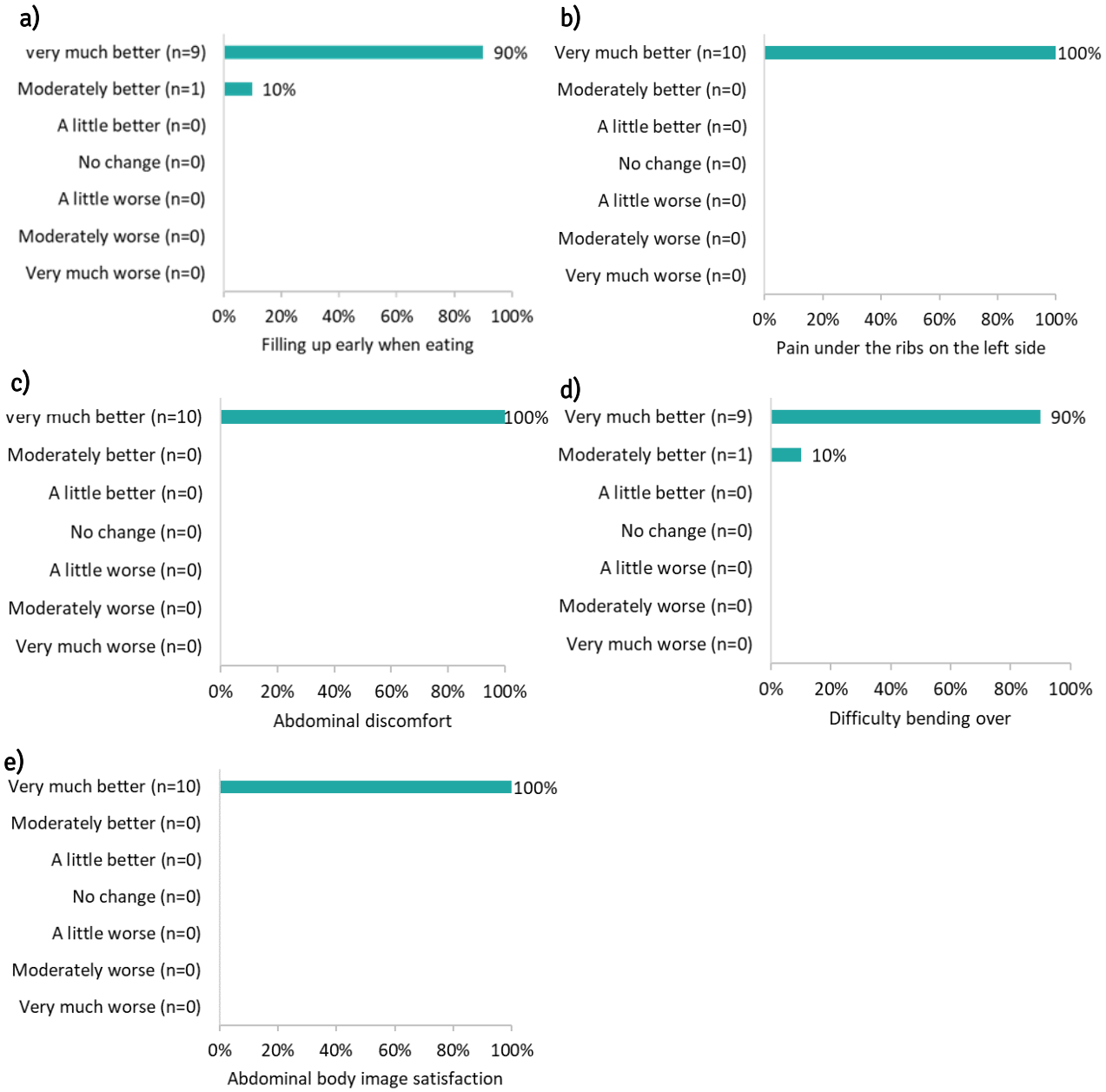


Figure 23. Overall change in specific abdominal symptoms since starting treatment with olipudase alfa (n=10): a) filling up early when eating; b) Pain under the ribs on the left side; c) abdominal discomfort; d) Difficulty bending over and e) satisfaction with abdominal body image.

Bodily pain

Bodily pain, other than pain under the ribs on the left side, was 'very much better' after treatment with olipudase alfa in 80% (8/10) of children, and 20% (2/10) reported 'no change' from before receiving treatment (Figure 24).

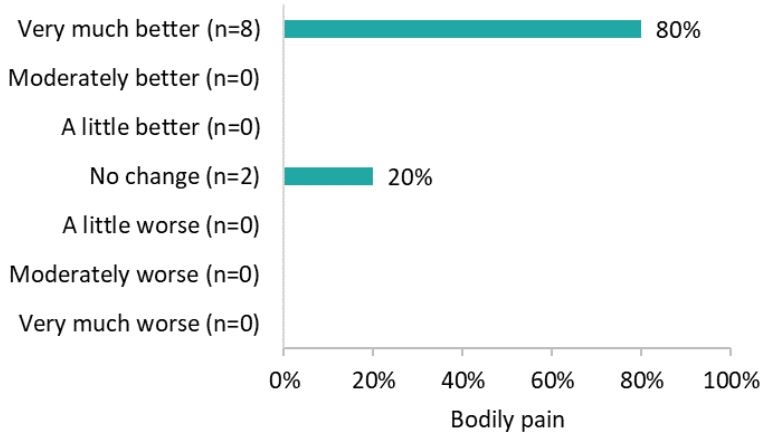


Figure 24. Overall change in bodily pain since starting treatment with olipudase alfa (n=10).

Fatigue

Fatigue, including weariness and tiredness was reported to be 'very much better' in 70% (7/10) of children and 'moderately better' in 20% (2/10) (Figure 25).

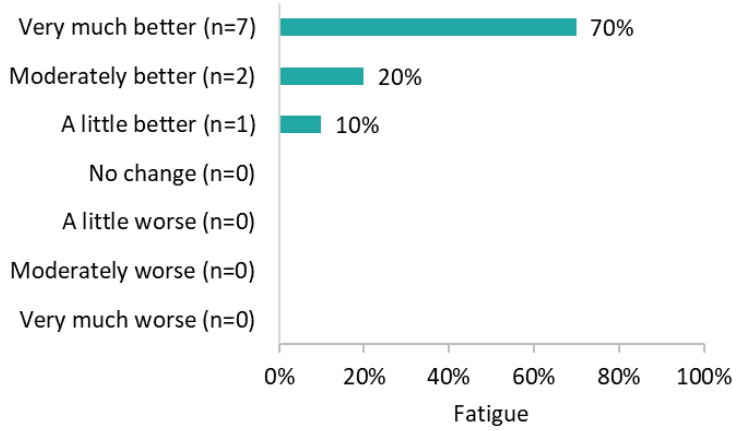


Figure 25. Overall change in fatigue since starting treatment with olipudase alfa (n=10).

Shortness of breath

Shortness of breath at rest and shortness of breath with activity had the same responses. In both cases, shortness of breath was 'very much better' in 70% (7/10) of children and 'moderately better' in 10% (1/10). There had been 'no change' in 20% (2/10) of children (Figure 26a & b).

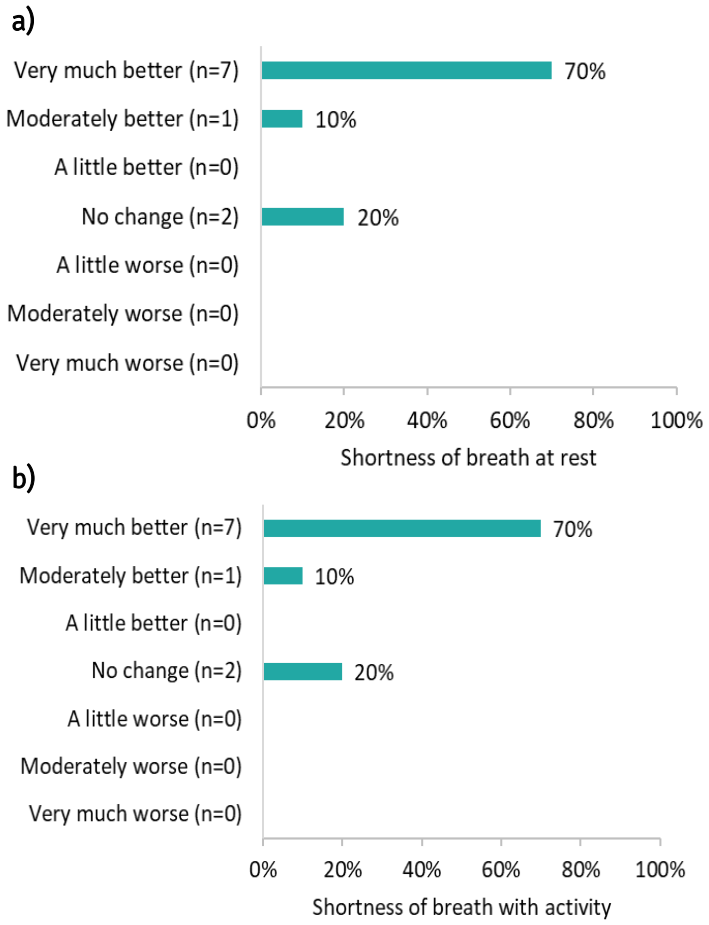


Figure 26. Overall change in shortness of breath since starting treatment with olipudase alfa (n=10) for a) shortness of breath at rest and b) shortness of breath with activity.

Daily activities

Parents/caregivers were asked whether there had been an overall change in the child's ability to perform daily activities since being on treatment. The overall change in ability to go to school was 'very much better' for 70% (7/10) of children, with 10% (1/10) of children's ability to go to school being 'moderately better'. Only one child did not experience any change (Figure 27).

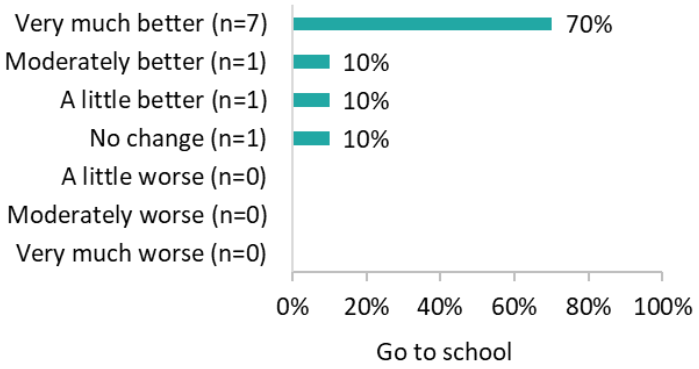


Figure 27. Overall change in the child's ability to go to school.

The overall change in ability to participate in exercise was 'very much better' since treatment with olipudase alfa for 80% (8/10) of children, with 10% (1/10) of children's ability to participate in exercise being 'moderately better' and 10% (1/10) 'a little better' (Figure 28).

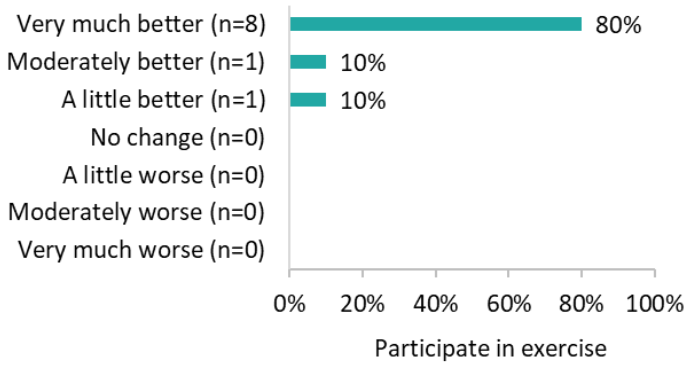


Figure 28. Overall change in the child's ability to participate in exercise.

The overall change in ability to do chores was not as prominent than with other activities, but the ability to do chores was 'very much better' since treatment with olipudase alfa for 50% (5/10) of children and 'moderately better' for 20% (2/10). No change was reported for 30% (3/10) of children (Figure 29).

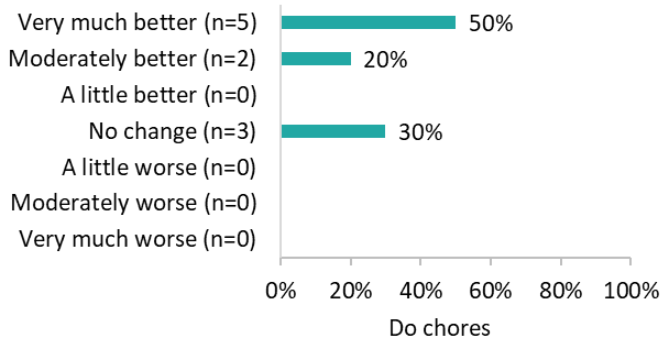


Figure 29. Overall change in the child's ability to do chores.

The overall change in ability to perform self-care activities was 'very much better' since treatment for 70% (7/10) of children and 'a little better' for 10% (1/10). No change was reported for 20% (2/10) of children (Figure 30).

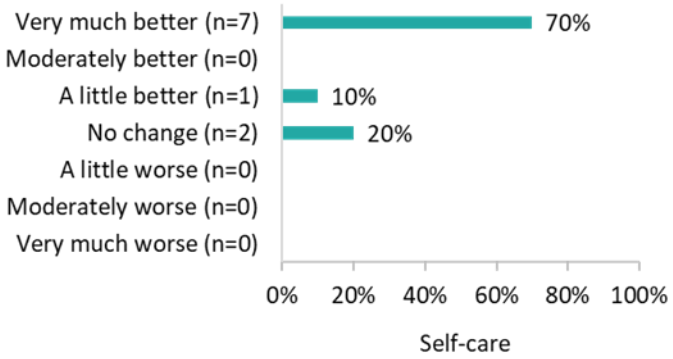
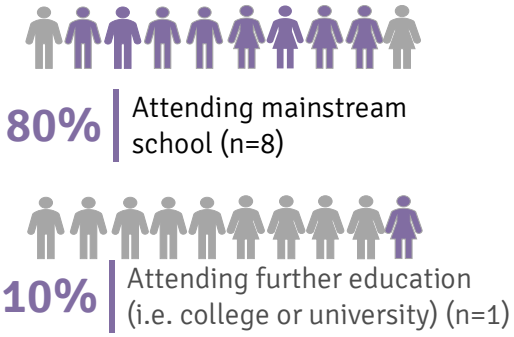


Figure 30. Overall change in the child's ability to self-care.

Impact of treatment with olipudase alfa on day to day life with ASMD

Impact of treatment on education of patient with ASMD

All ten patients included in this report were children of school age: 80% (8/10) were attending mainstream school and one further education (i.e. college or university). One child had reached pre-school age but was unable to attend due to seizures.



Parents/caregivers were asked if there had been any changes in the child's ability to attend school/college since starting treatment with olipudase alfa.
Sixty percent (6/10) of parents/caregivers said their child had to decrease their hours or days attending education due to treatment appointments, and 10% (1/10) due to medical appointments for symptoms of ASMD (Figure 31).

Thirty percent (3/10) of children did not have to make any changes to their attendance. (Figure 31). One parent/caregiver reported their child was able to increase their hours or days attending school, but this was because the child was too young to attend school when the trial started.

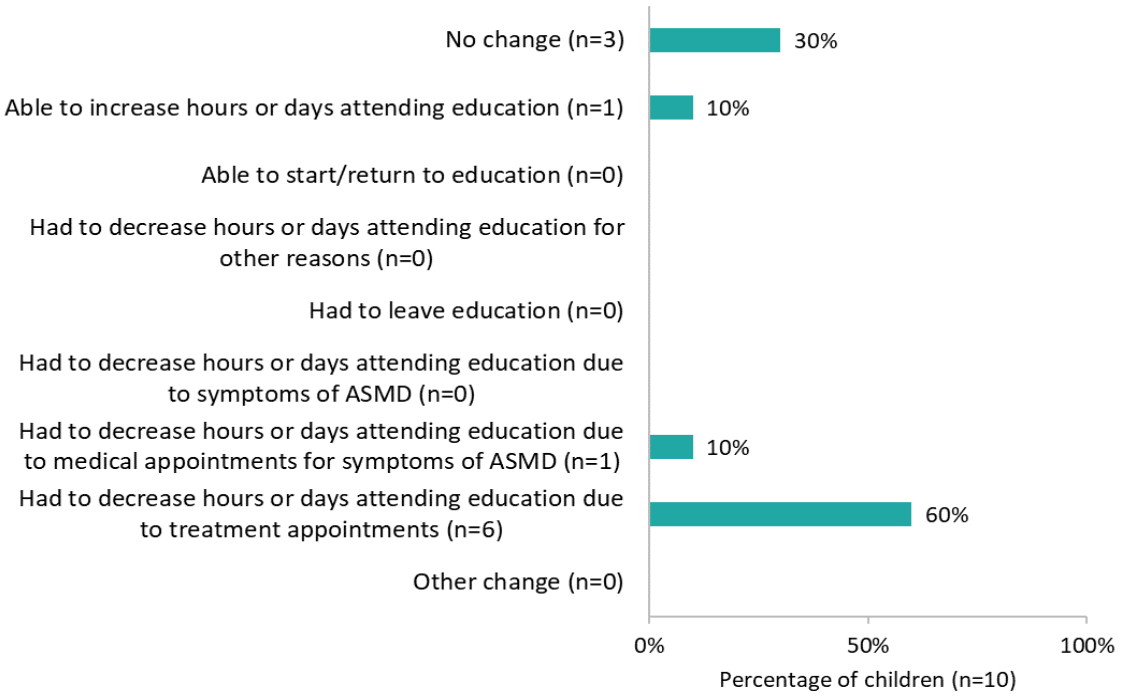


Figure 31. Changes in the child's ability to attend education since treatment with olipudase alfa (n=10).

> "At the start of the trial, my child had to miss 4 days of school every other week for treatment, monitoring, and testing. Currently my child misses 1 day of school every other week for treatment. And 3 days of school quarterly for monitoring/testing."
> *Survey response, 4 years and 11 months on treatment*

Parents/caregivers were asked if they had any concerns related to the effects of ASMD on the child's education before treatment with olipudase alfa. Sixty percent (6/10) of parents/caregivers said they were concerned about the child's school experience being more awkward due to ASMD (Figure 32) but all of these parents/caregivers' concerns had become 'much better' (4/6) or 'somewhat better' (2/6) after treatment with olipudase alfa (Table 4). Before treatment, half the parents/caregivers (5/10) were concerned about the child not being able to take part in extracurricular activities (Figure 32) but after treatment, these concerns were 'much better' in three parents/caregivers out of five although one parent/caregiver still had the same concern (Table 4).

> "I definitely held him back one year, he went to a preschool that was… designed around kids with other special needs and development needs, and I shortened his day. Trying to think, it was just harder to play and interact for him, he just didn't have the mobility and that's all about how learning was in preschool."
> *Interview, before treatment, started treatment at 6 years of age*

One parent/caregiver explained during the interviews how the child's kindergarten was too worried about the child getting hurt due to the large spleen, so they would not allow the child to partake in normal activities, or even to go to the playground. It was only once the child started treatment at 7 years old that he was allowed to play at school (due to the abdomen becoming normal size). Now, the child leads a normal life and receiving the infusions does not interfere with school more than ASMD did before treatment.

> *Before treatment:*
> "…he went to kindergarten. The school was nervous about him because they had never dealt with anything like that, and him having an enlarged spleen. So, he was restricted in both physical education class and even recess. The school wouldn't allow him to go on the playgrounds, we had to have him aid and he could only do certain things, so he wasn't getting that play and exercise that he needed so much at five years old when he was in kindergarten. […] They didn't want him playing. So, that went on. And that's about it until he started the study at seven years old."
> *After treatment:*
> "Other than on infusion days he'll go to school in the morning and then come out for the afternoon for the infusion. And he catches up on his work. So, he lives as normal of a life as someone could. He virtually has no real restrictions at all."
> *Interview, started treatment at 7 years of age*

Before treatment, 40% (4/10) of parents/caregivers were concerned about the time the child may need to take away from school due to symptoms (Figure 32), but these concerns became 'much better' after treatment for 3 out of these 4 parents/caregivers (Table 4).

> "She did have headaches. She did have other issues that probably took her away from her studies a little bit, but she's always been incredibly smart. I wouldn't say that she had significant cognitive... It would be a bit limited to a small amount, just due to the other things that were going on."
> *Interview, before treatment, started treatment at 7 years of age*

During the interviews, one parent/caregiver said it was difficult for their child to attend school due to being tired, but this completely changed after treatment:

> "Before the treatment, she was always very tired when she came home from school, and that is not the case anymore. In the mornings she had difficulties getting up, and she was still very tired, and it was a struggle to get her to school. If we walked to school, it was really a struggle, and that is not the case anymore. Now she's really an early bird, she's awake very early, and it's not a problem for her to handle these long schooldays anymore. […] she is really full of energy now. It's amazing. She's very active and she likes to do sports."
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

Thirty percent (3/10) of parents/caregivers were concerned for the time away from school due to medical appointments (Figure 32) and after treatment, the changes were varied, with one parent/caregiver's concerns being worse, one better and one the same (Table 4). The same pattern was reported for concerns regarding the child's reduced performance at school. The parent/caregiver that was concerned about their child not being able to attend school and graduate before treatment, continued to have the same concern after treatment (Figure 32; Table 4). Two children were too young to attend school at the time (other in Figure 32).

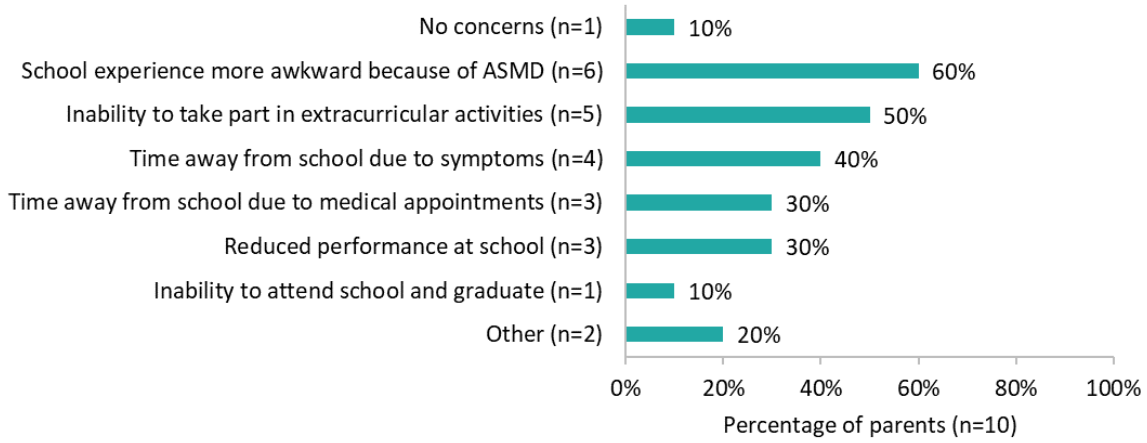


Figure 32. Concerns related to the effects of ASMD on the child's education before treatment with olipudase alfa (n=10).

Table 4. Change in concerns regarding education since staring treatment with olipudase alfa (n=10).

Change in concerns about the child's education	Much worse		Somewhat worse		About the same		Somewhat better		Much better	
	n	%	n	%	n	%	n	%	n	%
Time away from school due to symptoms (n=4)	—	—	—	—	1	25	—	—	3	75
Time away from school due to medical appointments (n=3)	—	—	1	33	1	33	—	—	1	33
Reduced performance at school (n=3)	—	—	1	33	1	33	—	—	1	33
Inability to attend school and graduate (n=1)	—	—	—	—	1	100	—	—	—	—
School experience more awkward because of ASMD (n=6)	—	—	—	—	—	—	2	33	4	67
Inability to take part in extracurricular activities (n=5)	—	—	—	—	1	20	1	20	3	60

Impact of treatment on education/employment of parent

None of the nine parents/caregivers that filled out the questionnaire were attending further education (e.g. college or university) alone, but one parent/caregiver was in full-time education while also working full-time. Two-thirds of the parent/caregivers (6/9) were in full-time employment, but none worked part-time, while two parent/caregivers were caring full-time for their child (Figure 33).

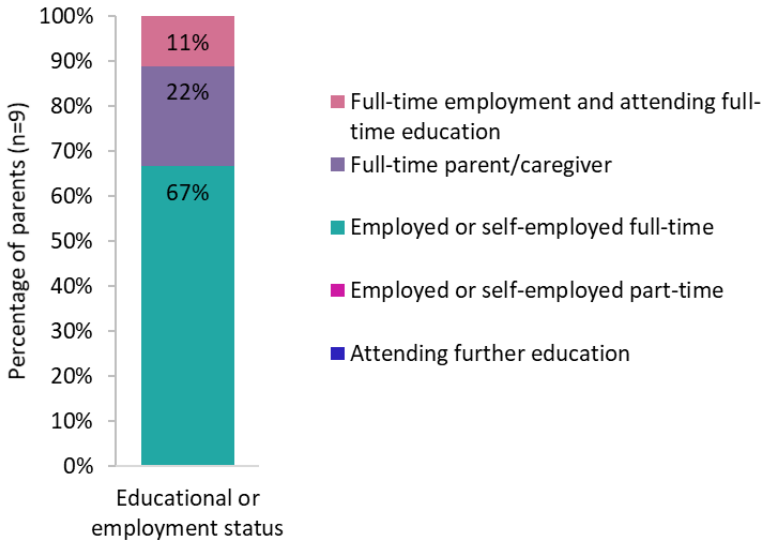


Figure 33. Parent educational or employment status (n=9).

Parents/caregivers were asked if there had been any changes in their ability to attend education or work since their child had started treatment with olipudase alfa. Note that the parent/caregiver with two children provided different responses for each child.

None of the parents/caregivers were able to increase hours or days of work, and the only parent/caregiver that was able to, also responded that they had to decrease hours or days due to medical appointments for symptoms of ASMD (Figure 34). None of the parents/caregivers were able to start or return to work or education but one had to leave work or education since the child had started treatment and had become a full-time caregiver. Although none of the

parents/caregivers had reduced their hours of work due to symptoms of ASMD per se, hours had to be reduced for two parents/caregivers due to medical appointments for ASMD symptoms. Three parents/caregivers had to decrease their hours of work due to treatment appointments (Figure 34).

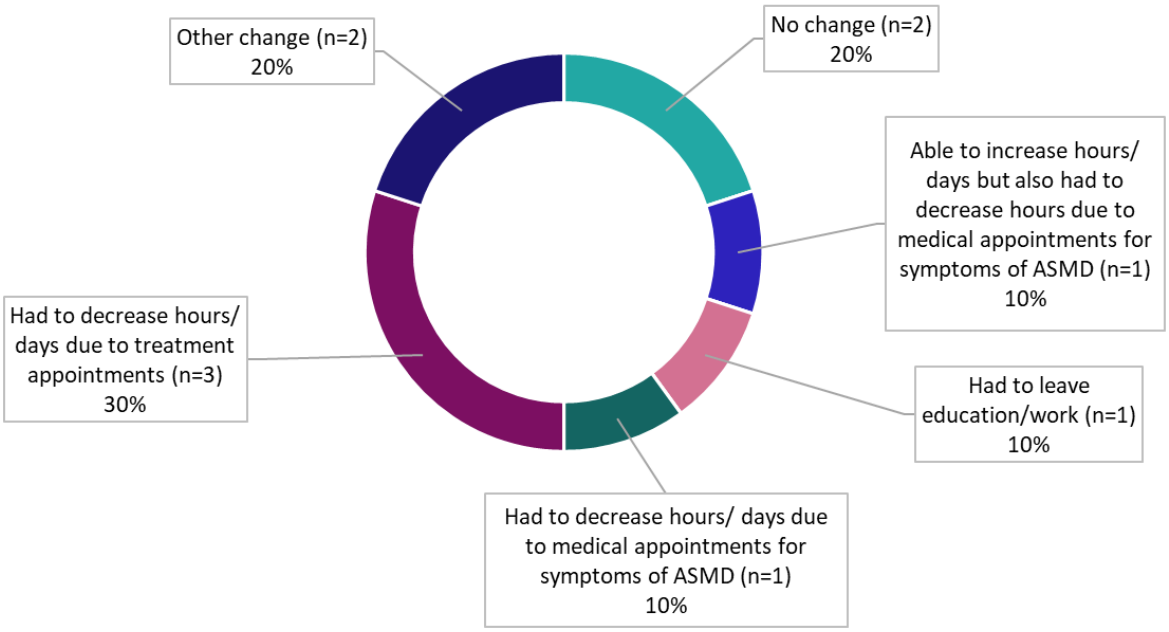


Figure 34. Change in the parent/caregiver ability to attend education/work since the child started treatment with olipudase alfa (n=10).

> "At the start of the trial had to miss 4 days of work every other week. Currently miss 1 day of work every other week and 3 days of work quarterly for monitoring/testing."
> *Survey, started treatment at 2 years of age, 6 years and 1 month on treatment*

> "The infusion days are intense and I need to be fully available for the medication application."
> *Survey, started treatment at 3 years of age, 5 years and 1 month on treatment*

Other responses included some parents/caregivers being able to make arrangements or change their work patterns to accommodate treatment appointments.

> "Some days per year, however we divide the appointments and get help from grand-parents so it does not have a significant impact."
> *Survey, started treatment at 4 years of age, 3 years and 6 months on treatment*

> "Mom began working every weekend and working twelve hour shifts in order to stay full time and travel to […] to participate in the trial."
> *Survey, started treatment at 1.5 years of age, 3 years and 10 months on treatment*

> "Requested flexibility from work to work remote. Left prior job for more flexibility."
> *Survey, started treatment at 7 years of age, 5 years and 9 months on treatment*

Impact of treatment on physical activities and related concerns

Survey results showed that 20% (2/10) of children could not participate in physical activities or sports before treatment with olipudase alfa, with one parent/caregiver explaining the child was physically impaired due to the size of their organs hence was unable to participate. However, 80% (8/10) of children were 'somewhat' able to participate (Figure 35).

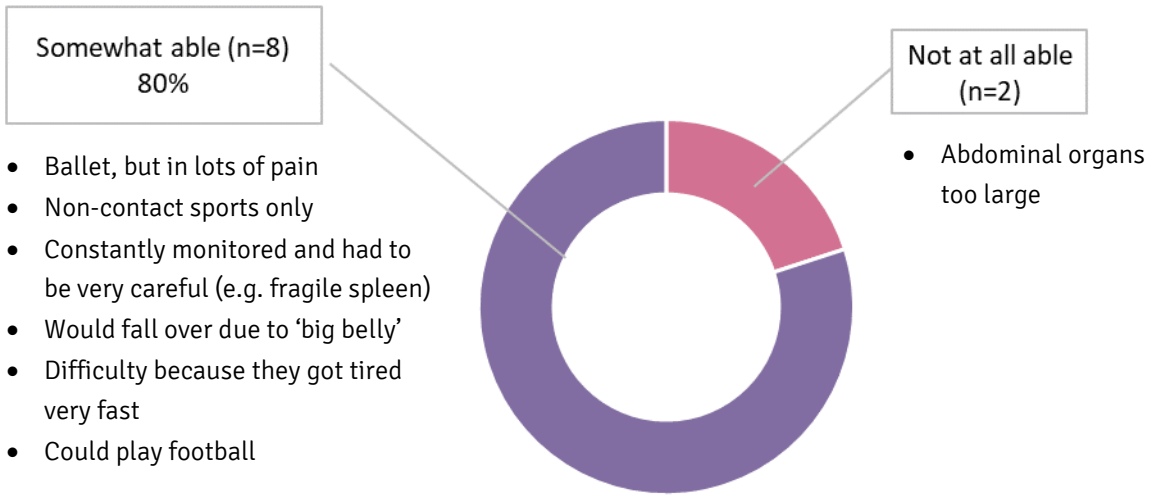


Figure 35. Child's ability to participate in physical activity or sports before treatment with olipudase alfa (n=10).

Parents/caregivers were asked in the survey if there had been any changes in their child's ability to participate in physical activity or sports since starting treatment with olipudase alfa. Eighty percent (8/10) of the children had increased their ability to participate in physical activities (Figure 36). Increased abilities included now being able to play football, finally joining competitive gymnastics, and in general, less restrictions to be able to join with sport activities due to an increase in energy and a decrease in the size of their abdominal area. One of the children who could not participate at all in sports before treatment, was still hindered by neurological symptoms from participating in mainstream sports but could now enjoy most physical activities due to an increase in stamina, strength and comfort.

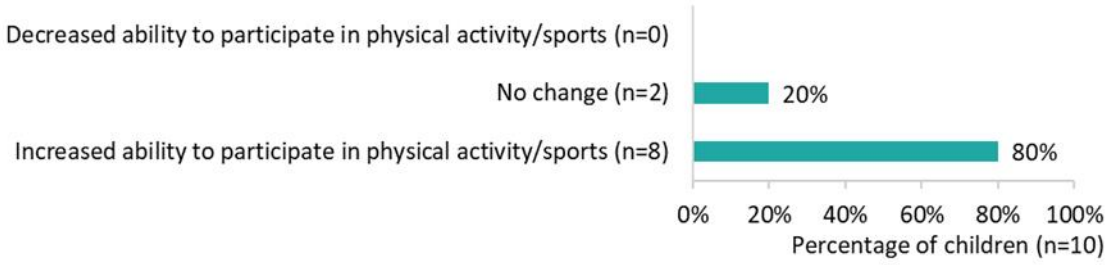


Figure 36. Change in the child's ability to participate in physical activity or sports since starting treatment with olipudase alfa (n=10).

Before treatment, all parents/caregivers (10/10) reported having concerns related to their child participating in physical activities or sports. Most parents/caregivers (90%; 9/10) were concerned about the harm physical activity or sport could cause to their child's enlarged organs (Figure 37) but all parents reported these concerns were 'much better' (8/9) or 'somewhat better' (1/9) after treatment (Table 5).

> *Before treatment:*
> "We did let her participate in everything she wanted to participate in, except for gymnastics, which we deemed to be a little bit too dangerous, especially if she landed on her stomach.[…] she couldn't do a cartwheel. Her body was so just not normal, her cartwheels, she would just plop to the ground because her stomach was sticking out. […] Not being able to do what she really wanted to do, which was gymnastics, I think, was really tough on her."
> *After treatment:*
> "so it must have been about six months after she started the treatment, we allowed her to do gymnastics. And she literally went from not being able to do a cartwheel to being a state champion. So, now she's a competitive gymnast. So, she is completely done a complete 180, 360, whatever you want to call it. Everything has completely changed. I never, ever worry anymore about her health."
> *Interview response, started treatment at 7 years of age*

> "He got the okay to start participating in contact sports a couple of years ago. Now he plays, he's on a travel soccer team where he plays year-round. […] No issues running, he plays midfield, and he's up and back all game long. So, running is not an issue. […] He actually does kickboxing […] The doctor gave him the okay to ride a bike, so he's been riding a bike for a couple of years.
> *Interview response, started treatment at 7 years of age, 4 years and 1 month on treatment*

Before treatment, 40% (4/10) of parents/caregivers were worried about their child's shortness of breath (Figure 37), but after treatment, these concerns became 'much better' for 100% (4/4) of the parents/caregivers (Table 5).

Four parents/caregivers reported having other concerns, including fear of the child dying while undertaking the physical activity or sport, a ruptured spleen, the implications for the child's future ability to take part in certain activities and the inability of the child to stand on their own. Half of these parents/caregivers (2/4) said their concerns were 'much better' after treatment. One parent/caregiver reported concerns for shortness of breath, harm to enlarged organs and bone fractures were 'much better' after treatment but concerns about their child not being able to stand were 'somewhat worse'.

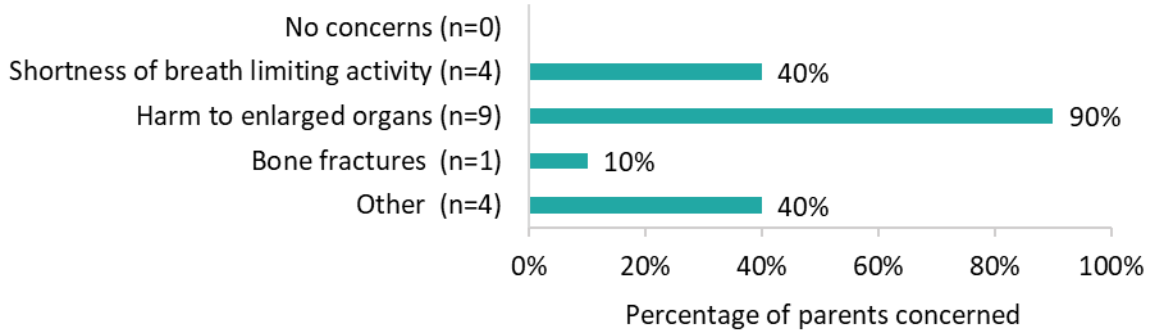


Figure 37. Concerns related to the child participating in physical activity or sports before treatment with olipudase alfa (n=10).

Table 5. Change in concerns related to the child participating in physical activity or sports after treatment

Change in concerns related to the child participating in physical activity or sports after treatment	Much worse		Somewhat worse		About the same		Somewhat better		Much better	
	n	%	n	%	n	%	n	%	n	%
Shortness of breath limiting activity (n=4)	—	—	—	—	—	—	—	—	4	100
Harm to enlarged organs (n=9)	—	—	—	—	—	—	1	11	8	89
Bone fractures (n=1)	—	—	—	—	—	—	—	—	1	100
Other (n=4)	—	—	1	25	—	—	1	25	2	50

Other changes

Parents/caregivers were asked if there were any other changes experienced by their child before and after treatment with olipudase alfa. Participants were asked about mental health (e.g. anxiety, stress, depression, feelings of isolation, grief, blame), family and social life (e.g. inability to go out, restricted in where going, family acceptance), relationships with partners/family/friends (e.g. relationship issues, separation, loss of contact with family/ friends, lack of understanding), independence (e.g. not able to go out or work due to caregiver role), or any other change they would like to report. Thirty percent (30%) of parents/caregivers reported their child experienced no other changes before treatment, and 20% (2/10) no other changes after treatment. One parent/caregiver noted under 'other', that their child was too young to experience these changes, but their health was rapidly declining before treatment. Another parent/caregiver noted that their child's mental health and confidence dramatically increased after treatment.

CHANGES IN MENTAL HEALTH

60% **Before treatment:**
6 out of 10 parents/caregivers reported changes in their child's mental health before treatment

Changes before treatment included:

- — Being bullied for being short
- — Being bullied for having a big belly
- — Poor self-image
- — Feelings of isolation
- — Anxiety
- — Depression
- — Feelings of guilt

60% **After treatment:**
6 out of 10 parents/caregivers reported changes in their child's mental health after treatment

Changes after treatment included:

- \+ Bullying is better
- \+ Better self-image and confidence
- \+ Parents feeling better knowing the child is physically more comfortable
- \+ No limitations
- ± Some have less feelings of isolation but others still have those feelings
- ± For some, there are less feelings of anxiety and depression, others are still suffering anxiety and depression
- — Having to miss school for treatment and having to explain why feels different
- — Anxiety about being sick and dying
- — Feelings of guilt

> "He's open, he feels like a normal kid, he pretty much has no restrictions at all. He lives a normal life. [after the treatment we could see] he was changing as a person. He was starting to get more confident and everything."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

Further insights from the interviews revealed that having a large abdomen had had a big impact on the self-image of some of the children before treatment started but after treatment the abdomen became normal size. Having a large abdomen also limited children's independence as they felt too uncomfortable to be active. One parent/caregiver said that if their child "hadn't gotten the treatment at this point, she would look like a completely different person, and probably have a different outlook on life".

> "He was just very limited, he couldn't do a lot by himself, he couldn't explore by himself." *Interview, before treatment, started treatment at 6 years of age*

> "I feel like with him being in the trial and his liver and spleen being normal sizes, when you help him walking around, he's happy because he knows he can do it."
> *Interview, after treatment, started treatment at 1.5 years of age, 3 years and 10 months on treatment*

> “The drug has drastically improved our son's life. He looks and acts like any other kid his age. He is much more confident now that his belly is small and he is similar in size to his peers. […] You would never know that he has ASMD.”
> *Survey, diagnosed at 3 years of age, started treatment at 7 years of age*

Parents/caregivers thought the pain in the abdomen impacted the wellbeing of the child.

> “Every day she told us that she was having pain in the belly, and of course, yes, she didn’t like it. So, from that point of view, it had an impact on her wellbeing, of course.”
> *Interview, diagnosed at 2 years of age, started treatment at 4 years of age*

Children knew their abdomen was different to other children and this largely impacted their mental health.

> “I remember that sometimes she cried, and when I tried to explain that her belly was somewhat different from the belly of other children, and that we had to be careful with it, sometimes she really started to cry and she was very sad. Sometimes she really got sad and she said, I don’t want to have another belly than other children.”
> *Interview, diagnosed at 2 years of age, started treatment at 4 years of age*

Childrens’ self-esteem improved once their abdomen shrank and their health improved, especially when praised by adults about how well they now looked. Changes in the abdomen happened within a few months after starting treatment and parents/caregivers agreed they seemed to happen very quickly.

> *Before treatment:*
> “And it was very obvious through her leotard that her stomach was somewhat extended for a certain reason. Kids would ask her every once in a while why is your stomach so big, blah, blah. So, it was noticeable, not to us, but just to other people, as well. […] I think she was just a little bit distracted, to a degree, and thinking about other issues within her body that were uncomfortable. […] I think it was more of a psychological impact, possibly, because she was so much smaller than everyone, and her stomach was bigger.”
> *After treatment:*
> “Kids no longer ask my daughter why her stomach is so large. Additionally, she is no longer in pain or having shortness of breath when she runs.”
> *Interview, started treatment at 7 years of age*

> “Also just a very positive outlook, he could tell when he saw people he hadn’t seen in a while, how much better he was doing, look how big you’ve gotten, look at your belly, look at everything. I think that was a reward for him and he felt better and he knew it was what he needed.” *Interview, started treatment at 6 years of age*

> “He started in January, by that summer, when it was time for swim season, to go in the pools, it was visible how much his belly had shrunk. So, physically that change happened quick. […] He started to feel better because he was aware of the size of his belly, he wasn’t at the point where kids were making fun of him, but he was aware of it. And since that decreased, he started feeling better, he was no longer the smallest kid in the class by far, that’s what he used to be.”
> *Interview, started treatment at 7 years of age*

Besides a large abdomen, parents/caregivers explained their child’s development, day-to-day activities and socialisation with other children were hindered by other ASMD symptoms that constantly made the child feel uncomfortable, such as the regular vomiting, the lack of sleep, tiredness or shortness of breath. Some parents/caregivers reflected during the interviews that although the child had been limited, they did not know otherwise before the treatment, so this was their norm.

> Lack of sleep to eat at night:
> “Uncomfortable all the time, but it was his normal so he never said. Just the lack of sleep I would say that probably affected how he felt all day long, the falls, the fear. Very limited, but also very happy, and he did well that it just became his norm for everything.” *Interview, before treatment, started treatment at 6 years of age*

> Vomiting:
> He is still a very happy boy, but no child wants to be throwing up five times a day. And he’d wake up first thing in the morning throwing up, and it was just uncomfortable for him to sit for really short periods of time. You could just tell it was uncomfortable in his belly. So, it affected really all areas of his development.
> *Interview, before treatment, started treatment at 2 years of age*

> Shortness of breath and fatigue:
> “I think it was limited, in terms she would get fatigued pretty easily and had to sit out or rest for a little bit and couldn't keep up with everyone else. She would, obviously, always want to go to the park, always was invited to birthday parties, and would have a blast. But you could also tell that if the kids were playing tag and running around, she would have to take random breaks and catch her breath.”
> *Interview, before treatment, started treatment at 7 years of age*

Many parents/caregivers said in the interviews their child had no energy limits after receiving treatment, and nobody could tell they had ASMD.

> “No limitations, there’s nothing that this kid can’t do, and if I tried to limit him, I don’t think I’d be successful. He’s one of those, he’s always going to push the limits, he’s that type of kid. You would never suspect anything with him by any means. Looking at his energy and everything that he’s able to do.”
> *Interview, started treatment at 2 years of age, 6 years and 1 month on treatment*

Before treatment, being physically impaired implied fewer social interactions. The child could sometimes not understand why they were excluded from certain activities or not allowed to do certain things, and parents/caregivers were aware this created frustration in their child. These restrictions were no longer necessary once treatment started to improve their child's life.

> "It was super hard, I think the mental part of frustration not being able to walk, not do the things that other kids were doing her age. She wasn't allowed to go do, like go to playgrounds or go into a toddler activity because she wasn't able to do those things."
> *Interview, before treatment, started treatment at 3 years of age*

> *Before treatment:*
> "…when she was at a party, and there was a trampoline or something like that. She could not play on it, and for her, that was really a problem. She really became mad at that. All this time she was very angry because she really loved it, but it was very specifically told [by the doctors] that she could not do that."
> *After treatment:*
> "That is not a problem anymore, now she can do everything, so that's very good. And she does athletics, and that's it. And she uses some things to do some sports here in the basement"
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

There was also isolation within the home, as the fragility of the child before treatment meant some parents/caregivers were adapting their home so the child would not get hurt.

> "So it was just very much isolation and even in her home creating safety measures with toys, furniture, everything had a bumper on it."
> *Interview, before treatment, started treatment at 3 years of age*

One parent/caregiver explained that the advantage of getting the diagnosis early, when the child was very young, followed by early treatment was that their child could not remember her physical symptoms and the enlarged abdomen.

> "And that's one of those things where we're lucky, she doesn't remember. Like we remember, her sister remembers a little bit, but one thing about getting a diagnosis early on she'll only be able to see through pictures. She won't physically remember that she didn't get to do those things."
> *Interview, diagnosed at 2 years of age, started treatment at 3 years of age*

During the interviews, some parents/caregivers suggested that being in the trial had allowed their children to have a sense of purpose (they were doing it for their health and for the health of other children) and found they were able to have a say in their own choices.

> "I think he was very aware that what he was doing was necessary for his health, and he knew he was helping a lot of other kids too, so I think that there was a sense of purpose in him for everything that he did."
> *Interview, started treatment at 6 years of age, 5 years and 8 months on treatment*

> "So I do feel like being in the trial, I feel like he's discovered he is his own little person. And that's made him happy because he's able to learn things that he can do, how to get out of doing things that he doesn't want to do."
> *Interview, started treatment at 1.5 years of age, 3 years and 10 months on treatment*

> "He doesn't question why, he's just all right, this is what I need to do. And I get this medicine every couple weeks and that's it. Which is a good mentality because he knows that's what he needs in order to be living his normal life that he's able to live. So, that's great for him."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

However, for one child the infusions were very traumatic at the beginning and created anxiety and upset for both the child and the parents/caregivers, but the child has now become accustomed and sees the infusions as part of his life's routine.

CHANGES IN FAMILY OR SOCIAL LIFE

60% **Before treatment:**
6 out of 10 parents/caregivers reported changes in their child's family or social life before treatment

50% **After treatment:**
5 out of 10 parents/caregivers reported changes in their child's family or social life after treatment

Changes before treatment included:

- – Child not being able to play/ride bike with other children in the family
- – Parents isolating themselves because their child was constantly vomiting
- – Feeling restricted as to where to go
- – Becoming overprotective and not allowing others to take care of the child
- – Child not being allowed by their school to play with others or go to the playground

Changes after treatment included:

- \+ Less restrictions to play with other children and to go to places
- \+ Less travel restriction (e.g. no vomiting)
- – Missing many activities (e.g. holidays, school activities) because of the strict treatment schedule (e.g. infusion fell of the child's birthday)
- – Feeling restricted as to where to go

The improvement in symptoms of ASMD has meant children can travel and socialise in a way they were not able to do before treatment.

> "We have been able to go more places and enjoy more experiences with our kids since he began treatment. We no longer have to lug around feeding pumps and oxygen and never have to worry about him vomiting anymore."
> *Survey, diagnosis at 1 years of age, treatment started at 2 years of age*

It was a recurring theme during interviews that, before treatment, children only socialised and played with adults and older children because they were wary of being hurt by children their own age and being unable to partake in the same activities as they required energy they did not have. After treatment this changed, and children were now socialising with children their own age.

> *Before treatment:*
> "He was definitely more comfortable with adults and older kids, I think he felt like they were aware of his needs as far as like balance, and just he got along better with them. Peers his own age, he was a little bit suspicious, especially two and three year olds, who weren't as body aware. He was always nervous they were either going to hit him, bump him, knock him down, because it didn't take much to get him off."
> *After treatment:*
> "…the initial benefits [of treatment], just being able to play with his peers and hang in there, he definitely loves his same age school children now, and playing and keeping up with them, he has a great time."
> *Interview, started treatment at 6 years of age*

Parents/caregivers explained that thanks to the treatment their children are now able to have many friends and do what their friends do.

> "People just come to her. She attracts friends. So many friends, more friends than I ever had my entire life. People, just, are attracted to her, and she's the centre of attention now. That definitely would not have happened if she hadn't received the treatment." *Interview, started treatment at 7 years of age*

> "He was happier, he was able to do things that other kids were doing. He has a friend in the neighbourhood that would come over and always ask do you want to go on a bike ride? So, he was able to do those things which he wouldn't have been able to."
> *Interview, started treatment at 7 years of age*

One of the parents/caregivers explained that their child was too young, and the situation was not that bad, as to have affected their child social's life.

CHANGES IN RELATIONSHIPS WITH PARTNERS, FAMILY OR FRIENDS

30% **Before treatment:**
3 out of 10 parents/caregivers reported changes in their child's social relationships before treatment

Changes before treatment included:

- Strained relationships with friends due to being unable to socialise

10% **After treatment:**
1 out of 10 parents/caregivers reported changes in their child's social relationships after treatment

Changes after treatment included:

- Able to go to more places and enjoy experiences as a family

> “We’re able to take him more places now, too, which is good for his mental health and development, just to get out of our house and see and experience other things.”
> *Interview, after treatment, 1 year and 3 months on treatment*

CHANGES IN INDEPENDENCE

10% **Before treatment:**
1 out of 10 parents/caregivers reported changes in their child’s independence before treatment

Changes before treatment included:

- Parents/caregivers not being able to leave their child with anybody else due to their medical needs

10% **After treatment:**
1 out of 10 parents/caregivers reported changes in their child’s independence after treatment

Changes after treatment included:

- Able to go and travel to more places

> “It really impacted us to really stay home and isolate because we were fearful of her not being able to do the things and then also with the spleen enlargement and liver involvement, she couldn’t get hit in the stomach. So we would be very isolated and just at home and not being able to do typical children things at toddler age.”
> *Interview, before treatment, started treatment at 3 years of age*

Health, emotional and social impacts of ASMD on parents

Note: The parent/caregiver with two children gave different responses for each of the children hence total population of parents/caregivers has been kept at ten for this question.

Parents/caregivers were asked about the impacts of ASMD on their physical health, their emotional health and on their social life before treatment with olipudase alfa. In addition, they were asked if these impacts had changed, or not, for the worse or for the better after treatment. Parents/caregivers could chose multiple responses for the impacts of ASMD on their physical health (e.g. neck pain, bad back), mental health (e.g. anxiety, stress, depression, feelings of isolation, grief, blame), family/social life (e.g. inability to go out, restricted in where going, family acceptance), relationships with partner/family/friends (e.g. relationship issues, separation, loss of contact with family/friends, lack of understanding) and independence (e.g. not able to go out or work due to caregiver role). Parents/caregivers could also respond that ASMD had no impact or to suggest other impacts not on the list.

Health, emotional and social impacts of ASMD on parents before treatment with olipudase alfa

The majority of parents/caregivers (90%; 9/10) responded that ASMD had an impact on their mental health, with stress, anxiety and depression being reported by many parents/caregivers (Figure 38). Parents/caregivers also reported impacts on their family and social life (3/10), on their relationships with partner, family and friends (3/10) and on their physical health (2/10).

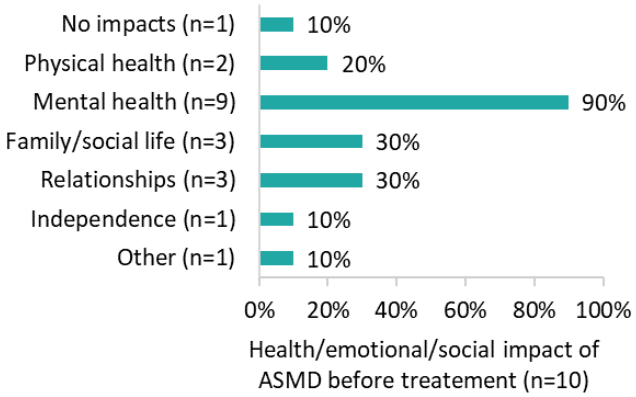


Figure 38. Impacts of ASMD on parents'/caregivers' health, emotional health and social life before treatment with olipudase

In the survey and through the interviews, parents/caregivers were able to explain the impacts of ASMD on their physical health, emotional health and social life, **before** treatment with olipudase alfa. The following section summarises the main themes from both the survey and the interviews.

PHYSICAL HEALTH BEFORE TREATMENT

Pain on back and neck from lifting the child and from stress

Parents/caregivers reported in the survey severe back and neck pain from having to lift their child and from stress and fatigue.

Physical exhaustion

Due to lifting the child and lack of sleep.

MENTAL HEALTH BEFORE TREATMENT

Anxiety, stress and depression

Parents/caregivers reported feelings of anxiety, stress and depression with one parent/caregiver stating they had extreme mental health issues once the child was diagnosed. These feelings were linked to keeping the child safe, the child's health, feeling isolated, feeling guilty, worried about the child's quality of life and what the child is missing out and lack of sleep and constant fatigue from the child waking up at night. Sadness was also an issue for parents/caregivers who saw their child not being able to do what they wanted to do.

The disease overtakes the parents'/caregivers' lives:

> "I think you think of them every day and you think of them every night. You wake up thinking about it. That takes over your life, how am I going to normalise my child's life? How is she going to be able to live normal and not be constantly sick and in the hospital?"
> *Interview, before treatment, started treatment at 7 years of age*

> "Extreme anxiety, extreme depression on my end, a lot of frustration. My husband and I, you go from living this typical life essentially to being thrown with a potentially life-threatening diagnosis of your child."
> *Interview, before treatment, started treatment at 3 years of age*

> "In terms of stress. There were times when my wife would go in her bedroom and cry."
> *Interview, started treatment at 7 years of age*

Anxiety and depression were also a consequence of not being able to go to places as a family.

> "He would throw up so frequently, we would be scared to go anywhere because we're like, he's probably going to puke. And it is just too much to take him anywhere, really. So, not being able to just pick up and go out with your kids alone is a struggle, and definitely went through some bouts of depression and just anxiety […] which has gotten immensely better now [after treatment] but it affects all areas of our lives."
> *Interview, before treatment, started treatment at 2 years of age*

Constant worry about safety

Parents/caregivers were constantly concerned about their child's safety, especially when the child was not with them.

> "We did become extra cautious because we now knew, with that enlarged spleen, if something was to happen, blunt force trauma of any kind, that could be detrimental.[…] So we were very… And so was the rest of the family. We all were on heightened alert, just to make sure he was being safe."
> *Interview, before treatment, started treatment at 1.5 years of age*

> "There was always a concern of who was watching her and who was doing what for her, and they had to really know."
> *Interview, before treatment, started treatment at 7 years of age*

> "I used to be laid back and then that happened and it turned us both neurotic about a lot of things. So, that was some challenging times through a lot of different aspects. […] It's with little things, I like to hike, we would go for walks and one time he was just being a kid and he'd stepped on top of a rock and fell. And I was like if he fell and his stomach landed on a rock sticking up out of the ground. It created a world of not being able to enjoy the things, you have a different outlook on life and what could happen? Everything could be a potential disaster if something happened."
> *Interview, before treatment, started treatment at 7 years of age*

Difficulty of accepting the diagnosis

Some parents/caregivers found coming to terms with the diagnosis very challenging

> "It was a lot of tough times accepting what was happening at that point when he was first diagnosed. and not knowing what the future would hold, because we had no ideas of a trial at that point. We didn't know anything. So, that was a difficult time. And when [name] was diagnosed, my wife was pregnant with our other child. It turned our world as parents upside-down. It took time to accept and figure out what to do, how we could give them their best life without endangering it. And then we would have these discussions and we would both wake up at different hours of the night thinking about it."
> *Interview, diagnosed at 3 years of age*

Fear of losing their child

A recurring theme was being under extreme stress not knowing how the disease was going to progress and waiting for the child to die knowing that this was the outcome if the disease was left untreated.

Emotional exhaustion

Emotional exhaustion was a consequence of constantly waiting for ASMD to progress and dealing with everyday symptoms, while some families were also trying to keep their jobs and deal with siblings, so they did not focus on their own wellbeing.

> “We already thought that he was on borrowed time, but I think there’s emotional exhaustion that you don’t even notice, you’re just kind of waiting for the ball to drop sort of, like the whole time you’re just waiting for him to lose an ability. […] you’re always looking for the regression.” *Interview, before treatment, started treatment at 6 years of age*

> I can’t even tell you how mentally exhausting it is to clean up vomit so many times a day. It just wears on you, not even physically, but emotionally it’s really hard to just watch your child constantly throwing up, and just looking like they feel awful.”
> *Interview, before treatment, started treatment at 2 years of age*

> “We counselled ourselves, looking back on it, I wish we did [attend support groups or counselling]. But we were grinding, we were trying to maintain our jobs and we were trying to raise our other kid. And we didn’t cut out time for ourselves. But luckily, we were able to get through that. And my wife and I grew stronger as a team in that sense. I’m fortunate of that because it very easily could have gone another direction. We were so caught up in the grind of life and trying to do everything for our kids that we did not focus on ourselves.”
> *Interview, before treatment, started treatment at 2 years of age*

Guilt of passing the genes on to their children, including siblings

Some parents/caregivers felt guilty because they had passed on the genes to their children.

> “It was dark times. We questioned and felt a lot of guilt and questioned did we do the right thing looking to have kids? Should we have done more genetic testing? Were we selfish to think that we thought we didn’t have these mutated genes in our cells? There was a lot of stress for us as parents just knowing that we brought kids into this world who were going to have an uphill battle.”
> *Interview, before treatment, started treatment at 2 years of age*

One family explained the distress of having their child diagnosed with ASMD while being pregnant and feeling guilty knowing the child could also inherit the disease (one of the two siblings with ASMD).

> “And when [name] was diagnosed, my wife was pregnant with our other child. And at the time of diagnosis, they told us that because we know [name] has ASMD, the Niemann-Pick B, that there will be a one in four chance that the other child will as well. So, it was a whirlwind of information. We were putting a lot of blame on ourselves for did we go about this right? There was a lot. Especially knowing at that point [name] was on the way.”
> *Interview, before treatment, diagnosed at 3 years of age*

Dealing with siblings after diagnosis

Some parents/caregivers had other children to deal with and to try to give them a normal life.

> “Really trying to learn how to cope and still be a parent to another child that doesn’t’ have a medical diagnosis is a whole another chapter in our lives that we had to learn how to do.”
> *Interview, before treatment, 5-year-old sibling*

Hopeful

Parents/caregivers felt hopeful to find out there was a paediatric trial starting for ASMD and were distressed thinking their child may not be able to join.

> "It wasn't long after [name] was diagnosed that we found out that there will, in fact, be a paediatric trial. So, that was another reason why we were more hopeful. And then when we found out that [name] wasn't going to be chosen for the study in that age group, that made us upset. But we were still hopeful. And when eventually when we got [name] into the trial, it was emotions up and down."
> *Interview, before treatment, started treatment at 2 years of age*

Financial

Although most parents did not have any financial worries, one mother explained in the interviews that they had to give up their full-time job and become a stay-at-home mum after their child's diagnosis to be able to care for the child, explaining that this put some financial strains and pressure on the husband.

FAMILY/SOCIAL LIFE BEFORE TREATMENT

Isolation: family support and social or family life

Parents/caregivers said their families were understanding but had no social life as they could not to go to places and dealing with their child took all their time.

> "Even leaving the house to go anywhere was just too much to even handle, because we'd have to bring along pumps and oxygen. And there's just so much stuff that we have to cart along with us, that we're like, it's not even worth it."
> *Interview, before treatment, started treatment at 2 years of age*

A couple of families said they were very lucky at being able to leave their child with their family and being able to have this type of childcare.

Isolation: kept diagnosis to themselves

One family was so overwhelmed by the diagnosis that were not able to share it with anybody, as they thought they did not want to have to explain that the future of their child was unknown.

> "We actually chose to keep our diagnosis to ourselves in the beginning because as you know Niemann-Pick disease has three type of variations and every patient is completely different. So with that we were already inundated with questions with unknown answers, we couldn't even fathom trying to explain it to other people. […]I didn't share it with anybody, I fell off the face of the earth. People probably just thought oh, she doesn't want to talk to me anymore.[…] So it was just easier to be left alone and not have to explain because I wasn't confident enough yet as to what was going to happen to my daughter."
> *Interview, before treatment, started treatment at 3 years of age*

Lack of independence as parents/caregivers were concerned about others minding their child

The amount of care required before treatment (e.g. oxygen, feeding pump), meant the child could not be left with anybody else but the parents/caregivers. Some parents/caregivers were so concerned that would not even allow close members of the family take care of their child.

> "At that point we really couldn't leave [Name] with anyone but one of us. Both of our parents live close by, and they're always willing and wanting to help, but there's only so much they can do and so much that they're comfortable with doing, just because of his health needs. Especially back then, we would always be scared if he was going to throw up and we're not there, and what if he choked on it?"
> *Interview, before treatment, started treatment at 2 years of age*

> "We didn't trust anybody to babysit her, we didn't want anybody handling her even. She felt like almost like a fragile sheet of glass after she was diagnosed."
> *Interview, before treatment, started treatment at 3 years of age*

Continued with normal life

One of the families continued with normal life and travelled for holidays before treatment, as although they were aware their child had issues, they wanted to continue doing things as a family.

> "We weren't restricted in any way. We knew that there was something there, but it didn't stop us from doing things that I think we'd want to do as a family like taking vacations and stuff." *Interview, before treatment, started treatment at 7 years of age*

FAMILY RELATIONSHIPS BEFORE TREATMENT

Strained marriage due to pressures caring for the child

One parent/caregiver said in the survey that before treatment, ASMD had caused stress in their relationship with their spouse. In the survey, one parent/caregiver said the constant care their child required also affected their relationship with their husband.

> "It is heart-breaking to watch your child go through everything that he's been going through. Really, it puts a lot of stress on us as parents, but also me and my husband's relationship, and it affects all aspects of our lives. Before his infusions and stuff, he required so much care." *Interview, before treatment, started treatment at 2 years of age*

Strained marriage because of being carriers

One parent/caregiver said in the survey their marriage became strained after they found out they were carriers of ASMD.

Strained relationship with extended family due to being carriers

One family explained the grandparents of the children refused to believe they were carriers.

> "I would say that certain people didn't want to believe that they were a carrier of her disease, especially my wife's father refuses, I think, to this day, to say that she is a carrier. And then, on my side, my mother […] obviously, it was confirmed that she was a carrier. I think just certain relationships. People wanting to not believe it or think it's a little farfetched, just given the odds of it all taking place in that she had an issue or didn't have an issue. I think some people didn't really think she [the child] had an issue." *Interview, diagnosed at 7 years of age*

Extended family: worry and understanding

Parents/caregivers explained during interviews that the extended family can also suffer emotionally as they worry about the child with ASMD.

> "So you have to really stop and realise that you're not the only one going through this. Everyone else around you is. [Name] is going through it. It's just been very eye-opening." *Interview, before treatment, started treatment at 1.5 years of age*

> "If I'm talking about my parents, the parents of my wife, and my brothers and sisters, yes, of course they don't feel it to the same extent as we do, but it was very similar. They were all very worried about how things would turn out in the end." *Interview, before treatment, started treatment at 4 years of age*

Parents/caregivers also said that it was emotionally difficult to explain ASMD to their families, as they did not fully understand the implications.

> "Even just trying to explain it to other people, family, it took them some time to get it. I can't tell you how many times I would say there's build-up in his spleen, and oh, well can't they just remove it? And it's like no, because then all that build-up is going to go into other organs. It was a lot trying to come out and tell family and friends." *Interview, diagnosed at 3 years of age*

EMOTIONAL IMPACT OF ASMD ON SIBLINGS

Parents/caregivers had concerns about the emotional wellbeing of the child's sibling, especially if they were too young to understand what was happening.

Siblings were limited in family activities

Siblings were aware that their family could not do certain things because their brother or sister was not able to.

> "…they understood we were limited, couldn't do this because of [Name], couldn't do that or some other things." *Interview, before treatment*.

Sports activities were more difficult

The logistics of undertaking extra-curricular activities were more difficult than for normal families.

> "Our older kids started doing sports, so we just went along with him. And it made it a little bit more difficult with him, just having to haul him around."
> *Interview, before treatment.*

Child with ASMD took most of the parents' /caregivers' time

Although some parents/caregivers said they managed to treat their other children normally, most said they could not give them as much attention as the child with ASMD took most of their time.

> "All of our attention went immediately to this diagnosis... Family was flying in to help us figure it out, there's doctors' appointments, why would mom just start crying at the top of. Something would happen and it would just trigger fear and tears and anger erupts at that different times. So it completely changed our household environment and tone that we weren't… A lot of attention went onto all the phone calls. And then her looking at her, she was five at the time, she already had to deal with having a sibling but now we're having a sibling with all of the energy about her."
> *Interview, before treatment, 5-year-old sibling at the time of diagnosis*

Siblings were left with other family members

Children were aware their sibling was unwell and had to get used to be left with other people when their sibling was taken to hospital or to doctor's appointments for their ASMD.

> "I mean they were aware of that their little brother was sick. They had to be prepared for those times that Mum, Dad had to go to the hospital again with your brother, you're going to be with your grandparents for a few days."
> *Interview, before treatment.*

Older siblings tried to help with what they were able to do

> "Our older son took it in stride and he was a trooper through it. He understood it, but he tried to focus on what he was able to do."
> *Interview, before treatment ASMD sibling diagnosed at 3 years of age.*

Health, emotional and social impacts of ASMD on parents that have worsened since starting treatment with olipudase alfa

Sixty percent of parents/ caregivers (6/10) responded that their health, emotional and social impacts of ASMD had not worsened since their child started treatment (Figure 39). Some parents/caregivers reported that their physical health (3/10) had worsened since treatment, but reasons had changed in relation to the impacts before treatment. For example, while before treatment the main physical impacts were neck and back pain due to lifting the child, after treatment, bad eating and exercise habits due to the demands of the clinical trial were mentioned. Other impacts that have worsened after starting treatment included mental health (3/10), independence (2/10) and relationships (1/10) (Figure 39).

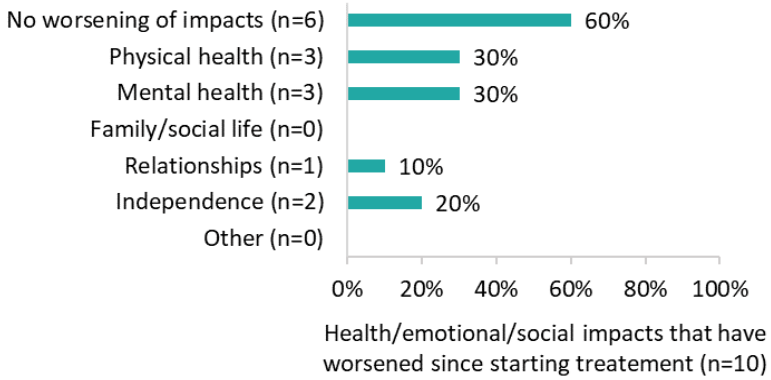


Figure 39. Impacts of ASMD on parents' health, emotional health and social life that worsened after treatment with olipudase alfa (n=10).

In the survey, parents/caregivers briefly explained why some health, emotional health and social life impacts had **worsened after** their child started treatment with olipudase alfa:

PHYSICAL HEALTH

Poor eating and exercise habits

Parents/caregivers reported developing poor eating and exercise habits due to the demands of travelling and hospital stays during the clinical trial.

Back ache

Pain in the back as the child is getting bigger due to the treatment and age and is difficult to lift. This parent/caregiver observed that although their back hurt, that the child was getting bigger was a good sign on their child's health. This same parent/caregiver explained during the interviews that although the child is heavier, going to places has been easier since the treatment as they do not need to carry bottles of supplementary feed anymore and the child no longer vomits.

MENTAL HEALTH

Anxiety and stress

Stress and anxiety were due to the demands of the trial and having to take time off work and having to spend time away from home.

> "The hardest part of everything is the strict rules of the trial. The trial itself was the harder part than the drug itself. That is what caused the majority of the stress, getting the MRIs, getting the ultrasounds. And even something as little as them being done with their infusion and then having to wait an hour to get their vitals done, that hour time frame, that's always been the hardest thing out there. Because the kids are done, they want to be up and go round. It's just that extra hour after a four-and-a-half-hour infusion just adds to the point."
> *Interview, siblings, started treatment at 2 and 7 years old.*

One child had a difficult time at the start of the trial in getting used to the needles and infusions, and it was a very stressful time on the parents who questioned their decision to put him through the trial.

> "He was so young, he couldn't comprehend what was going on, he had no idea. It just caused a lot of stress, anxiety, and screaming and pain. And a lot for him, as well as us. Us questioning our decision, should we really be doing this? Putting him through this? It was torture for us to put him through that."
> *Interview, started treatment at 2 years old.*

INDEPENDENCE

Impact on work

Some parents/caregivers felt they had lost independence by having to take significant time off work due to the demands of the clinical trial. Another family explained how the husband was able to keep his job, but jobs done as extra-income had to stop so the wife could work and they could both be available to meet the demands of the trial.

RELATIONSHIPS

Reliance on family members

Parents/caregivers now had to rely on family members to help when having to go for treatment.

Deciding not to have more children

One parent/caregiver explained how before treatment, they were unsure about having more children due to the complications involved in undertaking in vitro fertilisation and genetic testing but after staring in the trial, they decided not to expand their family and concentrate on the needs of their child, which involved lots of appointments and travel.

> "There was a time to where we thought about having more children. But it was advised for us to do… Which we didn't have to do in vitro or anything with [Name]. But it was recommended that if we wanted to have more children, to do genetic testing, and in vitro with genetic testing in that way, because there's a 25% chance our next child would have ASMD and it affects them all differently. So we wanted to get [Name] to a point where he was okay, and then we would revisit. But with us being in the trial now for four years, we're back to travelling every two weeks, I think we've just decided [Name] is going to be our one and only. And we just want him to be okay. We want him to be able to have everything he needs, have our full attention, because he does have special needs. So that's probably the biggest thing that affected our family, which it's not a bad thing that we only have one child. I know that sounds… When someone says we only have one, sometimes you feel like you're not grateful for just having one, which we're extremely grateful. But that's probably been the biggest thing, is that we decided not to expand our family."
> *Interview, started treatment at 1.5 years of age*

Health, emotional and social impacts of ASMD on parents that have not changed since starting treatment with olipudase alfa

Most parents/caregivers (80%, 8/10) responded that the impacts on their health, emotional and social life had changed since starting treatment (Figure 40). One of the parents/caregivers who had issues with back ache before treatment as a consequence of having to lift their child, continued to have the same physical health issues after treatment as the child still had to be lifted.

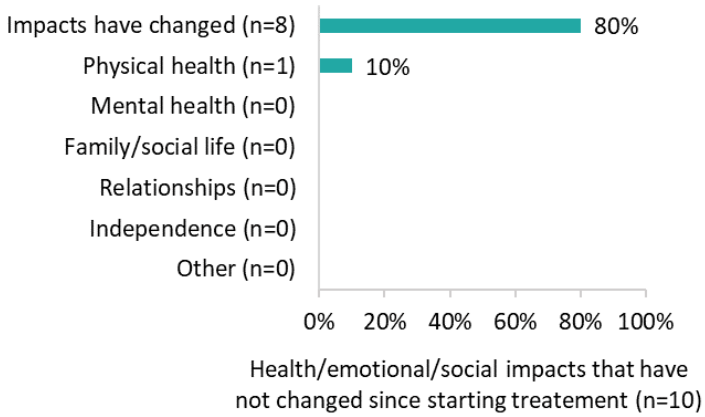


Figure 40. Impacts of ASMD on parents'/caregivers' health, emotional health and social life that had not changed after treatment with olipudase alfa (n=10).

For example, one family explained that at the start of the trial they had to take one hour flight for almost two years for their child to receive the infusions every two weeks, but that this was not an issue as they wanted their child to receive their treatment. Although it seems some families had to travel six or more hours, this never came up as an issue in any of the interviews.

Health, emotional and social impacts of ASMD on parents that have improved since starting treatment with olipudase alfa

Most parents/caregivers (80%, 8/10) responded that their mental health had improved since their child started treatment and 40% (4/10) said their family/social life had improved (Figure 41).

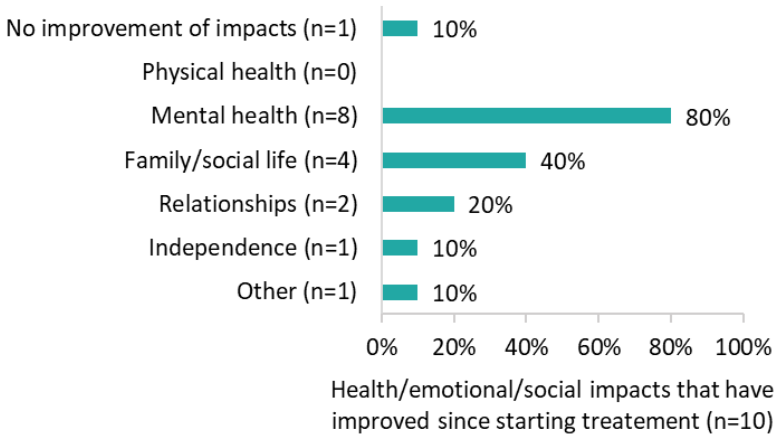


Figure 41. Impacts of ASMD on parents'/caregiver's health, emotional health and social life that have improved since treatment with olipudase alfa (n=10).

In the survey and the interviews, parents/caregivers explained how their health, emotional health and social life impacts had **improved after** their child started treatment with olipudase alfa:

MENTAL HEALTH AFTER TREATMENT

Less anxiety, depression, stress and concerns about the child's health

Parents/caregivers reported their stress and anxiety about their child's health had lessen or even disappeared after treatment.

> "The constant worrying that was taking place before she got the treatment, I don't worry anymore. She goes to school and I'm not worried that I'm going to get a phone call that she got hit in the stomach or she's rushed to the hospital, which was a constant concern at the back of my mind. I don't have those concerns anymore."
> *Interview, started treatment at 7 years of age, 5 years and 9 months on treatment*

> "It's more so thinking in the future and anticipating what could happen. But when you put it up against where we were four, five years ago, it's improved drastically, the mental state of both my wife and I."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

> "And we see her every day being very happy and joyful, and we see a healthy girl now, although we know that she has this illness. But we cannot notice it anymore, so it doesn't give us every day this stress and this angst, anxiety anymore. So, yes, it improved. It improved a lot."
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

Parents/caregivers that had felt depressed before treatment, were now hopeful for the future and wanted to tell other people that the treatment works.

> "We kind of breathed again. Before you just felt like you were no sleep, so fearful to look forward to the future. Now we just, it's hard to describe without getting emotional. Everything has just changed. It's completely changed. We're able to breathe again, we're able to have hope again, we love sharing about it.[…] Our anxiety level has reduce tremendously, our depression has lifted."
> *Interview, started treatment at 3 years of age, 4 years and 11 months on treatment*

Relief that a treatment is available and that it can reverse symptoms

Parents/caregivers were relieved that a treatment is available and that their children can get access to it. This changed their emotional health for the better.

> "After [name] started treatment with olipudase alfa my stress level went way down. I no longer felt like he was running out of time, and it was amazing to watch him grow, eat, and gain strength." *Survey, started treatment at 6 years of age, 5 years and 8 months on treatment*

> "From everything that we were being told was things get progressively worse over time. The sooner you get a treatment, the better. Because once you hit adulthood, you may have certain impacts to your life that you can't reverse. The damage may have already been done. So, I think there was always that's stress that, oh, my God, is she ever going to get this treatment? What if she doesn't get this treatment, what's her life going to look like? And what are the challenges that she's going to have? Is she going to be able to have kids, and so forth? And I think, after the treatment, all that stress all those concerns have definitely alleviated."
> *Interview, started treatment at 7 years of age, 5 years and 9 months on treatment*

> "…relief we[…]… Are taking the disease off of his body, like it's just we're reversing things instead of watching him slowly deteriorate and get worse, we were watching the effects of the drug, which was just great."
> *Interview, started treatment at 6 years of age, 5 years and 8 months on treatment*

> "And then, once we knew it was ASMD, we were hopeful because we knew there was a clinical trial on adults ongoing."
> *Interview, diagnosed at 2 years of age, started treatment at 4 years of age*

Get on with life

Although after starting the trial, one parent/caregiver explained their lives revolved around the uncertainty of the future, they were able to accept their child's disease and treatment and continue to make the most out of their lives.

> "When we began this trial, I feel like our life stopped. It just stopped because we didn't know what was going to happen. And then one day, I was getting ready and I realised, our life was not going to revolve around this diagnosis. It's going to be a part of our life. Because the other families were going on vacations, building homes, changing jobs, having more children. And that's when I was like, they're not letting this run their life. It's a part of who they are."
> *Interview, started treatment at 1.5 years of age, 3 years and 10 months on treatment*

More enjoyment out of life due to improvement in symptoms

Once the parents'/caregivers' worries decreased after treatment, they were able to sleep better and improve their mental health with one of the parents/caregivers saying "I think sleep was the biggest improvement" after treatment.

> "Just being able to enjoy things because you, I don't know, were well rested and at peace from getting him what he needed and watching it work and do great things for him."
> *Interview, started treatment at 6 years of age, 5 years and 8 months on treatment*

> "And there're also feeding pumps that are going off at night, and him waking up constantly, not sleeping well. Like you said, then we're waking up constantly, and having to get up and clean up puke in the middle of the night, and then change bedsheets. It's a lot. So, it's definitely improved our sleep, too, our sleep habits, which is vital to your mental health." *Interview, started treatment at 2 years of age, 1 year and 3 months on treatment*

> "We're at a good stage where everything has settled down and everything is good now in a lot of ways. Yes, it was tough. But once again, when we look at what we have now and look at our boys, you do what you've got to do. And to be at where we are now is amazing."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

> "So, everything's lifted in that sense that we're thrilled knowing that our kids, during these prime years of the ages that they're at, they're able to do what any other kid is doing right now, and that means everything to us."
> *Interview, started treatment at 2 years of age, 6 years and 1 month on treatment*

Sharing their child's story

The parent/caregiver that had been unable to share the diagnosis of their child with family and friends before treatment due to the uncertainty of their future, explained during the interviews that they are now able to share their child's story as the child is thriving after the treatment.

> "So it was just easier to be left alone and not have to explain because I wasn't confident enough yet as to what was going to happen to my daughter. I didn't know is she going to get treatment, is she going to live a long life. I mean you Google it, it says they could pass

> away at a young age. I didn't have those answers and I didn't want to have to explain it and I wasn't confident enough to share it and not break down and cry. Whereas now that [name] is where she is I love sharing it, I love sharing her story, I love educating people. And making people aware of that chapter of our lives."
> *Interview, started treatment at 3 years of age, 4 years and 11 months on treatment*

Feeling the treatment is life changing for parents

> "It has been life changing for us as parents. Just to know that his organs are normal sized, and just to know that he's not in that pain and discomfort all the time, is everything to us. And getting him off of oxygen, and just having him feel more like a normal child, not being hooked up to things all the time, is a really big deal for us and for him, where it's been a lot easier to go places now. Because we're not constantly having anxiety about him throwing up in the car, or when we get there, we're not having to pack five changes of clothes to leave the house. So, it's gotten drastically better."
> *Interview, started treatment at 2 years of age, 1 year and 3 months on treatment*

FAMILY/SOCIAL LIFE AFTER TREATMENT

Most parents/caregivers were able to gain their independence and to improve their social and family life after treatment. One family explained that to accommodate the trial, they had to change their working patterns and had to work weekends. This implied they had to sacrifice their social life but that "in the grand scheme of things, that was not where our focus was. We could care less if we weren't able to go out to eat with our friends because we knew what was more important".

Independence: now leaving the child with other people

Parents/caregivers who could not leave their child with somebody else before treatment now felt they could leave their child with family and babysitters, as they would do with any child without ASMD.

> "We are comfortable having babysitters and mom and dad can go on a date night, it's awesome."
> *Interview, started treatment at 3 years of age, 4 years and 11 months on treatment*

Better health of the child: travel, going to places, socialising with friends

Parents/caregivers could now manage the needs of their child easily enough to go to places and would no longer have to constantly schedule hospital appointments. The improvement in the health of the child has allowed some parents/caregivers to meet friends and socialise again as they are less fearful something will happen with the child outside the home.

> “But we have been able to do more things and go more places, see friends who we haven’t been able to see in a really long time, and get together with our family more often now… We still get worried if he gets sick, but there’s a little less of a fear now that we know his lungs are stronger and he’s just feeling better physically. So, yes, I would say our relationships with friends and family have gotten better.”
> *Interview, started treatment at 2 years of age, 1 year and 3 months on treatment*

> “We definitely gained tonnes of time, and it’s definitely a lot more manageable to manage her schedule. It’s definitely a lot easier on our schedule that she can do things. We don’t have to worry about her. She can go off and do what she wants to do, we’re not constantly making hospital plans or doctor plans.”
> *Interview, started treatment at 7 years of age, 5 years and 9 months on treatment*

Extended members of the family mental health

Other members of the family are also affected mentally by the child’s ASMD, especially grandparents, who became happier once the treatment was working.

> “As the treatment started to be more and more apparent that it was working, I think my mother-in-law definitely was more welcoming and happier. Yes, I definitely think there was a lot of stress within the grandparents.”
> *Interview, started treatment at 7 years of age, 5 years and 9 months on treatment*

Treatment has brought the family together

The family of one child who receives their infusion at home said that on infusion days they take the opportunity to be together as a family.

> “Our family has kind of come together like infusion days people would think oh, what a pain in the butt you’re stuck at home for six days. But no, it brings us together, we all are there together as a family during infusion days. So the hardest thing has brought us closest if that makes sense.”
> *Interview, started treatment at 3 years of age, 4 years and 11 months on treatment*

OTHER IMPACTS

Being grateful

Parents/caregivers were grateful their child is receiving treatment and can live their life.

Better person

One parent/caregiver thought their child’s journey had made them a better person and had made their marriage stronger.

Home infusions

Parents/caregivers of children who have been able to receive home infusions after the initial trial period said that their stress had decreased, and it has made a large difference in their lives.

> "For the past year and a half, or two years, we've been getting in-home treatments. Where the nurses are able to come to the house and give them their infusions here at the house. Which has made a world of difference."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

Connecting with other families

ASMD and the treatment allowed parents/caregivers to connect with other families with children with ASMD and share their stories while supporting each other.

> "And what also helped was connecting with some other families and talking to them. That was good, the Facebook group, seeing things like that and seeing other people experiencing things that were the same. That all helped as well."
> *Interview, started treatment at 2 years of age, 6 years and 1 month on treatment*

Parents'/caregivers' concerns about their child's future before and after treatment

Concerns about their child's health in the future

> "We had such negative thoughts about his future early on that right now if you can tell us this is the best it's going to get, that's incredible. We're thrilled. Because he's able to live a normal life and there're no concerns I have at all about it."
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

Parents/caregivers were asked if they had concerns about their child's future were before receiving treatment with olipudase alfa and how these concerns had changed since starting treatment. Parents/caregivers were asked about their concerns regarding their fear of their child losing physical abilities (e.g. walking, exercising, working), fear of their child being increasingly socially isolated from family, friends and co-workers, concerns about their child not finding a life partner given the impact of ASMD, or the uncertainty of the future in general.

Before treatment, all parents/caregivers had concerns about their child's future. All parents/caregivers (10/10) unanimously responded that they had concerns about the uncertainty of the future in general, but these concerns improved after treatment for 9 of the 10 parents: 60% (6/10) responded these concerns were 'much better' and 30% (3/10) 'somewhat better', while one parent/caregiver thought their concerns were 'about the same' (Figure 42). Before treatment, 90% (9/10) of parents/caregivers feared their child would lose their physical abilities but 56% (5/9) and 22% (2/9) responded this concern was 'much better' or 'somewhat better', respectively, after treatment. However, one parent/caregiver responded that this concern had become

'somewhat worse' and another 'much worse' since starting treatment (Figure 42). Before treatment, 60% (6/10) were concerned their child would be increasingly isolated from family and friends but 83% (5/6) said this concern was 'much better' since treatment and one parent/caregiver that it was 'somewhat worse'. Forty percent (4/10) of parents/caregivers were concerned their child would not find a life partner due to ASMD, but since treatment, one out of these four parents/caregivers said this concern was 'much better' (1/4) or 'somewhat better' (2/4), while one parent's/caregiver's concern remained the same (Figure 42). The parent that chose 'other' said that before treatment "I felt as if [name] was already living on borrowed time" but this concern was 'much' better after treatment.

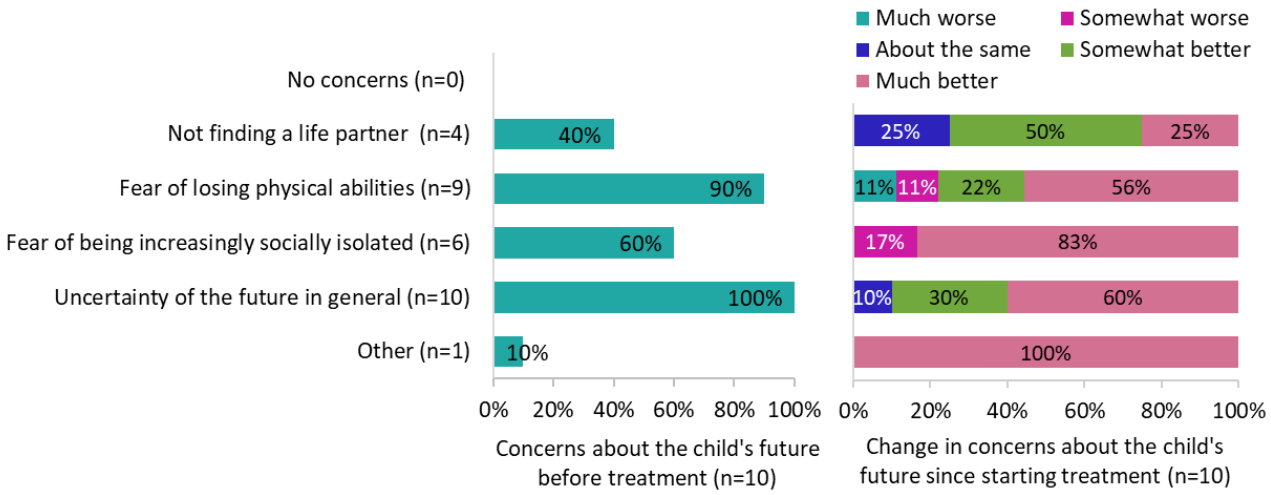


Figure 42. Parents' concerns about their child's future before and since treatment with olipudase alfa (n=10).

Further insights were gathered from the interviews. Parents/caregivers were asked how they felt about the future with regards to their child's health and various themes were mentioned. Parents/caregivers were very optimistic about the future now their child was on treatment, regardless of the child being neurologically affected or not:

> "We feel optimistic, we feel like we look forward to seeing the future. Where before we didn't even think about the future, we didn't think about what ifs, we didn't think about what could be. And it's amazing because [name] all she talks about is wanting to be a doctor because of all her experiences. So to see a child that was forced into a world of medicalness as a necessary situation to now say that she knows that she wants to do the same thing to help little people like her." *Interview, 4 years and 11 months on treatment*

> "I think he's kind of a big unknown, no-one has ever just… So I don't know what the neurological portion of things will look like for him, but I know that he has a chance now and we can see what it is because of this drug, we can see… His body will keep doing good things now and it's only going to either maintain or get better at this point, so I feel like he's fairly stable." *Interview, 5 years and 8 months on treatment*

> “I feel very hopeful. This treatment has given us a lot of hope in regard to our kids’ health. We know we still need to find treatment for the neurological aspect of things, but it’s given us a lot of hope. We just feel like it’s taking care of their bodies and keeping them as healthy as possible.”
> *Interview, 1 year and 3 months on treatment*

> “As a parent, you’re always going to feel anxiety and stress about your kid’s future. So yes, but considerably less. There are times, come high school if he does make the soccer team, that could impact when he gets his drug and so on. So, there’s always going to be that degree of anxiety and uncertainty. And you think well, could it impact him having a family of his own one day? There’re all the things that you worry about in your head as a parent. So, yes, it’s still there but it’s significantly less on the day to day.”
> *Interview, started treatment at 7 years of age, 4 years and 1 month on treatment*

Parents/caregivers referred to the ‘unknown’ future of their child’s patient journey, but that they realised the child can be as happy as any other child without the disease and the best is to take one day at a time, enjoying that their child is healthy now with the treatment.

> “So we do wonder, if he’s not ever able to walk independently, what will we do? And I came to the realisation that, you know what? If he can’t ever walk, he’s still going to have a wonderful life. He’s still going to go and do things. That’s not the end of the world.”
> *Interview, 3 years and 10 months on treatment*

Some parents/caregivers explained that they feel like their child can be anything they want now that the treatment is working:

> “I've made a complete 180 now. I think she can be whatever she wants to be as long as she puts her mind to it. Everything’s opened up, and she wouldn't have had those opportunities if she hadn't been in the treatment.” *Interview, 5 years and 9 months on treatment*

> **“There’s always going to be uncertainty about their future, but like I said, this medication has given us a lot of hope, which I think is very important, especially for parents, to just continue on and keep going.”**
> *Interview, 1 year and 3 months on treatment*

Parents/caregivers still had some concerns, including:

- Being worried about how they will be able to physically deal with the child as they get older

> “I wonder about the bigger he gets. Because we still are able to carry him. The bigger he gets, how will we get him from point A to point B? How will we lift him up?”
> *Interview, 3 years and 10 months on treatment*

- Being worried about the child's independence when the parents/caregivers die

> "I wonder about his independence. I wonder about when my husband and I get older, if [Name] is not able to take care of himself, I worry about, and when we pass away, what's going to happen to [Name]. But fortunately, we have family members. I have two sisters, I have a niece, [Name] has got a brother. We have family that has assured us, if something was to happen, we'll make sure he's taken care of."
> *Interview, 3 years and 10 months on treatment*

- For those children neurologically affected, parents/caregivers worried about their neurological deterioration even though the treatment was working for everything else

> "There's just nothing treating the neurological portion of this disease that… It's a fear but it's a fear that we get to experience because he's still doing great with us, so it's just something that we are aware of because this treatment doesn't help with the neurological things and we're looking into other things. It's just an unknown, we don't know how long things will last with him or what it will look like in the future for him, but I would say more of an unknown. I mean the fear I mean is… We just don't know what it will look like."
> *Interview, 5 years and 8 months on treatment*

Satisfaction with olipudase alfa

Note: The parent/caregiver with two children gave different responses for each of the children hence total population of parents has been kept at ten for this question.

Both in the survey comments and in the interviews, parents/caregivers reiterated that the treatment had been life-changing.

> **Your constant fear is gone, you know that… We knew this drug was working, it was obvious it was working and you just saw the benefits so frequently. So it was life changing for all of us, just to watch him go through it. There is challenges, it's difficult to do what we did, but it was worth it at every step, and just seeing him feel and look so much better was great."** *Interview, 5 years and 8 months on treatment*

> **"I feel like her future is in her hands and she can decide what her future is going to be. Without the medication, without the treatment, she would have very little control over what route she takes. So, as I said, I would do it 100 times over again."**
> *Interview, 5 years and 9 months on treatment*

Ninety percent (9/10) of parents/caregivers were extremely satisfied with olipudase alfa to manage ASMD in the ten children. One parent/caregiver was somewhat satisfied because, although better, the child was suffering from side-effects (Figure 43a).

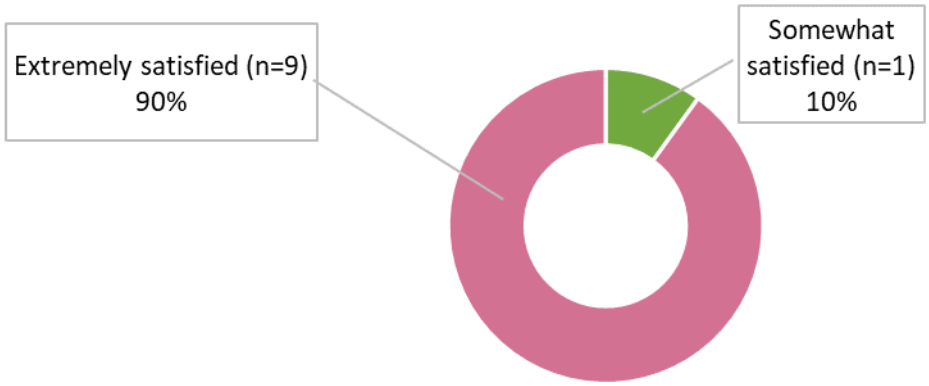


Figure 43a. Level of satisfaction with olipudase alfa to treat ASMD (n=10).

> "We have seen a drastic improvement in our child's physical, social, and mental health. He is able to engage and participate in age appropriate play with his peers. He feels better about himself and his condition knowing that it can be treated."
> *Survey, 4 years and 1 month on treatment*

> "We see that [name] is doing really well, there is not one symptom that we could wish to be further decreased. She has lots of energy, her belly is normal, she eats normal, she can play and do physical exercise like a normal 7-year-old girl. Also the doctors tell us that they could not have wished for any better result since all the parameters that are measured/followed up have gone towards normal a lot."
> *Survey, 3 years and 6 months on treatment*

> "I have seen almost complete resolution of disease manifestations with the treatment."
> *Survey, 6 years and 1 month on treatment*

> **"Our daughter leads a life just like any other 7-year-old without ASMD and that's all you ever want for your child."**
> *Survey, 4 years and 11 months on treatment*

Parents/caregivers were asked to choose the statement that best described the overall progression of ASMD while receiving treatment with olipudase alfa. Most parents/caregivers (80%; 8/10) reported that the 'condition improved', while one parent/caregiver chose the statement the 'condition stabilised' and one chose 'condition progressing slower than without the treatment' (Figure 43b).

Please note that one parent/caregiver incorrectly answered this question in the survey and clarified their response during the interview. They answered the survey 'Condition progressing faster than expected', however during the interview, they clarified that they meant the treatment worked more

rapidly than they thought it would, therefore they confirmed their correct response to this question is 'condition improved'.

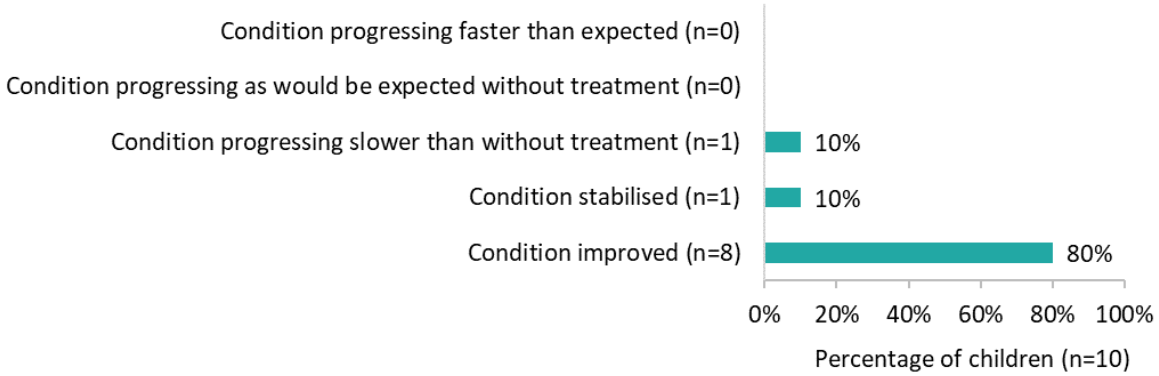


Figure 43b. Overall progression of ASMD while receiving treatment with olipudase alfa (n=10).

Parents/caregivers reiterated the benefits already described, with most parents/caregiver saying the reduction in size of their child's abdomen since starting treatment had changed their lives, as children are now able to participate in activities with children their own age and parents/caregivers stating that nobody can tell the child has ASMD.

Other benefits included no longer being in pain or out of breath, and that the treatment can be administered at home. Parents/caregivers reiterated in the interviews that this was a life-saving treatment, and that in some of these children there were no symptoms or signs of ASMD at all, as children could lead a normal life.

> "The best way to describe it is that she's just like a typical child. Like when we share now that [name] has an underlying metabolic genetic disease people are totally shocked and surprised, I have to fill that information out when she attends like trampoline parks or attends school and teachers and people are so confused because they look at her and they're like wait a minute what?" *Interview, 4 years and 11 months on treatment*

> "**It's a complete 360. Really, the healthiest person I think I probably know on the Earth right now is her.** So, she completely changed. It was not only her health but just her overall bodily figure just completely was altered. **She was a completely different person after receiving the treatment. And we noticed, I would say, within three months, that her figure was changing.** She didn't have the distended stomach anymore."
> *Interview, 5 years and 9 months on treatment*

> **"Honestly, it has saved his life. And I will tell anyone that this trial saved his life."**
> *Interview, 3 years and 10 months on treatment*

> "Everything changed for [name], physically, mentally, it changed our family for the better."
> *Survey, 4 years and 11 months on treatment*

> "it was life saving for him, I mean it was really was, I don't… I think his organs were failing, I think he couldn't sustain his system much longer, definitely was."
> *Interview, 5 years and 8 months on treatment*

Parents/caregivers mentioned that after their child was diagnosed, it was a relief to find out that there was a treatment for their child.

> "…that part [diagnosis] was almost harder, you get diagnosed but you can't do anything yet. And so that was even harder, definitely. So now that she's in the treatment and we see who she is today and where she's at, that definitely once the treatment started it was like the biggest sense of relief."
> *Interview, diagnosed at 2 years old, 4 years and 11 months on treatment*

One parent/caregiver mentioned in the interview that they were never depressed before treatment started but that once treatment began all their concerns concentrated on wanting the treatment to work for their child.

> "I think we were just worried because we wanted this trial to work for him, the trial drug. We wanted him to be okay. We wanted him to be able to live the best life he could live. But never depression. We just wanted him to be okay. It was just the worry."
> *Interview, started treatment at 1.5 years of age*

One parent/caregiver discussed during the interview how receiving treatment at an early age had been beneficial as the child never had the time to develop damaging symptoms.

> "We were very happy to get access to the trial while she was still very young, so we've not actually been in the situation where she was doing really badly, but we could clearly notice that there was progression in these things. […] the doctors told us that it's really improved from a pathologic situation to just a normal situation. […] there's really nothing that did not improve." *Interview, started treatment at 4 years of age*

Concerns about treatment

> "Concerns about the treatment? No, not at all. We've seen it works a miracle on the kids."
> *Interview, siblings started treatment at 7 years and 2 years, 4 years and 1 month and 6 years and 1 month on treatment, respectively*

Most parents/caregiver said in the survey that there were no disadvantages or adverse impacts on their child. Disadvantages mentioned in the survey included the treatment not crossing the

blood-brain barrier, the child missing school on some days to receive the treatment and the demands and challenges of the clinical trial.

BENEFITS OUTWEIGH THE RISKS

In the interviews, all parents/caregivers agreed that the benefits of the treatment outweigh the risks, especially since most children had not suffered any kind of side-effect or reaction to the treatment.

> **"We are absolutely thrilled with the treatment. The demands of the trial have presented numerous challenges, however the benefits of the treatment greatly outweigh them."**
> *Survey, 4 years and 1 month on treatment*

SIDE EFFECTS WERE MINOR ISSUES COMPARED TO THE EFFECTS OF ASMD

Parents/caregivers explained that, after what their child, and them as parents/caregivers, had been through with the symptoms of ASMD, mild side-effects were worth it for the benefits of the treatment in slowing disease progression.

> "The side effects for us were very mild and we had been through quite a bit with [Name] already, and his disease pretty progressed on the scale. So the slight things that happened at the beginning of the infusions and stuff, that didn't faze quite a bit or at all." *Interview, 5 years and 8 months on treatment*

One parent/caregiver was concerned about what the side-effects in the long-term could be, but also said the improvement in their child was worth it and would never regret the decision to start treatment as the alternative was for the disease to progress and for their child not to be able to live a full life.

> "I do still have concerns, maybe later in life, ten years down the road, will she have any side effects, I don't know. I don't think anyone knows. But at the same time, I would not take back the decision we made to have her in the trial because now she's living the best life she can live. There's absolutely no regrets there. And just thinking, the alternative there was her getting sicker and sicker. So, I definitely did a risk-benefit analysis before this all took place, and the benefits just seemed to far outreach the risk in her participating. Obviously, we were concerned, but very happy with the results, and look forward to her being a happy and successful adult."
> *Interview, 5 years and 9 months on treatment*

CONCERNS ABOUT THE TREATMENT WERE ADDRESSED BY THE CLINICIAN

Initial parents'/caregivers' concerns at the time children started the clinical trial, were addressed by the clinician. Concerns were linked to the fact the treatment was new and information they had about issues with the first trial.

> "In the beginning. Obviously, it's something that's never really been tested on that many individuals. I think I knew the facts around the trial in 2007, 2008, where certain people

got really ill, and they shut down the programme for a little bit. And I think where we gained a little bit more comfort was in some of the discussions we had with some of the experts on how they thought they had resolved the issue that occurred in 2007, 2008."
Interview, 5 years and 9 months on treatment

CONCERNS ABOUT THE TREATMENT VANISHED ONCE PARENTS SAW THE RESULTS

"[concerns] started lifting and once again, it was all the stress, we knew the end result was they're going to be better and they're going to be able to live normal lives. […] So, that was the light at the end of the tunnel and we're there now."
Interview, 6 years and 1 month on treatment

Views on current and new treatment options available for ASMD

In the survey, parents/caregivers were asked about their views regarding the level of need for a new treatment that would slow disease progression more effectively than olipudase alfa. Only one parent/caregiver thought there was no need at all for a new treatment, but half of the respondents (50%; 5/10) said there was 'a great need'. One parent/caregiver responded that there was 'a lot of need' and two that there was 'a moderate need' (Figure 44).

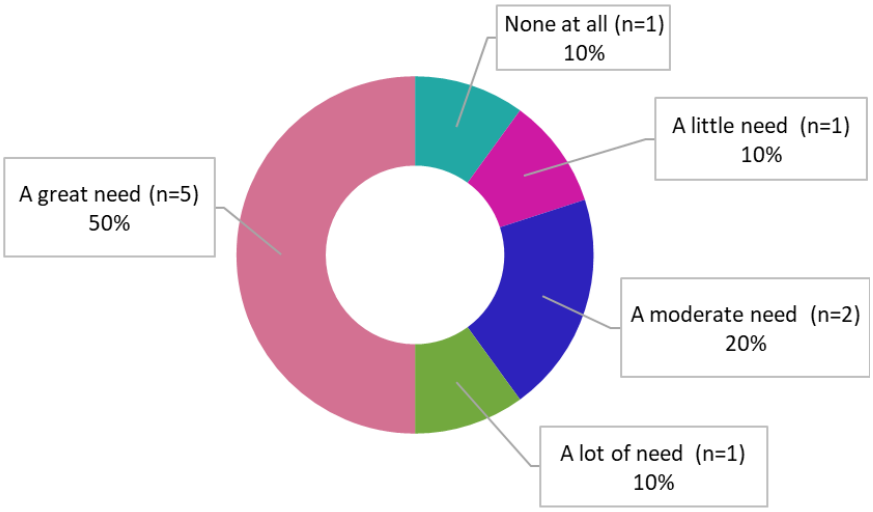


Figure 44. Level of need for a new treatment (n=10).

Respondents explained that although olipudase alfa had been effective in reducing symptoms of ASMD, new therapies may be needed for people with neurologic ASMD and for patients starting treatment as adults, as benefits are perceived to be only rapid in children. Other reasons for new therapies included avoiding side effects of olipudase alfa and the burden of biweekly infusions

and medical equipment, but also the difficulty to access infusion centres that offer olipudase alfa once studies have been completed.

> “This drug has saved my sons life, no doubt about that. We are so grateful and always will be, but it doesn’t cross the blood brain barrier to aid in neurological involvement.”
> *Survey, 3 years and 10 months on treatment*

In the interviews, some parents/caregivers mentioned that although other treatments are needed for children with neurological issues, olipudase alfa would still be needed to effectively treat all other symptoms. Parents/caregivers did not see the need for a replacement for olipudase alfa, but an add-on treatment.

> “Well, I feel like you couldn’t just jump in and save the brain in any other way, you would have to treat them with this drug first anyway before you went on another one. If there was a way for this drug to hit the brain, it would be great but… And there’s just going to be another need, not a replacement but just more."
> *Interview, 5 years and 8 months on treatment*

> “I feel like this treatment is working beautifully at reversing damage done to their bodies and basically making their bodies normal again, but now the second piece to the puzzle is finding treatment to slow down or stop the neurological disease progression, or even reverse it. And it’s so important.” *Interview, 1 year and 3 months on treatment*

One family explained this treatment had been so perfect for their child that there was no need for them to find a different one.

> “It may sound a bit selfish, and that’s not how I mean it, but in our case, in our case we don’t really see that need, because we see how she’s doing. And also, the medical specialists told us she is really doing very well. It’s unbelievable, because often in these types of diseases it’s very difficult to tackle all the symptoms, but in this case, it looks like it’s possible. So, they told us, we believe that as long as [Name] gets this treatment, she will do fine. From that point of view, we don’t really need other medication. I would say this treatment is perfect." *Interview, 3 years and 6 months on treatment*

Access to treatment

Parents/caregivers were so adamant about how this treatment had changed their child’s life, that they wanted everyone with ASMD to have access to it and they felt upset when thinking about other children who had no access, the adults for whom it was too late to receive treatment, and all other children that had died before this treatment was available. Parents/caregivers reiterated the feeling that their child was alive or living a normal life because of this treatment so could not understand why access would be denied.

> "**My heart breaks for the parents whose children have ASMD and they're not in the trial and they're not receiving anything**. […] And one particular family talks about how they've noticed their child doesn't do this anymore, and that. And it is heart-breaking, because you […] honestly also feel guilty because your child is receiving this medicine and you have seen the benefits of it. And you know they wake up every day and they're just… Oh. It's just devastating. It is devastating. And this medicine can… **It saved my child's life**."
> *Interview, 3 years and 10 months on treatment*

> **"They're the best kids, and they deserve every single opportunity that life can give them, and I'm just hoping and praying that this treatment gets FDA approved. And I'm hoping it can help so many other families in our position**…."
> *Interview, 1 year and 3 months on treatment*

Thinking about losing access to the therapy was unanimously devastating for all parents/caregivers and can be stressful to think about it:

> "It's something I don't even want to think about. […] **Without it, all those amazing things would go away.** [Name] wouldn't be [name] anymore she would be back to this fragile, sick, inability to walk, inability to run, inability to play, inability to go to school. All of those things that she can do now they would go away." *Interview, 4 years and 11 months on treatment*

> "It would be horrific. I cannot imagine not having it. It would... I don't even know. I'm lost for words to say. **If she didn't have access to it, it would be completely devastating. It, literally, has changed her life. She has been completely altered into a normal person living a normal life, all due to the treatment."** *Interview, 5 years and 9 months on treatment*

> **"Oh it would be horrendous. Yes it would just be awful to watch everything that was undone, redone slowly and surely, and know where you were going to end up."**
> *Interview, 5 years and 8 months on treatment*

> "It goes without saying that it doesn't even bear thinking about if [name] couldn't get this medication, you don't want to think about that."
> *Interview, 4 years and 1 month on treatment*

> "Will she have access to a treatment whatsoever in the future? Anything could go wrong. Maybe the study is stopped, or maybe for whatsoever reason she cannot participate or she cannot get treatment, for a medical reason or whatever. So, it was really stressful. […]I'm confident that if she can keep receiving medication, she will do very well, and I'm also quite confident that we will keep getting the medication. That's also what the doctors that treat her expect and what they tell us. They never say, we are sure of that, but that they expect it and they would be surprised if there is really an issue. So, as long as she can get the medication, we are very confident that she can have a rather normal life."
> *Interview, started treatment at 4 years of age, 3 years and 6 months on treatment*

Parents/caregivers believed that the benefits of this treatment on their children are so obvious and life changing, and that their children are the living proof this treatment works, that it must continue and be accessible to everyone with ASMD:

> "… **It saved my child's life**, and I know so many. And even though it's a rare drug, I mean a rare disease, and this drug isn't going to be as popular or help as many people as aspirin or whatever, insulin, but it shouldn't matter. **One child's life saved is a huge impact.** *Interview, 3 years and 10 months on treatment*

> "I mean there's not not a need [for the tehrapy], right? You have a clear example in my child's, in other children, and I hate saying it but the children that have passed. The pre-teens that have passed, the people that have passed. And that's probably, without getting emotional, that's probably one of the hardest parts of this journey for the last five years, four years, is seeing that my child is living a typical life. **Our lives have returned to what you would call normalcy living because of this treatment for my daughter. And yet there have been other people that haven't had that ability to access it that may have lost their lives because of it**." *Interview, 4 years and 11 months on treatment*

> "From our whole vantage point and our whole desire to be involved is to, at least, push this forward to give them access, as well. Because at the end of the day, **it's not fair that they haven't had the chance, for those who haven't had the chance, to get this treatment and live the life that they want to live.** Not just now, but in the past too. We're just super-thankful or some of the adults and some of the things that they've done in keeping this alive and pushing forward. And even participating in some of the earlier trials. We really want them to also have access as soon as possible." *Interview, 5 years and 9 months on treatment*

> "It's absolutely needed in the sense just looking at both our kids. And we had two kids who started receiving it at different times of their lives. Right now, like I've said a few times, they're living a normal life. […] So, the fact that this medicine has made them like everyone else in 99% of ways, as a parent, you're in a much better mental state in a lot of ways." *Interview, siblings started treatment at 7 years and 2 years, 4 years and 1 month and 6 years and 1 month on treatment, respectively*

Access to treatment with siblings

There were two families in this study, who had two children with ASMD and were receiving treatment, however, one of the children did not meet the inclusion criteria because they had only been receiving olipudase alfa for a couple of months.

The parent/caregiver with two children with ASMD included in this study, explained that initially, only the younger of the siblings was accepted in the trial, and they went through the distress of knowing only one of their children would be receiving the treatment.

> "We're unique in which we had two kids going through the trial and our younger one was experiencing less symptoms because he got on early. " *Interview, siblings started treatment*

> *at 7 years and 2 years of age, 4 years and 1 month and 6 years and 1 month on treatment, respectively*

It was also difficult having to explain to their five year old child who was not going to receive treatment that only their younger sibling was going to get better for now, and had to find ways to explain to their young child he may also receive it in the future, but this was difficult for the child to understand. The sibling was eventually included in the trial.

> “it was difficult for us to be explaining to [name]. Because he did question why he wasn’t able to get it. We just kept saying by [name] doing this, and by that point, the whole idea was by [name] doing this and getting the treatment now and showing that it works, one day it’s going to help you get it. And it might be five years and it might be ten years, but know that one day you’re going to be able to get this treatment because of what your brother’s doing. So, it was tough for him to comprehend that at five, six years old. But when we became aware that the trial was going to have a couple of more participants, we were right on that. And fortunately, they accepted [name]. Him being within the right conditions and everything worked out for him to be able to do that, thankfully. That was good, and it wasn’t that much difference of a time. It only turned out being a couple of years. " *Interview, siblings started treatment at 7 years and 2 years of age, 4 years and 1 month and 6 years and 1 month on treatment, respectively*

The parents/caregivers also went through the distress of seeing the child who received treatment at a very early age improve with treatment while the other child’s physical symptoms were progressing and was emotionally and socially affected at school by the progression of ASMD. Parents/caregivers said it was difficult to deal with the happiness of seeing a child get better with treatment and the other get worse because they had no access, but they hoped that the good results of the trial would mean their eldest child would eventually receive treatment as well.

> “To pinpoint emotionally what we were going through was virtually impossible, because we had both ends of the spectrum. We had one kid who was able to do it and get the treatment so young where it had so much less of an impact on his body. And we were so hopeful in that sense. And yet we felt on the other end another kid knowing, which we saw physically what it was doing to him and emotionally and socially how he was struggling in school and so on. We were seeing all ends of every emotion possible. " *Interview, siblings started treatment at 7 years and 2 years of age, 4 years and 1 month and 6 years and 1 month on treatment, respectively*

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2. Schuchman EH, Wasserstein MP. Types A and B Niemann-Pick disease. *Best Pract Res Clin Endocrinol Metab*. 2015; 29:237–47.
3. Diaz GA, Jones SA, Scarpa M, Mengel KE, Giugliani R, Guffon N et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. *Genet Med.* 2021;23(8):1543–1550.
4. Imrie J. A guide to ASMD Niemann-Pick disease types A and B: Understanding acid sphingomyelinase deficient Niemann-Pick disease types A and B and their potential treatment. 1st ed. Washington: Niemann-Pick Disease Group (UK); 2010.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Olipudase alfa for treating Niemann-Pick disease types A and B [ID3913]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Inherited Metabolic Disease Group. Also representing University College London Hospitals NHS Trust.
3. Job title or position	Consultant adult inherited metabolic disease – Charles Dent Metabolic Unit, UCLH.
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes – as above. A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Inherited Metabolic Disease Group – a charity with the aim of advancing the education of individuals (doctors, nurses, dietitians, psychologists, clinical scientists and pharmacists) involved in the diagnosis, care and treatment of people with inherited metabolic disease, and promoting research in the field. Funded by membership subscriptions.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	BIMDG has received sponsorship for its annual conference from the manufacturer. The Charles Dent Unit has participated in clinical trials of olipudase alfa in adults.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. To improve hepatosplenomegaly and associated complications. 2. To improve respiratory disease / interstitial lung disease. 3. To improve haematological disease. 4. To improve bone disease and associate complications. 5. To prevent significant morbidity and premature death from pulmonary and liver disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Studies have shown clear (clinically significant) improvements in: • Liver volume (can reach normal volume with treatment) • Spleen volume (can reach normal volume with treatment) • DL_{CO} of the lung (can reach normal values with treatment) • Forced vital capacity (can reach normal values with treatment) • Interstitial lung disease (significant improvements in most individuals; stability in some) • Bone mineral density (increase from osteopenia to normal BMD) • Reductions in biomarkers (lyso-sphingomyelin and chitotriosidase) to normal / close to normal ranges. • Lipid profiles (reductions in HDL-cholesterol can reach normal values)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – this is the only disease specific treatment available for NP A/B that can address all non-neurological aspects of the condition. It is life-transforming.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Supportive measures. • Nutritional support (+/- feeding tubes) • Respiratory support (including supplemental oxygen and treatment of infections) • Support for liver disease (including consideration of liver transplant on occasion) • Blood products if required. • Treatment for low bone mineral density eg. calcium, vitamin D.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Wasserstein M, Dionisi-Vici C, Giugliani R, Hwu WL, Lidove O, Lukacs Z, Mengel E, Mistry PK, Schuchman EH, McGovern M.Mol Genet Metab. 2019 Feb;126(2):98-105. doi: 10.1016/j.ymgme.2018.11.014. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, Eugen Mengel K, Mistry PK, Schuchman EH, Wasserstein MP.Genet Med. 2017 Sep;19(9):967-974. doi: 10.1038/gim.2017.7.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Patients should be referred to one of the paediatric or adult LSD specialist services. It would be expected that all diagnosed patients are known to a specialist centre.

9c. What impact would the technology have on the current pathway of care?	Patients would continue to be reviewed at specialist LSD centres. Once biochemical and clinical parameters had improved / normalised then supportive treatment measures could be reduced and patients would enter a surveillance programme, with minimal need for treatment other than ongoing enzyme replacement therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Similar to ERT for other LSDs eg. Gaucher disease.
10a. How does healthcare resource use differ between the technology and current care?	As for questions 9c and 10.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Diagnosis, initiation of treatment and surveillance via LSD specialist services. It is likely that dose escalation will take place in the specialist LSD centre (hospital environment). Ongoing treatment (regular intravenous infusions of olipudase alfa) could be moved to homecare once patients are stable.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As for questions 9c and 10. Dose escalation is likely to be done in a hospital setting.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – see above.
11a. Do you expect the technology to increase length of life more than current care?	Yes – see above.

11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – see above.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Olipudase alfa is not expected to directly impact on neurological disease in those patients who have neurovisceral disease (although it will still improve the visceral component of their condition).

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As above. Regular intravenous ERT is widely accepted among many different patient groups.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	

include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes – as above. See question 7.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – as above. See questions 7 and 8.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Infusion associated reactions are possible. Dose escalation is required in order to avoid the possibility of rapid release of active sphingomyelin metabolites. The specialist LSD centres are experienced in managing the above.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Patients who participated in clinical trials are now able to receive treatment at home.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s)	No.

since the publication of NICE HST guidance [HSTXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	In our experience (we have had a number of adult patients participate in the clinical trials and subsequent extension treatments), the benefits as listed above have continued and been sustained. No patient has relapsed.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Olipudase alfa is effective in improving clinical parameters (liver and spleen volumes, lung function, bone mineral density) • Olipudase alfa is effective in improving biochemical parameters (lipid profile, chitotriosidase, lyso-sphingomyelin) • Olipudase alfa is well-tolerated • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Olipudase alfa for treating Niemann-Pick disease types A and B [ID3913]

Clarification questions

August 2022

File name	Version	Contains confidential information	Date
ID3913 EAG clarification questions.docx	1.0	Yes	15/09/2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. Please confirm whether additional searches were conducted to identify conference abstracts in Ovid Embase and if so, please provide details of the search strategy. The search strategy for Ovid MEDLINE & Embase reported in Table 80 (Appendix D) applies a limit of 'Article' or 'Article in Press' in line #12. This limit excludes conference abstracts from search results.

Additional hand searches of the following conferences were conducted to identify relevant abstracts in Ovid Embase from the past two meeting years:

- WORLDSymposium
- European Society of Human Genetics
- Annual Symposium of the Society for the Study of Inborn Errors of Metabolism

Details of the search strategy are provided in Table 1.

Table 1: Search procedure for grey literature sources

Conference, HTA Body or Organization Name	Search Information	Website Navigation Pathway	Search Terms
WORLDSymposium, 2021	https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/132/issue/2	Use ctrl + f	Acid Sphingomyelinase Deficiency
WORLDSymposium, 2022	https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/135/issue/2	Use ctrl + f	NA
European Society of Human Genetics, 2021	https://www.abstractsonline.com/pp8/#!/10372	Use search bar	Acid Sphingomyelinase Deficiency
European Society of Human Genetics, 2021	https://www.abstractsonline.com/pp8/#!/10372	Use search bar	Acid Sphingomyelinase Deficiency
European Society of Human Genetics, 2022	NA- has not occurred	NA	Acid Sphingomyelinase Deficiency
Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2021	https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12458	Use search bar	Niemann
Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2021	https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12458	Use search bar	Niemann
Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2022	NA- has not occurred	NA	Niemann
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click methods in basic search	Acid Sphingomyelinase Deficiency

Conference, HTA Body or Organization Name	Search Information	Website Navigation Pathway	Search Terms
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click ratios in basic search	Niemann
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click utility weights in basic search	Acid Sphingomyelinase Deficiency
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click methods in basic search	Niemann
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click ratios in basic search	Acid Sphingomyelinase Deficiency
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click utility weights in basic search	Niemann
Clinicaltrials.gov	https://clinicaltrials.gov/	Search in conditions, apply "with results" in filters	Acid Sphingomyelinase Deficiency
Clinicaltrials.gov	https://clinicaltrials.gov/	Search in conditions, apply "with results" in filters	NA

Conference, HTA Body or Organization Name	Search Information	Website Navigation Pathway	Search Terms
International Guideline Library	https://g-i-n.net/library/international-guidelines-library/international-guidelines-library	Use search bar	Acid Sphingomyelinase Deficiency
International Guideline Library	https://g-i-n.net/library/international-guidelines-library/international-guidelines-library	Use search bar	Acid Sphingomyelinase Deficiency
ECRI Guidelines Trust	https://guidelines.ecri.org/	Navigate to library at bottom of page, click "clinical specialties"	Acid Sphingomyelinase Deficiency
ECRI Guidelines Trust	https://guidelines.ecri.org/	Navigate to library at bottom of page, click "clinical specialties"	Niemann

Abbreviations: CEA, cost-effectiveness analysis; ECRI, Emergency Care Research Institute

A2. Please confirm whether the references from conference abstract searches and other grey literature searches were screened by 2 reviewers? Were any records identified from these grey literature searches excluded, and for what reasons?

Grey literature was screened by two reviewers (initial screening by one and validation by a second senior reviewer). A total of 27 conference abstracts were identified through keyword searching, of which 19 of those records were excluded due to the following:

- Population: 10
- Outcomes: 4
- Duplicate: 5

A3. Please provide the search strategies used to identify unpublished trials at ClinicalTrials.gov, and strategies used in the Cost Effectiveness Analysis Registry.

Unpublished trials were identified at ClinicalTrials.gov by searching in conditions “acid sphingomyelinase deficiency” as well as “Niemann”, the “with results” filter was selected to only identify trials with results.

As for the Cost-Effectiveness Analysis Registry, a similar approach was used wherein each overarching topic of the basic search (i.e. ratios, utility weights, and methods) were searched for both “acid sphingomyelinase deficiency” and “Niemann”. This methodology resulted in six hits, all of which were excluded due to population.

Systematic literature review methods

A4. Please provide justification for the exclusion of non-medical interventions as comparators in the SLR.

The inclusion criteria of the SLR were limited to medical interventions for ASMD due to the fact that non-medical interventions such as supplemental nutrition, occupational therapy, etc. are aimed at reducing symptom burden rather than treating ASMD. In addition, there were no potentially relevant studies identified through the searches of grey literature that were excluded for evaluating a non-medical intervention.

A5. Please provide justification for not using NCT00410566 to provide supporting evidence in the submission (with particular reference to safety data) despite providing critical appraisal ratings for this trial.

Study NCT00410566 did not include patients treated with the licensed maintenance dose (3.0 mg/kg) and was therefore deemed to be of limited relevance. An overview of the study is provided below:

Study NCT00410566 was a phase I, single-centre, open-label, nonrandomised, single-ascending-dose trial which evaluated the safety of olipudase alfa (administered IV) at a dose of 0.03, 0.1, 0.3, 0.6, or 1.0 mg/kg in 11 adults (18–65 years of age) with ASMD type B (1, 2). Overall, no serious adverse drug reactions occurred during the study. The maximum tolerated starting dose of olipudase alfa in patients with ASMD type B was identified to be 0.6 mg/kg, with results of the study supporting the use of a within-patient dose-escalation strategy.

The company has also provided the CSR for NCT00410566 (1) in the updated reference pack.

A6. The ROBINS-I tool for critical appraisal requires researchers to pre-specify the confounders that will be considered in the appraisal. Please state which confounders were selected for this purpose.

As discussed in the company submission, a mix of clinical and demographic confounders were selected: age, gender, weight, medical history (history of blood, lymphatic system, or hepatobiliary disorders), prior treatments (including history of surgical/medical procedures), concomitant medication, age at symptom onset, age at diagnosis, genotype/phenotype subtype, disease severity and symptoms at baseline, and family history.

A7. Please provide full critical appraisal ratings (i.e. across all signalling questions) for trials of olipudase alfa.

Full ratings for Cochrane AROB and the ROBINS-I assessment are provided as a separate document (3).

A8. Further justification is needed for critical appraisal ratings given for ASCEND-Peds. We further note that the ROBINS-I tool was primarily developed to evaluate

risk of bias in comparative studies, and therefore the appraisal should explicitly consider the additional risks presented by single-arm trials. Please provide a justification for your following statements:

Justification for critical appraisal ratings for ASCEND-Peds have been provided in Table 21 of the company submission. Justifications have been extracted below.

- That the cohort of ASCEND-Peds was “representative of the relevant targeted population” (CS p. 87, Table 21);

The cohort of ASCEND-Peds was considered “representative of the relevant targeted population” as all eligible patients meeting the protocol-defined inclusion criteria were enrolled and completed the study.

- That the trial design adequately accounted for confounding factors in the design and/or analysis;

The inclusion criteria were designed a priori to help minimise confounding factors. Results were adjusted as needed for any remaining confounders.

- That the findings were sufficiently precise.

For exploratory efficacy assessments, observed measures and changes from baseline values were analysed with a regression model using baseline as the covariate, least squares mean, 95% CIs and p-values were provided. In addition, any concerns with precision could be driven by the smaller sample size.

A9. Please confirm that the critical appraisal ratings reported for the included trials were attributed to all reported trial outcomes.

The company can confirm that this is correct.

Administration of olipudase alfa

A10. The EAG understands that there is no diagnostic test to confirm type of ASMD (i.e. type A, B, or A/B), and that diagnosis is based on clinical presentation. The licence for olipudase alfa does not specify a minimum age for use, however do you

consider there to be a minimum age for use to ensure that a diagnosis of type A ASMD has been ruled out?

The diagnosis of ASMD is established by detection of biallelic pathogenic variants in SMPD1 and/or residual acid sphingomyelinase enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts) (4, 5). In a study evaluating the natural history of 10 type A patients, the results revealed that the natural history of this disorder is very similar amongst affected patients and is characterised by a relentless neurodegenerative course that leads to death usually within 3 years (4). According to clinical opinion, the distinction between patients with ASMD type A and other phenotypes (type B, and A/B) is clear (6).

A11. Would you please provide further information about the packaging of olipudase alfa and the potential for wastage when used in clinical practice? Please also explain about the shelf life of the medication and whether there are specific storage requirements.

Packaging of olipudase alfa

Olipudase alfa is a white to off-white lyophilised powder for concentrate for solution for infusion (powder for concentrate). Each vial contains 20 mg of olipudase alfa. After reconstitution each vial contains 4 mg of olipudase alfa per mL (7).

Potential for wastage

Enzyme replacement therapy doses are routinely rounded to the nearest vial to avoid wastage, according to clinical experts from three different centres (personal communication: [redacted] All three clinical experts confirmed that the standard procedure would be to round up or down to the nearest vial, if weight is halfway between two vials they would round down dose one week and up the next week to avoid wastage. Vial rounding is therefore expected to be the routine practice in England.

Shelf life and storage requirements (Section 6.3. of SmPC (7))

Unopened vials

Shelf life of unopened vials is 48 months.

Reconstituted medicinal product

After reconstitution with sterile water for injection, chemical, physical and microbiological in-use stability has been demonstrated for up to 24 hours at 2-8°C or 12 hours at room temperature (up to 25°C).

From a microbiological point of view, the reconstituted medicinal product should be used immediately. If not used for dilution immediately, in-use storage times and conditions prior to dilution are the responsibility of the user and should normally not be longer than 24 hours at 2°C - 8°C or 12 hours at room temperature (up to 25°C).

Diluted medicinal product

After dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, chemical, physical and microbiological in-use stability has been demonstrated between 0.1 mg/mL and 3.5 mg/mL for 24 hours at 2-8°C, and up to 12 hours (including infusion time) when stored at room temperature (up to 25°C).

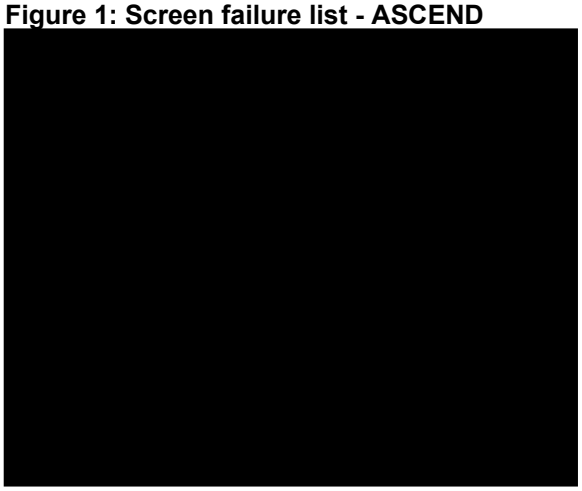
From a microbiological point of view, the diluted medicinal product should be used immediately. If not used immediately after dilution, in-use storage times and conditions are the responsibility of the user and should normally not be longer than 24 hours at 2°C to 8°C followed by 12 hours (including infusion time) at room temperature (up to 25°C).

Methodology used for clinical trials of olipudase alfa

A12. The CS reports that 62 patients were screened for ASCEND but 38 patients were considered eligible for inclusion. Can you please provide a breakdown of why these 24 patients were considered ineligible, and confirm whether all patients considered ineligible had a diagnosis of ASMD B or A/B?

Please consider the screen failure list below.

Figure 1: Screen failure list - ASCEND



A13. Please can you confirm whether any of the participants in the included trials had previously received treatment with olipudase alfa?

No participant in ASCEND and ASCEND-Peds had previously received olipudase alfa within 30 days before study enrolment, as stated on the protocol.

A14. Two participants discontinued from the olipudase alfa arm of ASCEND (11.1%) but the reasons for their discontinuation is unclear. Please can you provide further details, and/or confirm whether discontinuation was related to the efficacy or safety of olipudase alfa?

There were no discontinuations related to the efficacy or safety of olipudase alfa. The ID of the two ASCEND participants from the olipudase alfa arm that discontinued were . Both participants discontinued after the primary analysis period (PAP) (did not complete the extension treatment period [ETP]).

[redacted]

[redacted]

A15. Please provide the number of participants in each trial and trial arm diagnosed with ASMD type B vs. type A/B.

At the time ASCEND was initiated, no clear diagnostic classification criteria were available and the subtypes were considered to represent a disease spectrum rather than discrete entities. Consequently, while the inclusion criteria in ASCEND stated ASMD type B the study enrolled both patients with a clinical diagnosis consistent with ASMD type B and type A/B. Considering this, the trial protocols did not require investigators to sub-classify patients according to ASMD Type A/B and B subtypes at enrolment.

A16. Please provide population eligibility criteria for the included clinical trials (please note that we have accessed these from the trial CSRs, but we cannot report these without redaction unless you present them in your submission).

Eligibility criteria for participants are presented in the submission for the included clinical trials as follows:

- ASCEND-Peds and ASCEND is provided in Table 13 of the company submission
- DFI13412 is provided in Table 101 of Appendix M
- LTS13632 is provided in Table 40 of the company submission

The eligibility criteria are not deemed confidential.

A17. PRIORITY. Please provide data for the treatments received by participants in all treatment arms of the trials, including:

- dose received
- mean dose duration
- dose modifications
- details of background care received.

Please see below data for the treatment received by participants in all treatment arms of the ASCEND study.

Table 2: Treatment received by participants in all treatment arms of ASCEND study

Please see below data for the treatment received by participants in all treatment arms of the ASCEND study.

Table 2: Treatment received by participants in all treatment arms of ASCEND study

ASCEND	Placebo (N=15)	Olipudase alfa (N=18)
Cumulative dose (mg) on olipudase alfa in PAP		
Number of patients with value	0	[redacted]
Mean (SD)		[redacted]
Median		[redacted]
Patients not achieved the target dose of 3mg/kg on olipudase alfa, n(%)	0	1(5.6%)

Abbreviations: mg, milligram; PAP, primary analysis plan; SD, standard deviation

Please see below data for the treatment received by participants in ASCEND-Peds.

Table 3: Treatment received by participants in all treatment arms of ASCEND-Peds study

ASCEND-Peds	Olipudase alfa (N=20)
Number of infusions received	
Number of patients with value	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Patients not achieved the target dose of 3mg/kg on olipudase alfa, n(%)	0

Abbreviations: SD, standard deviation

Please see below a summary of concomitant medications in ASCEND PAP-mITT population.

Please see below a summary of concomitant medications in ASCEND PAP-mITT population.

Table 3: Summary of concomitant medications in ASCEND PAP-mITT

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Nervous System, n(%)	[redacted]	[redacted]
Analgesics	[redacted]	[redacted]
Psycholeptics	[redacted]	[redacted]
Anesthetics	[redacted]	[redacted]
Antiepileptics	[redacted]	[redacted]
Psychoanaleptics	[redacted]	[redacted]
Alimentary tract and metabolism, n(%)	[redacted]	[redacted]
Stomatological preparations	[redacted]	[redacted]
Mineral supplements	[redacted]	[redacted]
Vitamins	[redacted]	[redacted]
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	[redacted]	[redacted]
Antiemetics and antinauseants	[redacted]	[redacted]
Drugs for constipation	[redacted]	[redacted]
Other alimentary tract and metabolism products	[redacted]	[redacted]
Drugs for acid related disorders	[redacted]	[redacted]
Drugs for functional gastrointestinal disorders	[redacted]	[redacted]

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Antiobesity preparations, excl. diet products	[redacted]	[redacted]
Bile and liver therapy	[redacted]	[redacted]
Cardiovascular system, n(%)	[redacted]	[redacted]
Cardiac therapy	[redacted]	[redacted]
Lipid modifying agents	[redacted]	[redacted]
Agents acting on the renin-angiotensin system	[redacted]	[redacted]
Calcium channel blockers	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]
Vasoprotectives	[redacted]	[redacted]
Antihypertensives	[redacted]	[redacted]
Beta blocking agents	[redacted]	[redacted]
Dermatologicals, n (%)	[redacted]	[redacted]
Antipruritics, incl. antihistamines, anesthetics, etc.	[redacted]	[redacted]
Anti-acne preparation	[redacted]	[redacted]
Antibiotics and chemotherapeutics for dermatological use	[redacted]	[redacted]
Antifungals for dermatological use	[redacted]	[redacted]
Emollients and protectives	[redacted]	[redacted]
Other dermatological preparations	[redacted]	[redacted]
Respiratory system, n (%)	[redacted]	[redacted]
Cough and cold preparations	[redacted]	[redacted]
Antihistamines for systemic use	[redacted]	[redacted]
Nasal preparations	[redacted]	[redacted]
Drugs for obstructive airway diseases	[redacted]	[redacted]
Antiinfectives for systemic use, n (%)	[redacted]	[redacted]

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Antibacterials for systemic use	[redacted]	[redacted]
Vaccines	[redacted]	[redacted]
Antivirals for systemic use	[redacted]	[redacted]
Blood and blood forming organs, n (%)	[redacted]	[redacted]
Antihemorrhagics	[redacted]	[redacted]
Antianemic preparations	[redacted]	[redacted]
Blood substitutes and perfusion solutions	[redacted]	[redacted]
Antithrombotic agents	[redacted]	[redacted]
Musculo-skeletal system, n(%)	[redacted]	[redacted]
Antiinflammatory and antirheumatic products	[redacted]	[redacted]
Muscle relaxant	[redacted]	[redacted]
Drugs for treatment of bone diseases	[redacted]	[redacted]
Topical products for joint and muscular pain	[redacted]	[redacted]
Various, n (%)	[redacted]	[redacted]
All other therapeutic products	[redacted]	[redacted]
Allergens	[redacted]	[redacted]
Unspecified herbal and traditional medicine	[redacted]	[redacted]
Contrast media	[redacted]	[redacted]
General nutrients	[redacted]	[redacted]
Antiparasitic products, insecticides and repellents, n (%)	[redacted]	[redacted]
Anthelmintics	[redacted]	[redacted]
Genito urinary system and sex hormones, n (%)	[redacted]	[redacted]

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Sex hormones and modulators of the genital system	[redacted]	[redacted]
Sensory organs, n (%)	[redacted]	[redacted]
Ophthalmologicals	[redacted]	[redacted]
Systemic hormonal preparations, excl. sex hormones and insulins, n (%)	[redacted]	[redacted]
Thyroid therapy	[redacted]	[redacted]
Corticosteroids for systemic use	[redacted]	[redacted]

Abbreviations: n, number; mITT, modified intention to treat; PAP, primary analysis period.

Please see below summary of concomitant medications in ASCEND-Peds safety population.

Table 4: Summary of concomitant medications in ASCEND-Peds safety population

ASCEND-Peds	Olipudase alfa (N=20)
Summary of concomitant medications – Safety Populations	
Respiratory system, n (%)	[redacted]
Antihistamines for systemic use	[redacted]
Nasal preparations	[redacted]
Cough and cold preparations	[redacted]
Drugs for obstructive airway diseases	[redacted]
Other respiratory system products	[redacted]
Throat preparations	[redacted]
Nervous system, n (%)	[redacted]
Analgesics	[redacted]
Anesthetics	[redacted]
Psycholeptics	[redacted]
Other nervous system drugs	[redacted]
Antiinfectives for systemic use, n (%)	[redacted]
Vitmains	[redacted]
Antiemetics and antinauseants	[redacted]

ASCEND-Peds	Olipudase alfa (N=20)
Summary of concomitant medications – Safety Populations	
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	[redacted]
Mineral supplements	[redacted]
Drugs for constipation	[redacted]
Drugs for functional gastrointestinal disorders	[redacted]
Stomatological preparations	[redacted]
Musculo-skeletal system, n (%)	[redacted]
Antiinflammatory and antirheumatic products	[redacted]
Muscle relaxants	[redacted]
Topical products for joint and muscular pain	[redacted]
Dermatologicals, n (%)	[redacted]
Antibiotics and chemotherapeutics for dermatological use	[redacted]
Emollients and protectives	[redacted]
Corticosteroids, dermatological preparations	[redacted]
Antifungals for dermatological use	[redacted]
Antipruritics, incl. antihistamines, anesthetics, etc.	[redacted]
Medicated dressings	[redacted]
Other dermatological preparations	[redacted]
Preparations for treatment of wounds and ulcers	[redacted]
Blood and blood forming organs, n (%)	[redacted]
Antianemic preparations	[redacted]
Blood substitutes and perfusion solutions	[redacted]
Antithrombotic agents	[redacted]
Various, n (%)	[redacted]
Unspecified herbal and traditional medicine	[redacted]
All other therapeutic products	[redacted]
Homeopathic preparation	[redacted]

ASCEND-Peds	Olipudase alfa (N=20)
Summary of concomitant medications – Safety Populations	
Cardiovascular system, n (%)	[redacted]
Lipid modifying agents	[redacted]
Cardiac therapy	[redacted]
Vasoprotectives	[redacted]
Sensory organs, n (%)	[redacted]
Ophthalmologicals	[redacted]
Otologicals	[redacted]
Ophthalmological and otological preparations	[redacted]
Systemic hormonal preparations, excl. sex hormones and insulins, n (%)	[redacted]
Corticosteroids for systemic use	[redacted]
Thyroid therapy	[redacted]
Antiparasitic products, insecticides and repellents, n (%)	[redacted]
Anthelmintics	[redacted]
Antineoplastic and immunomodulating agents, n (%)	[redacted]
Immunostimulants	[redacted]
Genito urinary system and sex hormones, n (%)	[redacted]
Sex hormones and modulators of the genital system	[redacted]

Abbreviations: n, number

A18. Please confirm the number of participants available at reported follow-up timepoints in the extension period of ASCEND, and can you explain why sample size varies across outcome for the same time point?

The number of participants available at reported follow-up timepoints in the extension period of ASCEND are presented in Table 6.

Table 5: Number of participants available at follow-up timepoints in the extension period - ASCEND

Outcome	Follow-up timepoint	Number of participants available	
		Placebo/olipudase alfa	Olipudase alfa/olipudase alfa
% predicted DL_{CO}	Year 1	17	17
	Year 2	10	10
Spleen volume (MN)	Year 1	17	18
	Year 2	11	14
Liver volume (MN)	Year 1	17	17
	Year 2	11	14
Platelet count (10^9/L)	Year 1	16	18
	Year 2	15	13
Lung HRCT ground glass appearance score	Year 1	17	18
	Year 2	14	16
ALT (IU/L)	Year 1	16	18
	Year 2	15	12
HDL cholesterol (mg/dL)	Year 1	16	18
	Year 2	14	12
LDL cholesterol (mg/dL)	Year 1	15	18
	Year 2	14	12

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; MN, multiples of normal
Source: Villarubia et al, 2022 (8)

For the same visit (timepoint) the assessments (such as MRI or PFT) could be scheduled during a 7 day window from the visit date and could be performed separately of the infusion. For some reasons, patients could miss one assessment and perform the other for a given visit. Some assessments performed at a given visit were not included in the database due to technical reasons (assessments partially done or not readable).

A19. Please report descriptive statistics for the length of follow-up available in the included trials.

Please see below data on the duration of study treatment in ASCEND and ASCEND-Peds (Table 7 and Table 8, respectively). The duration of exposure is defined as the number of weeks between first infusion and disposition dates (i.e. end of study).

Table 6: Duration of study treatment - ASCEND

ASCEND	Placebo (N=18)	Olipudase alfa (N=18)
Duration (weeks) on study treatment in PAP		
Number of patients with value	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]

Abbreviations: PAP, primary analysis plan; SD, standard deviation

Table 7: Duration of study treatment – ASCEND-Peds

ASCEND-Peds	Olipudase alfa (N=20)
Duration (weeks) on study treatment	
Number of patients with value	[redacted]
Mean (SD)	[redacted]
Median	[redacted]

Abbreviations: SD, standard deviation

A20. For clarity, can you please confirm whether any data points reported in the CS or used in the model were derived from analysis sets other than the mITT set (for clinical data) or safety set (for safety data)?

In the economic model, no other analysis sets than the mITT or safety set from the clinical trials were used.

- The EAG understands that the mITT and safety populations are the same, since no participant received a treatment other than the treatment they were allocated to receive. Can you please confirm this is the case?

In ASCEND and ASCEND-Peds, mITT and safety populations are indeed the same. In study DFI13412 no mITT population was defined.

Clinical outcomes reported for trials of olipudase alfa

A21. A number of clinical data points are provided without accompanying variance data (i.e. SD, SE or 95% Cis). Moreover, several clinical data points are described in text without accompanying data (e.g. “significant improvement in exercise capacity” CS Doc B, p. 93). Please provide missing data points and variance data for all

clinical outcomes reported in the CS. Please ensure that baseline data for all reported outcomes are also reported as these are missing for some outcomes/trials.

Further data on the exploratory endpoints listed on page 93 of the company submission (liver function, lipid profiles, pulmonary function, and efficacy biomarkers (ACE, CCL18, and chitotriosidase) are provided in Appendix N.6. LS mean change from baseline and p-values for treadmill ergometry are provided in Table 26 of the company submission. However, additional data for treadmill ergometry including baseline mean (SD), LS mean change from baseline (SE), and 95% CIs are provided in Table 9.

Table 8: Treadmill ergometry (exercise capacity) – ASCEND PAP mITT population

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
O_2 uptake (mL/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 52	LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Calculate percent predicted O_2 uptake (%)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 52	LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Calculated maximal O_2 uptake (mL/min/kg)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 52	LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; O_2, oxygen; SD, standard deviation; SE, standard error.
† The 95% CI and p-values are based on a mixed model repeated measures approach with baseline test, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates

A22. In the CS Section B2.11.3 it is stated that the additional endpoints measured in LTS13632 are reported in Appendix O, however not all these data points are reported. Please provide complete data for missing endpoints.

Please see Table 10, Table 11, and Table 12 for the requested additional endpoints measured in LTS13632 as reported in Appendix O in the company submission (pulmonary function tests, fasting lipid profile, and exercise tolerance, respectively).

Table 9: Summary of pulmonary function tests in LTS13632 safety population

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
Pulmonary function tests					
% Change in FEV1 (% predicted)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 78 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]
% Change in FVC (% predicted)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 78 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
% Change in TLC (% predicted)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 78 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; dl, decilitre; FEV1, forced expiratory volume; FVC, forced vital capacity; mg, milligram; LS, least squares; SD, standard deviation; SE, standard error; TLC, total lung capacity.
† From ANCOVA model: change (or percentage change) from baseline = age group cohorts + baseline value. P-value is for the age effect
‡ From Wilcoxon-Signed Rank test

Table 10: Summary of fasting lipid profile in LTS13632 safety population

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
Lipid profile					
Total cholesterol (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]
HDL cholesterol (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
LDL cholesterol (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]
Triglycerides (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; dl, decilitre; HDL, high density lipoprotein; LDL, low density lipoprotein; LS, least squares; mg, milligram; SD, standard deviation; SE, standard error
† From ANCOVA model: change (or percentage change) from baseline value. P-value is testing of change or percentage change from baseline is different from zero.
‡ From Wilcoxon-Signed Rank test

Table 11: Summary of exercise tolerance measured by cycle ergometry in LTS13632 safety population

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
Cycle ergometry (exercise capacity)					
Workload	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Percent predicted maximum workload	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 36 (%	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
	change from baseline)	95% CI†	[redacted]	[redacted]	[redacted]
Working time (min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum heart rate (breaths/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum percent predicted heart rate (%)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum O_2 saturation (%)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum respiratory rate (breaths/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum ventilation (L/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum O_2 uptake (mL/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
	from baseline)	95% CI†	[redacted]	[redacted]	[redacted]
Maximum percent predicted O_2 saturation (%)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum CO_2 output (mL/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum respiratory exchange ratio	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]

Abbreviations: CO_2, carbon dioxide; CI, confidence interval; dl, decilitre; L, litre; ml, millilitre; O_2, oxygen; SD, standard deviation
† Based on regression of change from baseline with baseline value as covariate

A23. Data points for outcomes in LTS13632 are reported at different timepoints and the rationale for this is unclear. For example, for spleen volume the CS states that follow-up in paediatric participants is available at 66 months but the data point is provided for month 48 (p. 150). Please can you:

- Clarify if a rule was used to select timepoints reported in the CS

As patients entered the LTS13632 study at different times, the timepoint chosen for analysis was the latest assessment with at least 5 patients (adults and paediatrics separately), which was the number of patients deemed necessary for a meaningful analysis. For most outcome measures this timepoint was Month 78 in adult patients and Month 48 in paediatric patients. In a few cases, an earlier timepoint was used to obtain the minimum of 5 patients for analysis.

- Clarify the length of follow-up available for adult and paediatric participants for each outcome of LTS13632, including the available sample size.

The length of follow-up available for adult and paediatric participants for each outcome of LTS13632 are as follows:

Table 12: Length of follow-up for reported outcomes in LTS13632

Outcome	Population	Length of follow-up reported in CS (available sample size)	Maximum length of follow-up recorded (available sample size)
Spleen volume	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]
Platelet count	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]
Liver volume	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]
% predicted DL_{CO}	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide

- Please include outcomes at final available follow-up in your response to clarification question A21

The outcomes at final available follow-up have been provided by the company in response to question A21.

- On p.169 of the CS it is stated that data up to 9-years is available from LTS13632 to inform transition probabilities in the model. Can you please explain this assertion?

Data up to 9 years is available from LTS13632, however, patients receiving olipudase alfa can only transition to a new health state for up to 2 years.

A24. Please can you confirm whether a responder analysis was conducted for data gathered within the ASCEND extension period, and report these data if so?

As per the statistical analysis plan, responder analyses were carried out exclusively for the PAP.

A25. The CS states that all subgroup analyses conducted were post hoc. Please provide a rationale for the selection of subgrouping categories, including a rationale for why these were selected over other prognostic markers (e.g. those identified in Eskes 2020) or demographic markers such as age of onset/diagnosis and type B vs. type A/B.

These subgroup analyses were requested by the FDA who did not provide a rationale for the populations that they requested.

A26. The HRQoL results show that treatment results in a benefit for generic HRQoL in paediatric but not adult participants treated with olipudase alfa. In the CS, it is suggested that generic HRQoL measures in adults may be insensitive to change in HRQoL for people with ASMD. Do you have a rationale for why this may be different in the adult vs. the paediatric populations?

The concerns around the sensitivity of HRQoL measures apply to both adult and paediatric populations. The paediatric trial did not have a control arm, preventing evaluation of the treatment related benefit on quality of life.

Section B: Clarification on cost-effectiveness data

Cost-effectiveness evidence

B1. PRIORITY QUESTION. The CS contains deterministic ICERs only. Please provide the probabilistic ICERs for the paediatric, adult and overall populations. It would be helpful if you could present these in a table outlining incremental, costs, LYs and QALYs.

The company have run an additional probabilistic analysis to provide the requested data as shown in Table 14.

Table 13: Base-case (probabilistic) results

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/QALY)	ICER (£/Weighted QALY
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Weighted QALYs		
Paediatric	Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	318,668	107,079
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Adult	Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	467,695	213,062
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Combined	Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	376,800	141,049
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B2. Can you please confirm that the cost effectiveness results reported in Tables 72, 75 and 76 of the CS include the PAS discount for olipudase alfa?

This is correct – the company can confirm that the data shown in Tables 72, 75 and 76 of the submission includes the PAS discount for olipudase alfa.

B3. Please provide additional justification for your decision to conduct a subgroup analysis in the severe population.

Patients with severe disease have the poorest prognosis and are likely to benefit most from treatment with olipudase alfa. They would therefore be expected to have differential cost-effectiveness.

B4. PRIORITY QUESTION. For the severe subgroup, it would be helpful if you could outline what clinical data were used to inform transition probabilities for the paediatric and adult populations and provide clarity on how these were derived.

The data sources and derived transition probabilities applied to the severe subgroup are the same as those considered for the overall population, with the exception of the mortality data used. A pragmatic approach to modelling a severe subgroup was taken whereby the distribution of patients across health states at model entry was modified to represent a more severe population. In addition data from McGovern et al 2013 (9) was used to inform mortality as this was thought to better reflect mortality for the most severe patients. As discussed in the CS the use of SPHINGO-100 data likely underestimates the impact of ASMD on mortality. This is in line with the clinical advice received during an advisory board and from subsequent communications with a clinical expert. This is now being further investigated (10), with initial results suggesting higher mortality in ASMD patients than that derived from SPHINGO-100.

B5. PRIORITY QUESTION. In the CS, the time horizon is stated to be lifetime (100 years), however in the economic model the time horizon is set to 20 years. Can you confirm that the base case cost effectiveness results are estimated using a 20-year time horizon?

This is an error in the model provided – the data from the base case were generated using a lifetime horizon. A corrected version of the model has been provided.

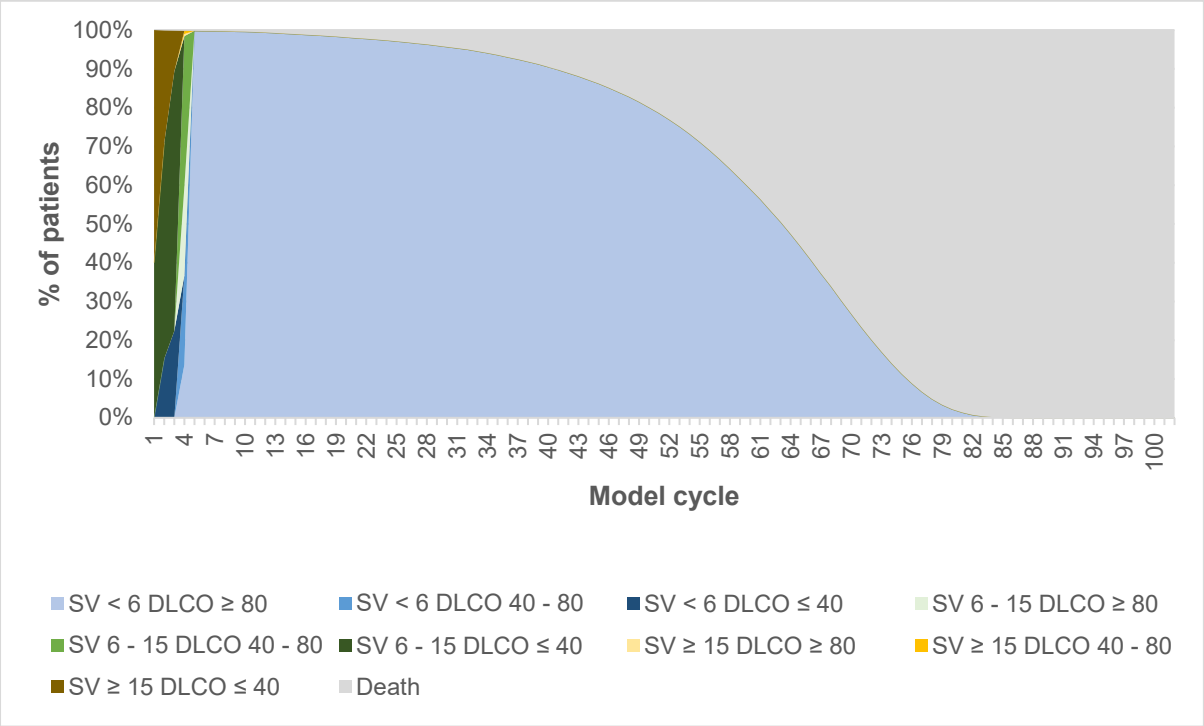
B6. PRIORITY QUESTION. Please provide additional justification for the model assumption for the clinical efficacy of olipudase alfa after year 2, i.e. that patients receiving olipudase alfa only transition to a new health state for up to 2 years, after which they transition to the SV <6 / DLCO >80 state until the end of the time horizon or death.

In the olipudase arm for the first two years patients transition between health states in line with the clinical trial data (11, 12); beyond two years an assumption is made. The assumption that patients transition to the SV <6 /DL_{CO} >80 state is made on the basis that longer term data indicate that patients continue to improve on olipudase alfa and that this is in line with clinical opinion that there would be continued improvement (13).

B7. PRIORITY QUESTION. Please provide additional granularity with respect to the incremental QALY gain (and cost) associated with olipudase alfa, i.e., for the paediatric, adult and overall populations it would be helpful to see a QALY and cost breakdown by health state. Additionally, for each patient population please provide a graphical chart outlining cohort distribution by health state.

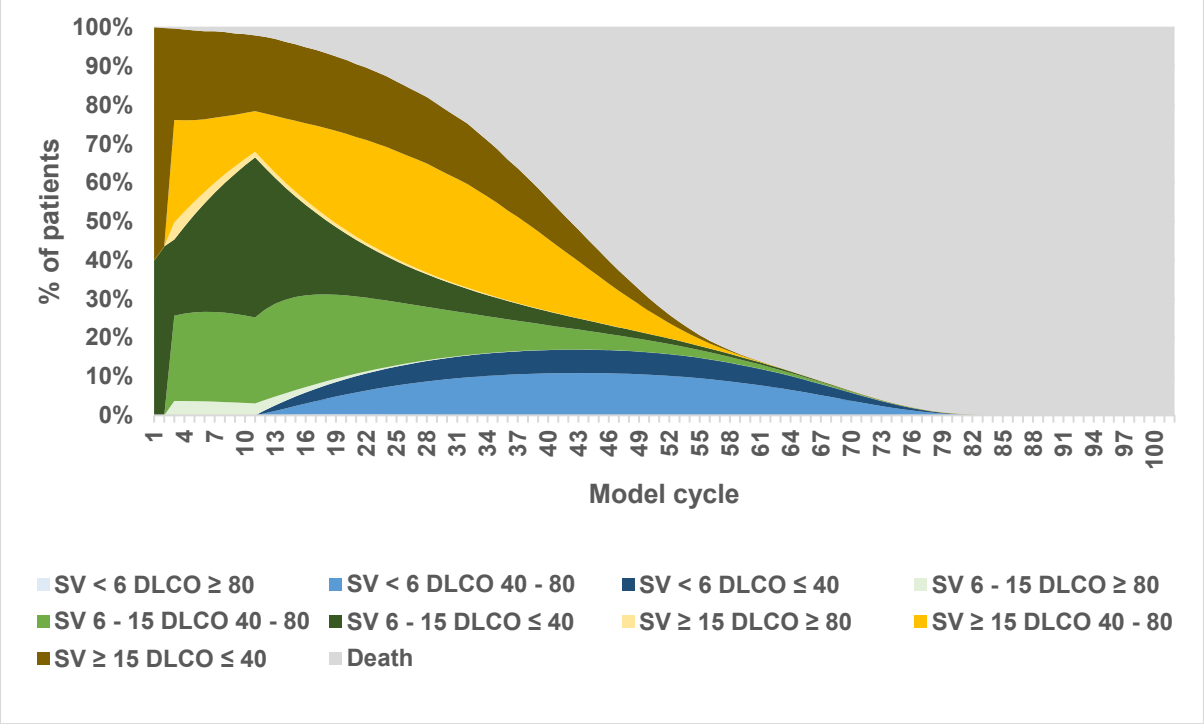
The disaggregated model outputs requested can be found in Tables 93 to Table 96 in Appendix J. Graphical charts outlining the cohort distribution by health state are provided for patients receiving olipudase alfa and BSC in Figure 2 and Figure 3, respectively.

Figure 2: State occupancy in patients receiving olipudase alfa



Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; SV, spleen volume

Figure 3: State occupancy in patients receiving BSC alone



Abbreviations: DLCO, diffusing capacity for carbon monoxide; SV, spleen volume

B8. In the CS, results for only six scenario analyses were presented (see p.224). Please clearly list all the scenario analyses that were undertaken and provide a rationale for the decision not to report the findings of other analyses in the CS.

All scenarios that were run have been presented in the submission, with no exclusion of scenarios; the model contains additional functionality that was not needed to run these scenarios.

B9. PRIORITY QUESTION. It would be helpful if you could clarify what is meant by 'compliance' in the model (p.210). Is this analogous to relative dose intensity? For instance, does 90% compliance mean that the drug cost for olipudase alfa is based on 90% of the total annual dose.

Compliance is used as a universal term that encompasses missed doses/administrations, alternate doses and so forth – so it is not exactly analogous to dose intensity and instead represents the likely real-world scenario where a proportion less than 100% of the prescribed and scheduled doses are administered.

We confirm the interpretation provided is correct - the compliance percentage is applied to the number of doses received (and thus proportionally to the acquisition and administration costs).

B10. Please provide additional justification for opting to define health states via a combination of spleen volume and lung diffusion of carbon dioxide. Why were other clinical outcomes, particularly those pertaining to the liver, not considered?

In a study designed to identify efficacy endpoints for clinical trials of enzyme replacement therapy, it was observed that SV is correlated with most aspects of disease progression (14). In particular, SV was significantly and strongly correlated with liver volume and negatively correlated with HDL, height z-scores, hemoglobin, and white blood cell count. Nonetheless, SV was weakly correlated with various pulmonary measures, including HRCT ILD score and percentage of predicted DLco. Therefore, defining health states via SV and DLco allows the model to encompass most aspects of disease progression. SV and DLco were the primary endpoints in the ASCEND trial.

Liver outcomes are considered in the model in two ways:

1. By capturing the benefit of olipudase alfa on liver complications through the FIB-4 scores derived from ASCEND liver function tests results

2. By capturing the HRQoL impact of organomegaly (liver volume and spleen volume) within the elicitation of utilities carried out in the ASMD vignette study.

B11. Mortality (standardised mortality ratios), were modelled based the presence or absence of severe splenomegaly. Please outline why severe splenomegaly was selected as the key determinant of mortality in the model.

The only available longitudinal study presenting both survival and clinical endpoint data was the prospective natural history study SPHINGO-100. All available clinical parameters were tested as potential predictors of survival, defined as the time from the date of birth to the date of last visit or death. The only parameter that presented a statistically significantly association with survival was severe splenomegaly as defined using the published threshold of 15 multiples of normal (15).

Clinical experts within an advisory board validated this parameter as indicative of ASMD severity and thus used in the model (6).

B12. Please provide justification for the weight applied to the QALYs for the base case analyses for the paediatric, adult and combined populations, referring to sections 6.2.23 to 6.2.25 of NICE health technology evaluations: the manual (2022).

The weighting applied to the QALYs for the base case analyses is in line with the Guidance provided by NICE– in that undiscounted QALY gains between 11 and 30 are multiplied by a proportional weighting between 1 and 3, and QALY gains above 30 are multiplied by a capped weighting of 3. There is compelling evidence that olipudase alfa offers significant QALY gains, with discounted QALY gains of 24.95 in paediatric patients and 16.44 in adult patients despite likely conservative assumptions regarding mortality and patient and family/carer utilities.

Economic model

B13. PRIORITY QUESTION. Please can you clarify the compliance rate used in the model for both the paediatric and adult populations? On p.210 of the CS it

is stated that a compliance rate of 90% is used, however in the 'Treatment costs' tab in the model, it appears that a 95% compliance rate has been used for paediatric patients and 90% has been used for adults.

There is an error in the model provided – the data from the base case were generated using a compliance rate of 90%. A corrected version of the model has been provided.

B14. Can you please confirm that zero drug wastage is assumed in the economic analysis, i.e. that clinicians will be expected to share vials between patients?

According to clinical experts from three different centres (personal communication: [redacted] enzyme replacement therapy doses are routinely rounded up or down to the nearest vial. The same practice was seen in a survey carried out for Pompe disease across all treatment centres and accepted as an appropriate input for the economic analysis in TA821. Vial rounding is therefore expected to be the routine practice in England. As the economic analysis is based on a cohort model, variation in patients' weight, and therefore the number of vials required, is not captured and when the number of vials can be rounded up or down an average number of vials is more appropriate.

B15. Could you please explain why there is a discrepancy between the ICERs reported for the paediatric and combined patient populations on p.213 of the CS, and the ICERs reported in the 'Base case results' tab of the model (see cells J:77 AND I:77).

This is an error in the model, the base case analysis had not been fully run before provision. A corrected version has been provided.

B16. In the 'Base case results' tab of the Base case CEM, please outline which population the ICER in cell F:77 refers to.

The model must be run for adults and children separately – as such the model is run for each in sequence and results/outputs stored in the tables on the right of the worksheet to calculate the weighted average. The values in F77 (and others in that

column) are those representing the last analysis run (adults or children, and by subgroup).

B17. In the 'Scenarios' tab of the Base case CEM, parameter inputs are not appropriately labelled and results have not been provided (for either the adult or the paediatric population). Please amend as appropriate and provide results for all scenarios for both the adult and paediatric populations. Furthermore, for each scenario analysis please provide incremental results.

Given the nature of the model (running child and adult populations separately) the scenarios were run manually rather than via this worksheet/table (as such the table is not informative). The relevant granular results for scenarios are provided in Table 15.

Table 14: Scenario analysis results by patient population

Scenario	Population	Incremental (olipudase alfa vs BSC)			ICER per QALY (£) versus BSC (unweighted)	ICER per QALY (£) versus BSC (weighted)
		Costs (£)	LYG	QALYs		
1.5% discount rate for costs in paediatric cohort	Combined	[redacted]	[redacted]	[redacted]	482,188	178,589
	Adult	[redacted]	[redacted]	[redacted]	436,237	170,818
	Paediatric	[redacted]	[redacted]	[redacted]	512,453	194,360
1.5% discount rate for costs in adult cohort	Combined	[redacted]	[redacted]	[redacted]	421,667	156,174
	Adult	[redacted]	[redacted]	[redacted]	591,690	263,621
	Paediatric	[redacted]	[redacted]	[redacted]	309,681	103,227
1.5% discount rate for costs in paediatric and adult cohort	Combined	[redacted]	[redacted]	[redacted]	543,918	201,453
	Adult	[redacted]	[redacted]	[redacted]	591,690	236,621
	Paediatric	[redacted]	[redacted]	[redacted]	512,453	170,818
Mortality modelled through parametric fit of data from McGovern et al. (2013) (9)	Combined	[redacted]	[redacted]	[redacted]	254,363	90,892
	Adult	[redacted]	[redacted]	[redacted]	434,557	190,245
	Paediatric	[redacted]	[redacted]	[redacted]	183,779	61,260
Discontinuation at 80 weeks of 5.56% (zero thereafter)	Combined	[redacted]	[redacted]	[redacted]	396,615	158,463
	Adult	[redacted]	[redacted]	[redacted]	345,905	264,795
	Paediatric	[redacted]	[redacted]	[redacted]	470,629	115,302
Patient compliance increased to 95%	Combined	[redacted]	[redacted]	[redacted]	379,930	139,928
	Adult	[redacted]	[redacted]	[redacted]	323,357	205,156
	Paediatric	[redacted]	[redacted]	[redacted]	460,467	107,786

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Section C: Textual clarification and additional points

C1. Please provide a reference list for the Appendices document.

The references for the appendices document have now been updated and a new version provided which includes the reference list. Reference documents have been previously provided in the original reference pack as part of the company submission.

C2. Table 83 in Appendix M is confusing as several columns do not align with the column headers. Can you please re-submit this table with correct formatting so that the selection criteria for each of the SLR aims is clear?

The selection criteria for each of the SLR aims is provided in Table 84 in Appendix D as opposed to Appendix M. Please find the amended Table 84 below as provided in the company submission.

Table 15: Study selection criteria

Domain	SLR 1. Clinical	SLR 2. Economic Evaluations	SLR 3. Economic Burden	SLR 4. Humanistic Burden	SLR 5. Natural History and Prevalence	SLR 6. Treatment Patterns
Population	Adults and children with a diagnosis of chronic forms of ASMD (i.e., chronic visceral / NPD type B or chronic neurovisceral NPD type A/B); Studies of mixed population of which 80% are of interest					
	Exclude: Non-human subjects, studies on other indications (e.g., infantile neurovisceral ASMD / NPD type A, and NPD type C); mixed populations for which the proportion of patients with chronic forms of ASMD cannot be ascertained.					
Interventions/ Comparators*	Any medical intervention treating the disease or symptoms of chronic forms of ASMD		Any medical intervention treating the disease or symptoms of chronic forms of ASMD, or studies not evaluating specific interventions		Studies not evaluating specific interventions	Any medical interventions treating the disease or symptoms of chronic forms of ASMD
	Exclude: Non-medical interventions, studies not evaluating specific interventions		Exclude: Non-medical interventions		Exclude: Studies evaluating specific interventions	Exclude: Non-medical interventions, studies not evaluating specific interventions

Domain	SLR 1. Clinical	SLR 2. Economic Evaluations	SLR 3. Economic Burden	SLR 4. Humanistic Burden	SLR 5. Natural History and Prevalence	SLR 6. Treatment Patterns
Outcomes	Efficacy: Changes in liver volume Platelet count Spleen volume DL_{CO} Pulmonary function tests Lipid values Safety: AEs Discontinuation rates Deaths	Cost-effectiveness measures: Cost per QALY ICERs Budget impact	Resource use Direct costs Indirect costs (including productivity impacts on patients and caregivers) Resource-specific costs	Validated QoL measures for patients and caregivers, including but not limited to: EQ-5D SF-36 BPI BFI FACIT-dyspnea Utility and disutility values	Mortality Drivers of mortality Complications: Respiratory Splenic Hepatic CVD Major bleeding Breathlessness Fatigue Joint pain Abdominal pain Neurological symptoms Haemoglobin level Liver biochemistry Comorbidities Lipid values Bone mineral density Impact on paediatric growth Prevalence	Current treatment pathways Drivers of treatment choice
Study Design**	Clinical trials, longitudinal studies	Economic evaluations and budget impact models	Clinical trials, observational studies		Observational studies	Observational studies, clinical practice guidelines

Domain	SLR 1. Clinical	SLR 2. Economic Evaluations	SLR 3. Economic Burden	SLR 4. Humanistic Burden	SLR 5. Natural History and Prevalence	SLR 6. Treatment Patterns
	Exclude: Case reports, preclinical studies, non-systematic reviews, commentary, and letters				Exclude: Clinical trials, case reports, preclinical studies, non-systematic reviews, commentary, and letters	
Sample Size	At least 5 patients with chronic forms of ASMD					
Other	English-language					

* “Medical interventions” may include enzyme replacement therapy, surgery, transplantation, pharmacologic treatments, oxygen supplementation; “Non-medical interventions" include approaches such as lifestyle modification, vitamin supplementation, physical exercise, educational progammes.
** “Clinical trials” include both randomized and single-arm designs; “Observational studies” include prospective, retrospective, and cross-sectional designs, such as claims database analyses, medical record reviews, surveys, registry analyses, and case series; “Economic evaluations” include cost-utility models, cost-benefit analyses, and other cost-effectiveness analyses.
▪ Sample size criteria will not apply to prevalence studies.
Abbreviations: AE, adverse event; ASMD, acid sphingomyelinase deficiency; BFI, Brief Fatigue Inventory; BPI, Brief Pain Inventory; CVD, cardiovascular disease; DL_{CO}, lung diffusion of carbon monoxide; EQ-5D(-5L), EuroQoL Five Dimensions (Five Levels); FACIT, Functional Assessment of the Chronic Illness Therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life; SF-36, 36-item Short Form health survey; SLR, systematic literature review

C3. PRIORITY QUESTION. Tables containing efficacy data from the trial CSRs have not been provided in the reference pack. Can you please provide all CSR appendices?

Efficacy data from trial CSRs, as listed below, have now been added to the updated reference pack provided.

- DFI12712 (ASCEND). CSR. 16.2.6. efficacy response data (16)
- DFI13803 (ASCEND-Peds) CSR. 16.2.6. efficacy response data (17)
- DFI13412. CSR. 16.2.6. efficacy response data (18)
- LTS13632. CSR. 16.2.6. efficacy response data (19)

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NICE National Institute for Health and Care Excellence

Frequently asked questions about NICE's technology appraisal and highly specialised technologies appeals

Whether you are interested in lodging an appeal or preparing for an appeal hearing, we have produced these frequently asked questions (FAQ) document to help. Throughout these FAQs, there are links to our appeals process guide and website for more detailed information.

Contents

Submitting an appeal

What is an appeal?

An appeal is a letter from a stakeholder organisation (a 'consultee') participating in the technology appraisal (TA) or highly specialised technologies (HST) process challenging NICE's proposed recommendations.

The appeal can only be on one or more of the two strictly limited grounds which are set out in legislation. Appeals on any other ground cannot be considered. Appeals will not be accepted simply because the consultee disagrees with the views or conclusions in the final draft guidance.

The grounds of appeal are:

Ground 1: In making the assessment that preceded the recommendation, NICE has:

a) failed to act fairly

b) exceeded its powers

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

An appeal is not an opportunity to consider new evidence or information that was not presented to the advisory committee or reopen arguments and issues that the advisory committee has decided on.

Further information on the grounds of appeal can be found in the Guide to the technology appraisal and highly specialised technologies appeal process.

Who can submit an appeal?

Only stakeholder organisations called 'consultees' that have agreed to participate in the appraisal development process and signed a confidentiality agreement have the opportunity to appeal against the recommendations in the TA/HST final draft guidance. This can include patient/carer organisations, healthcare professional bodies, and companies. The appeal must be submitted within 15 working days from the release of the final draft guidance. A consultee is referred to as an appellant once an appeal is received.

How do I submit an appeal?

To submit an appeal we ask you use the appeal letter template which is sent to you when you received the final draft guidance.

The appeal letter must contain the following information.

- the ground(s) for appeal

- the aspect(s) of the final draft guidance or evaluation process being appealed against
- the reasons why the aspect(s) of the final draft guidance or evaluation process being appealed against fall within the specified ground(s) of appeal, in enough detail to demonstrate an arguable case
- a brief summary (no more than 100 words) of each appeal point, which can be cut and pasted into a summary document and shared with other appellants
- the concluding statement indicating whether the appellant wishes to be heard at an oral or written appeal

See section 4.5 of the appeals process guide.

You must submit your appeal by 5pm to appeals@nice.org.uk by the deadline date given in the notification email when the final draft guidance is issued to stakeholders. **Please do not upload your appeal to NICE Docs**.

What does 'unfairness' and 'unreasonableness' mean?

Appeals lodged under 'Ground 1(a) NICE has acted unfairly' means that the appellant believes that they have not been treated fairly by NICE or the advisory committee because the published process has not been followed. This ground relates only to the fairness of the process followed and not to the content of the final draft guidance. This ground of appeal does not cover unfairness in the colloquial sense, for instance that it is 'unfair' to patients not to provide a treatment.

Appeals lodged under 'Ground 2 The recommendation is unreasonable in light of the evidence submitted to NICE' means that the appellant believes that the guidance is obviously and unarguably wrong, illogical, or so absurd that a reasonable advisory committee could not have reached such conclusions. Appeals on this ground would also argue that the recommendations in the final draft guidance cannot reasonably be justified from the evidence presented to the committee.

Who decides whether an appeal submission is valid?

The lead non-executive director for appeals is responsible for undertaking an initial review of the submitted appeal letters and will decide if an appeal should proceed to either an oral appeal hearing or written appeal (all communication is done through an exchange of letters). The lead non-executive director for appeals may also decide to reject the appeal if the points presented do not meet one or more of the grounds of appeal, and in doing so, may take legal advice.

The appeal letter goes through a process of initial and then final scrutiny by the lead non-executive director for appeals, where the appeal points are carefully considered. During the scrutiny stage the appellant(s) are given one opportunity to provide

clarification on any appeal points the lead non-executive director for appeals has requested before he or she makes a final decision. This process is undertaken formally in writing.

Please note that copies of your appeal letter(s), the scrutiny letters from the lead non-executive director for appeals and your responses to these letters will be made available on the day of the appeal to the general public attending and will also be published on the NICE website. Therefore, you should ensure that if your appeal contains commercial in confidence or academic in confidence information that the information is clearly labelled or that you submit a second version of your appeal with the commercial in confidence or academic in confidence information removed. We also recommend that appeal letters are sent electronically on headed paper.

When will I hear about my appeal?

We will send you confirmation of receipt of your appeal.

The lead non-executive director for appeals will write to you, usually within 5 working days with their initial views. This is called the initial scrutiny letter.

If you are requested to give more information, you will be given 10 days to submit your response letter.

The lead non-executive director for appeals will respond to your response letter within 5 days of the given deadline. This is called the final scrutiny letter.

Are all valid appeal submissions heard in public?

The default is that appeals are held in public, however there are occasions when an oral appeal hearing is not required. In some cases, the appellant may request the appeal proceed as a written appeal. For written appeals, all communication with the appellant and NICE/advisory committee representatives is fulfilled through an exchange of letters, and the appeal is considered by an appeal panel at a private meeting where no appellants, advisory committee members, NICE staff, press or public are in attendance. There are also cases where an appeal can be rejected, where appeal points do not meet one or more of the grounds of appeal; or an appeal is cancelled, when NICE withdraws the final draft guidance or an appellant withdraws their appeal.

Occasionally an appellant may wish to make statements that involve disclosing confidential information. These requests are considered by the appeal panel in advance of the appeal hearing. If the appeal panel agrees, then the relevant appeal points will be heard in private (that is, in the absence of the other appellants, the public and the press). The appeal panel will only allow a statement to be made in private if it is satisfied that the disclosure of confidential information is necessary for an effective oral appeal. In addition, a private appeal will only be granted for specific

submissions containing confidential information; any other submissions will be heard in public.

Who is the appeal panel, and what is their role?

The appeal panel consists of five people drawn from a group of individuals appointed by NICE as appeal panel members and approved by the Secretary of State for Health and Social Care.

The appeal panel is chaired by a member who is engaged in the provision of healthcare in the health services (health service representative); or someone who has experience in representing patients or carers or who is a patient or carer (patient representative).

In addition to the chair of the panel, one non-executive director of NICE, one health service representative, one representative of the life sciences industry, and one patient representative will join the appeal panel.

The appeal panel is responsible for considering the valid appeal points approved by the lead non-executive director for appeals during the scrutiny stage, at either an oral appeal hearing or written appeal meeting and formulating the appeal decision outcome. The appeal panel is not expected to redo the work of the appraisal committee.

The role of the appeal panel is to make an independent decision based on the statements presented during the appeal. It is therefore very important that no one tries to influence an individual appeal panel member's view during the hearing, the breaks or outside the hearing on any topics that are under discussion by NICE.

The appeal hearing

What happens at an appeal hearing?

The appeal panel chair will open the appeal hearing, welcome the appellants and NICE staff and committee representatives, briefly explain the process of the hearing before asking the appellants and NICE staff and committee representatives to introduce themselves.

Each appellant organisation is invited to make a brief 5-minute introductory statement. Appellants may have up to five representatives at the appeal hearing.

The NICE/committee representatives, usually the chair of the TA or HST committee is also invited to make an introductory statement of similar length.

Hearings are led by the appeal panel in an inquisitorial rather than an adversarial manner to gain a greater understanding of the appeal points that have been confirmed as meeting one or more of the grounds of appeal during the scrutiny stage. The appeal panel may ask the appellant(s) questions on any relevant issue,

and representatives of the TA/HST committee and NICE may be asked to comment on the appellants' statements.

All questions must be made through the appeal panel chair. At the end of the hearing, each appellant and the representatives from the TA or HST committee (or NICE) are invited to make a brief concluding statement.

Will representatives at the hearing be required to declare interests?

The appeal panel and NICE representatives are required to declare any interests relevant to the appeal. NICE's policy on declaring interests does not apply to those representing the appellants. This is because the appellants will have a clear interest in the technology that is subject of the appeal, often as the manufacturer of the technology, or other stakeholder organisations.

Will all of the discussion be in public?

If you wish to make a statement that involves disclosing confidential information, the appeal panel will allow you to be heard in private (that is, in the absence of other appellants, the public and the press). We advise you not to rely on confidential information in your appeal letters and statements if your appeal could be supported equally strongly by information in the public domain. The appeal panel will only allow you to make a statement in private if it is satisfied that the disclosure of confidential information is necessary for an effective oral appeal. In addition, a private appeal will only be granted for specific submissions for which that test is satisfied; any other submissions will be heard in public.

How long will the hearing last?

The length of a hearing varies depending on the number of appellants involved in the appeal and the number of appeal points the appeal panel consider. This makes it difficult to predict how long an appeal hearing will last and when it will end. It is advisable to set aside a full day when attending hearings.

What happens after an appeal?

When will I find out the outcome to the appeal?

In both the oral and written appeal processes, the appeal panel aim to send its decision in writing to NICE within 15 working days of the appeal. There may be circumstances in which more time is needed. The appeal panel's decision is required to go through a number of formal internal processes before it is distributed to the appellants and other stakeholders involved in the appraisal/HST topic.

Once NICE receives the appeal panel's decision it is then considered by the NICE guidance executive, responsible for formally receiving and taking action on appeal decisions regarding the technology appraisal and highly specialised technologies

programmes. The guidance executive consists of members of NICE's executive team and is chaired by the NICE chief executive. Following this stage, the appeal decision document is distributed to consultees, including appellants, and commentators (in confidence) and then published on the NICE website on the web page for that specific appraisal or evaluation (under the project documents tab) two working days later.

This process usually takes approximately 8 to 9 weeks following the appeal hearing.

What are the possible outcomes from an appeal hearing?

The decision document provides a summarised account of what was said during the appeal hearing or written appeal meeting, the appeal panel's conclusions and the appeal panel's final decision on each appellant's appeal points.

There are three possible outcomes to an appeal:

Appeal upheld

If one or more of the appeal points are upheld the final draft guidance is returned to the advisory committee. Details of when the final draft guidance will be reconsidered by the advisory committee are communicated to the consultees, including appellants, and commentators of the appraisal/HST topic with a copy of the appeal panel's decision, in confidence. The decision is then published on the NICE website two working days later. The advisory committee meet to consider the decision and later produce revised final draft guidance. When the revised final draft guidance is produced, it is distributed to the consultees and commentators of the appraisal/HST topic, and the consultees have a further opportunity to appeal.

Appeal dismissed

If all of the appeal points are dismissed a copy of the appeal panel's decision is distributed to the consultees, including appellants, and commentators of the appraisal/HST topic along with the guidance, in confidence. The appeal panel's decision is then published two days later at the same time as the guidance.

Appeal panel requests changes to the final draft guidance but no further consideration by the committee

There are occasions where the appeal panel may suggest changes are made to the final draft guidance before it's published as guidance, however the final draft guidance does not require further consideration by the committee. Once changes are made, a copy of the appeal panel's decision is distributed to the consultees, including appellants, and commentators of the evaluation topic along with the guidance, in confidence. The appeal panel's decision is then published two days later at the same time as the guidance.

What do we do if we do not agree with the appeal panel's decision?

You cannot appeal further against the decision of the appeal panel. However, you may challenge the appeal panel's decision and NICE's decision to issue the final guidance by applying to the High Court for permission to apply for a judicial review. You must do this within three months of NICE publishing the final guidance.

Can new evidence be presented to the appeal panel?

You should submit all the evidence you consider relevant to the guidance topic to the advisory committee as part of the evaluation process as described in the NICE process guides. You cannot present new evidence or information that was not presented to the committee, or re-analysis of existing evidence or information in the appeal letter or at the hearing; it will not be considered by the appeal panel.

If we have additional papers that we consider important for the appeal panel to receive in advance of the hearing. What do we do?

Ordinarily appeals are conducted on the basis of the appellants' written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let the NICE appeal team know as soon as possible indicating what the material is, why it is desirable to submit it, and when it will be available. The material must then be submitted by the deadline given by the NICE appeal team, usually 3 weeks before the hearing. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Does the appeal decision overturn the guidance recommendations?

Please note that the appeal decision document **does not overturn the guidance recommendations** (in itself), nor is it final guidance. Depending on the outcome of the appeal (see possible outcomes of an appeal above) final guidance may be published at the same time as the appeal decision or if appeal points are upheld, the committee meet to consider the decision and produce revised final guidance (which may still contain the same recommendations). The timeline for when the topic is rescheduled to the committee is determined by the committee project team.

What do I do if my question isn't answered in these FAQs?

Please contact the appeals project manager, or your public involvement adviser for help.

Further information is available in the Guide to the technology appraisal and highly specialised technologies appeal process.

Please do give us any feedback on how helpful you find these FAQs. We will update these FAQs when we get asked additional questions frequently and based on your feedback.

Thank you.

February 2022

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGIES (HST)

APPEAL HEARING

Advice on olipudase alfa for treating Niemann-Pick disease types AB and B [ID3913]

Decision of the panel

Introduction

1. An appeal panel was convened on 24 May 2024 to consider an appeal against NICE's final draft guidance (FDG), to the NHS, on olipudase alfa for treating Niemann-Pick disease types AB and B [ID3913].

2. The appeal panel consisted of:

- Professor Jon Cohen — Chair
- Chris Rao — Health service representative
- Kawitha Helme — Industry representative
- David Chandler — Lay representative
- Professor Gary Ford — Non-executive director of NICE

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

4. The panel considered the appeal submitted by Niemann-Pick UK (NPUK).

5. NPUK was represented by:

- Toni Mathieson CEO of NPUK
- Will Evans NPUK Trustee
- Dr Simon Jones Paediatrician and Medical Adviser to NPUK
- James Dyson Patient Expert
- A Patient Carer representative

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

- Dr Paul Arundel Chair, Highly Specialised Technologies Committee
- Richard Diaz Associate Director, NICE
- Professor Jonathan Ives Member, Highly Specialised Technologies Evaluation Committee
- Dr Jacoline Bouvy Programme Director, NICE
- Yelan Guo Technical Adviser, NICE

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

8. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings, which were held via Zoom.

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

   Ground 1: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

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

10. Sharmila Nebhrajani OBE, NICE non-executive director and chairman, in preliminary correspondence had confirmed that NPUK had valid grounds for appeal under Ground 1(a) and Ground 2.

11. The evaluation that is the subject of the current appeal provided advice to the NHS on the use of olipudase alfa for treating Niemann-Pick disease types AB and B. Niemann-Pick disease, also known as acid sphingomyelinase deficiency (ASMD), is a rare genetic disease. There are approximately 50 people diagnosed with ASMD in England at any one time. A deficiency of the enzyme acid sphingomyelinase results in an accumulation of sphingomyelin in the cells of affected people. ASMD type AB and B are considered in this evaluation. Both ASMD type AB and B result in liver and splenic enlargement, causing reduced appetite, abdominal distension, and pain. Accumulation of sphingomyelin in the liver, spleen, lungs and bones can also result in fatigue, respiratory failure, liver failure, clotting and immune deficiency, delayed growth and development, and impaired mobility. Type AB can also include slowly progressive neurodegeneration. ASMD is associated with increased risk of death.

12. The numbering of appeal points in this letter reflects those that were used during the hearing. The text of this document does not represent a verbatim or comprehensive account of the proceedings nor a documentation of the order of events that took place, but rather provides a brief summary of the submissions from both NPUK and the committee for the points that were discussed relevant to the decisions of the panel.

13. Before the appeal panel inquired into the detailed appeal points the appeal panel heard preliminary statements on behalf of Niemann-Pick UK from Toni Mathieson, William Evans, Simon Jones, and a patient carer representative. The appeal panel also heard a preliminary statement from Dr Paul Arundel, on behalf of NICE.

14. The appeal panel recognised from the patient evidence given during the evaluation process, the preliminary statements made on behalf of Niemann-Pick UK, and evidence given during the appeal hearing, that the diagnosis of ASMD was often delayed, and that prior to the introduction of olipudase alfa no treatment was available to patients except best supportive care. The appeal panel understood the progressive nature of ASMD, the significant impact that ASMD has on the quality-of-life, psychological wellbeing and social functioning of effected people, their carers, and family.

Appeal by NPUK

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

Appeal point 1(a).2 a: The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities, because it misrepresented the patient expert's position by stating in paragraph 3.17 of the FDG that "[T]he patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD".

15. The patient carer representative for NPUK explained that in all of her written submissions she felt she had made clear her view that carer input is needed across all levels of severity of the disease. During the first committee meeting, she said that the chair was controlling time very tightly, and questions were 'fired at' participants. She explained that she was asked a

question along the lines of '*if the patient's health is bad, is more care needed?*'. The patient carer representative had answered 'yes' but subsequently thought that did not really represent her view. She tried to expand on her answer but was not given the opportunity to explain and therefore felt that her view was misrepresented.

16. The patient carer representative explained that her view is in fact that the amount of care given is not necessarily directly proportional to the severity of the illness. She agreed that, considering the three stages of splenic enlargement that define health state, a patient does need the highest level of care at the highest health state (i.e. the most advanced disease), but also that a patient still needs a significant amount of care in other health states. She noted that the care level is not directly proportional to the health state level as not all symptoms are derived from spleen and lung function. She considered that she had very clearly showed that the impact of caring for a child in the lowest health state was all consuming, and that as the child moves into the next health state, caring requirements were exacerbated by other symptoms such as neutropenia and fatigue. She also noted the emotional impacts on child and carer.

17. Dr Paul Arundel, for NICE, noted he was not the chair in the first committee meeting. He noted that the input from patient experts throughout this evaluation had been outstanding. He explained that there was no intention of the committee to misrepresent the patient carer expert and apologised. He noted also that the explanation provided in Paragraph 3.17 was unchanged in the FDG from the wording of the draft guidance, upon which NICE had consulted, and which he said received no objection from NPUK in consultation.

18. Dr Jacoline Bouvy, for NICE, appreciated that the language of health economics can cause confusion for lay people, and that there is a difference between the formally defined 'health state' used for modelling purposes, and the general state of a patient's health.

19. Dr Jacoline Bouvy assured NPUK that the committee were provided with and had considered all the information presented in the meeting well in advance, so they were well acquainted with it by the time of the meeting. She explained that committees will always have to make difficult choices about the key issues for discussion in committee meetings, from several hundred pages of material received from stakeholders. She observed that NICE could in future explain more clearly that the fact of a subject not being discussed in the meeting does not indicate that the subject has not been considered by the committee.

20. The appeal panel concluded as follows:

21. There are several instances in the written patient carer evidence and in the oral evidence heard by the appeal panel in which the patient carer representative described drivers of carer disutility that are independent of the health state of the person with ASMD such as emotional stress, financial loss, anticipatory grief, and guilt at passing on this genetic condition.

22. The panel therefore concluded that the statement in paragraph 3.17 of the FDG that, "[T]he patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD", misrepresented the patient carer's position. After hearing oral evidence from NICE the panel accepted that the patient carer representative's position was not deliberately misrepresented and that this may have occurred inadvertently.

23. The scenario analysis presented in the External Assessment Group (EAG) report suggested that carer disutility had a significant impact on the incremental cost-effectiveness ratio.

24. As carer disutility was a significant driver of the cost-effectiveness of the technology, the panel therefore considered that misunderstanding the significant drivers of carer disutility could potentially have an effect on the outcome of the economic analysis.

25. The appeal panel concluded, therefore, that there was evidence of procedural unfairness on this issue and upheld the appeal point.

Appeal point 1(a).2 b: The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities, because it cut short patient experts with the consequence that the Committee did not receive sufficient patient testimony to enable the Committee to understand their position.

26. James Dyson, for Niemann-Pick UK, noted that the meeting process felt very rushed, and some questions were asked of him which he felt should have triggered a discussion but he was not given the opportunity to discuss them fully. He added that he sent several emails to clarify his points to the committee after the meeting. He explained that if he had understood from the outset that his written submissions were intended to stand alone, and that the meetings were there only to discuss points arising, he would have added additional context to his written submissions.

27. He raised two specific points that he considered had been inadequately addressed in the meeting, and on which he had sent follow-up emails. The first was that patient weight is not necessarily a reliable indicator of health state. A patient could have higher body weight (driven by higher spleen weight) but still be malnourished. Treatment may not lead to much difference in overall body weight, because organ weight reduction is counterbalanced by increased body weight as health improves, but treatment does nevertheless lead to a huge difference in wellbeing. The second point was that an enlarged spleen is not inconsistent with good health. He noted that his own spleen has reduced in size with treatment but remains considerably bigger than normal, but that with treatment his overall health state was good.

28. Dr Paul Arundel, for NICE, explained that for HST cases, more time was allocated to hear topics but he recognised timing was still a challenge. He

explained the main purpose of the meeting is to give the committee the opportunity to ask more questions, having digested and considered the voluminous written materials. He accepted the importance of NICE explaining the precise role of patient experts in committee. He confirmed that the committee had considered the points raised by James Dyson in his subsequent emails. The Panel noted the detailed discussion of the 'burden of the condition' in paragraph 3.2 of the FDG.

29. Dr Jacoline Bouvy, for NICE, explained that the meeting format had recently been amended to support Chairs to improve timekeeping in meetings. This was driven by a desire to avoid running over time, which means that stakeholders waiting to participate in discussions for the next technology under consideration by committee that day are kept waiting. The key change is that the chair is now asked to talk through the slides first (without discussion), and then move to discussion on the topic.

30. Toni Mathieson, for NPUK, explained her view that paragraph 3.2 did not provide a complete picture of the burden of the disease, and that this raised a concern for her that the committee could have benefited from listening to the patient expert more.

31. Richard Diaz, for NICE, noted that NPUK would have been given an opportunity to share any final thoughts, including any comments they were unable to make in the questioning section of the meeting. He also noted that the committee appreciated the exceptional input from stakeholders in the evaluation, including written submissions, which may have meant relatively few committee questions were required.

32. Professor Jonathan Ives, for NICE, also highlighted the incredibly powerful patient testimony and noted that the testimonies were discussed by the committee.

33. The patient carer representative noted that they were informed that the summarised slides did not contain all the information the committee were

given about the disease and that they had been provided with an extended slide deck however the patient carer noted there were omissions in the extended slide deck.

34. Dr Paul Arundel reassured the patient carer representative that the extended slides were not a comprehensive guide, but a summary.

35. In response to a question from the Chair, the patient carer representative accepted that notwithstanding the fact that she felt not everyone had a chance to contribute as they would have wished during the meeting itself, she was able to correct errors and omissions in written submissions, so the committee were informed. However, in the absence of discussion, she noted that she could not check the committee's understanding.

36. The appeal panel concluded as follows:

37. The appeal panel recognised the engagement of NPUK and other key stakeholders in the evaluation process, resulting in a comprehensive body of written evidence that was considered by the evaluation committee. The appeal panel are satisfied that this evidence was appropriately considered by the committee, and accorded due significance as evidenced by paragraph 3.2 of the FDG.

38. With the exception of the point 1(a)2 a, the appellants did not highlight any issues that may potentially have changed the outcome of the evaluation, and/or that did not appear to have been fully understood by the committee, that they were unable to raise in the evaluation committee meeting because of insufficient time.

39. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness on this issue and dismissed the appeal point.

40. The appeal panel noted the apology on behalf of NICE by Dr Jacoline Bouvy, and the determination of the NICE team to manage patient

engagement better in the future to try and avoid patient experts feeling that the committee did not understand their position.

Appeal point 1(a).2 c: The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities, because it unfairly failed to consider outputs from the recent study by Raebel.

41. Toni Mathieson, for NPUK, explained that the Raebel study is a highly relevant global study initiated by national patient organisations, which uses retrospective case series, online surveys and semi-structured interviews. The study outputs were provided pre-publication to the committee. She noted there was no reference to this study in the FDG or committee papers, and that NPUK felt it was essential for this evidence to be considered before a final decision was reached.

42. Richard Diaz, for NICE, reassured NPUK that the committee was provided with the study and it was fully considered. He explained that it is NICE's standard practice not to include references to specific papers, particularly when received pre-publication, to limit the risk of referring to unpublished evidence directly in the guidance. He identified several instances in the committee papers of conclusions that could only have been reached following consideration of Raebel.

43. Toni Mathieson noted that NPUK's concern had been that as Raebel was pre-publication at the time of its submission, it would not be taken into account, and that this concern was exacerbated because there was not express reference made to it in the FDG or committee papers. She appreciated the reassurance provided by the committee that it was considered.

44. The appeal panel concluded as follows:

45. The appeal panel noted the oral evidence from NICE confirming that the unpublished manuscript by Raebel et al was received by the evaluation

committee, that the importance of the information presented had been recognised, and that it had been appropriately considered.

46. The appeal panel noted that figures from the unpublished manuscript by Raebel et al. were reproduced in the evaluation committee slides.

47. The appeal panel concluded, therefore, that there was no evidence of procedural unfairness on this issue and dismissed the appeal point.

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

48. No appeal points on ground 1(b) were heard by the panel.

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

Appeal point 2.3: The Committee's conclusion regarding the impact of a patient's death on carer disutility is unreasonable.

49. Toni Mathieson, for NPUK, noted the all-consuming nature of the disease for parent carers, including emotional, physical and financial loss, anticipatory grief, and guilt at passing on this genetic condition. She also highlighted that siblings of children with the disease often became carers too, and experienced 'survivor guilt'. She explained that the impacts are different for everyone, but were long-lasting, and impacted upon mental wellbeing. Living with grief has a profound impact on every facet of life, and while the nature of the impact and burden changes over time, the burden remains.

50. James Dyson, for NPUK, added that he had lost friends to the disease who had been refused access to the trial of olipudase alfa. He said that the grief and psychological impact is widespread; he was grieving for his friend, and there was psychological impact on his friends and family as they contended with the understanding that he might also die from the disease. He said that if no treatment is available at all, then inevitable death is something one can

come to live with. However the psychological impact is greater if there is a treatment that is inaccessible.

51. Toni Mathieson questioned how the committee undertook the qualitative assessment of carer disutility and how it affected their decision making. She noted the lack of explanation about this in the FDG.

52. Dr Paul Arundel, for NICE, begun by apologising if any stakeholder felt that the committee didn't recognise the profound effects of bereavement. He explained that the committee had tried to summarise their understanding of the devastating effects on parents and carers in paragraphs 3.2 and 3.20 of the FDG. He acknowledged that it is challenging to recognise this impact within the framework of health evaluation, and that there is a lack of research on the subject. He accepted that there is no generally accepted methodology for accounting for carer disutility. In that context, he explained that the committee considered the impact of carer disutility qualitatively, in discussion, rather than applying a quantitative value to it. He pointed to paragraph 3.22 of the FDG, which records that notwithstanding uncertainties, considering the entirety of the evidence, the committee agreed that a full Quality Adjusted Life Year (QALY) weighting of 2.7 should be applied. He further pointed to the committee's conclusion (in paragraphs 3.12-3.15) that a 1.5% discount rate should be applied to both costs and benefits, rather than 3.5% as used in the NICE reference case and as preferred by the EAG. He explained that this conclusion followed consideration of all the evidence presented and patient testimonies. He added that they tried to capture a number of non-numeric factors in their decision making, but recognised they needed to make this clearer in the papers.

53. Dr Jacoline Bouvy, for NICE, reinforced this point, explaining that the committee recognised that seeking to take account of carer disutility in a quantitative way would potentially underestimate the impact of the treatment for carers. This was reflected in the decision-making by acknowledging that

despite the uncertainty in the evidence presented, which usually means that the committee will be more cautious in accepting QALY weighting or a lower discount rate value, in this case the committee accepted that it was appropriate to accept the full QALY weighting and 1.5% discount rate. She further noted that committees typically aim to be succinct when drafting decision-making sections of guidance. She said that especially in relation to non-numerical factors, committees tend to shy away from being overly explicit as to the impact of different non-numerical factors beyond explaining that the totality of evidence was taken into account, because to do otherwise would risk becoming numerical about non-numerical factors, and the extent to which they influenced decision-making. She accepted that will always lead to a degree of vagueness in the description of decision-making.

54. In response to a question from the Chair, Dr Jacoline Bouvy acknowledged that NICE committees had on occasion in the past accepted quantitative evidence on carer disutility, but explained that in this case the committee's position was driven by the utility values proposed and the uncertainty of the evidence base for those values.

55. In response to a question from the Panel, Dr Paul Arundel acknowledged that it was plausible that in other HST evaluations a committee might decide to apply a full QALY weighting and 1.5% discount rate, where the impact of bereavement on carer disutility was not also an issue. In this case, however, he explained that he is satisfied that the measures adopted did fully capture the impact of carer disutility and the other factors considered by the committee.

56. Dr Paul Arundel further noted that the quantitative modelling proposed by the Company applied a disutility of -0.5 over a time horizon that assumed no waning of disutility for 100 years. Without wishing in any way to minimise the impact of bereavement, the committee did not consider that to be credible. By contrast the EAG dismissed the impact of bereavement as highly speculative. In response to a question from the Chair, Dr Paul Arundel

agreed that the EAG comment that inclusion of carer disutility associated with patient death “potentially biased the analysis in favour of olipudase” was inappropriate. The committee was not provided with a sensitivity analysis. The committee's view was that the evidence was so uncertain that they could not apply a figure to it, but rather, would account for it qualitatively, falling between the approaches proposed by the Company and the EAG respectively.

57. The appeal panel concluded as follows:

58. The appeal panel noted that there is no consensus in previous NICE evaluations and the academic literature on how a quantitative approach should be taken to recognising the effect of a patient’s death on carer disutility. In several other economic analyses and technology appraisals performed by NICE or published in the academic literature this has resulted in adoption of a qualitative approach. The appeal panel therefore did not consider that adoption of a qualitative approach was unreasonable.

59. The appeal panel noted the approach of the committee described in oral evidence. The appeal panel did not consider adopting a lower discount rate and a higher QALY weighting to account for carer disutility to be an unreasonable approach to qualitatively account for the carer disutility associated with death.

60. The appeal panel concluded, therefore, that there was no evidence that the evaluation committee had acted unreasonably on this issue and therefore dismissed this appeal point.

61. The appeal panel considered however that the approach used to qualitatively account for the carer disutility associated with death had been insufficiently described in the FDG. The appeal panel therefore suggest that this should be appropriately clarified in a revised FDG.

62. The appeal panel noted that there was a contradiction between the answer given by Dr Jacoline Bouvy in how the carer disutility associated with death was modelled in the company model in oral evidence (suggesting that carer life expectancy was modelled according to population norms) and how this was represented in the FDG (suggesting that carer life expectancy was assumed to be 100 years). This should be clarified in the FDG to ensure that the company model is not misrepresented.

Conclusion and effect of the appeal panel's decision

63. The appeal panel upheld the appeal by NPUK on appeal point 1(a)2a.

64. The appeal panel dismissed all other appeal points but would draw the attention of NICE to paragraph 61 of this appeal decision that suggests further clarification in the FDG following the panel's consideration of appeal point 2.3.

65. The evaluation of this technology is remitted to the evaluation committee in order to allow them to reconsider whether misunderstanding the patient expert's opinion regarding the significant drivers of carer disutility could potentially have had an effect on the outcome of the economic analysis.

66. 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.

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID3913]

A Highly Specialised Technology Appraisal

Additional Analyses requested by the committee post-appeal

September 2024

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1. INTRODUCTION

Following the appeal decision for olipudase alfa for treating acid sphingomyelinase deficiency published 24th July 2024, NICE requested the EAG to provide two scenario analyses in preparation for AC3, scheduled for Thursday 7th November 2024. Specifically NICE requested analyses that:

1. Remove carer disutility from the olipudase alfa arm, and
2. Lower carer disutility from the olipudase alfa arm

NICE requested the EAG assess the impact of these on the ICERs for adults, children and the combined population (50/50 adult, children). NICE also requested the EAG to provide any additional analyses it suggested; the EAG conducted an analysis where carer burden is reduced in the early stages of disease, then increased to equal that of BSC in the most severe state. As per the previous addendum produced by the EAG following AC2, the EAG also calculates the price discount required to achieve an ICER of £300,000 / QALY in the paediatric and adult populations. For scenario 2, the EAG chose a disutility that was half that in the post AC2 analysis (Table 1). For scenario 3, the caregiver disutility is halved in the early disease stage (spleen volume 1-6), reduced by 25% in the mid disease state (volume 6-15), and not reduced in the severe disease stage (>15).

Table 1: Caregiver disutility

	Olipudase alfa			BSC		
Spleen volume	**1-6**	**6-15**	**>15**	**1-6**	**6-15**	**>15**
Paediatric						
Post AC2	-0.023	-0.023	-0.080	-0.023	-0.023	-0.080
Scenario 1: Removing caregiver disutility in olipudase arm	0.000	0.000	0.000	-0.023	-0.023	-0.080
Scenario 2: Halving caregiver disutility in olipudase arm	-0.012	-0.012	-0.040	-0.023	-0.023	-0.080
Scenario 3: Sliding disutility in olipudase arm	-0.012	-0.017	-0.080	-0.023	-0.023	-0.080
Adult						
Post AC2	-0.010	-0.010	-0.045	-0.010	-0.010	-0.045
Scenario 1: Removing caregiver disutility in olipudase arm	0.000	0.000	0.000	-0.010	-0.010	-0.045
Scenario 2: Halving caregiver disutility in olipudase arm	-0.005	-0.005	-0.023	-0.010	-0.010	-0.045
Scenario 3: Sliding disutility in olipudase arm	-0.005	-0.008	-0.045	-0.010	-0.010	-0.045

Note the disutilities in the committee's preferred scenario are assumed to vary only by spleen volume and not by DLCO

These analyses were conducted on top of the committee's preferred assumptions following AC2. These were:

- Long-term treatment effect – EAG's approach preferred for base case;
- Discount rate – 1.5% for both costs and benefits
- Carer's disutility:

  - Disutility for both arms;
  - Differential disutility: EAG approach preferred, by severity (vs. non-severe) and children (vs. adults);
  - Number of carers: 1 carer;
  - Carer's disutility associated with patient death: considered qualitatively rather than numerically;
- Mortality – company's parametric approach preferred
- Weight: EAG's approach preferred (HSE data with lower mean but different implementation from company's)

2. RESULTS

Under scenario 1 (no carer disutility in olipudase arm), the unadjusted ICER is [redacted] per QALY gained in the paediatric population and [redacted] in the adult (Table 2). Treatment is associated with an undiscounted incremental QALYs of 37.84 in the paediatric population and 19.21 in the adult.

This compares with the committee's preferred base case post AC2 yielding ICERs of [redacted] in the paediatric population and [redacted] in the adult (see EAG report appendix ID3913 Olipudase EAG post AC2 analyses, December 2023).

Assuming 50% of patients are adult and 50% are children, the ICER is [redacted], compared with [redacted] in the post AC2 analyses.

Due to the structure of the model calculating the discount required to achieve an ICER of £300,000/QALY for the 50/50 adult/paediatric population is not straightforward, but a reasonable approximation would be midway between the adult and paediatric populations, namely [redacted] (compared with [redacted] in the previous post-AC2 analysis) (Table 3).

Scenario 2, assuming a 50% reduction in carer disutility generates results mid-way between the post-AC2 results and those of scenario 1, with a combined ICER of [redacted] (Table 4 & Table 5). Scenario 3 yields a combined ICER of [redacted] (Table 6 & Table 7).

Table 2: Scenario 1 – removing carer disutility in olipudase arm

	Total costs	Total QALYs	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	Cost per QALY gained
Paediatric						
BSC	[redacted]	9.86				
Olipudase alfa	[redacted]	31.62	[redacted]	37.84	21.76	[redacted]
Adult						
BSC	[redacted]	13.77				
Olipudase alfa	[redacted]	25.84	[redacted]	19.21	12.07	[redacted]
50/50 population						
BSC	[redacted]	11.82				
Olipudase alfa	[redacted]	28.73	[redacted]	28.53	16.91	[redacted]

Abbreviations: QALYs, quality adjusted life years; BSC, best supportive care

Table 3: Scenario 1 - Price discount required to achieve ICER of £300,000/QALY

£/20mg vial	% vs list price	Incremental Cost	Incremental QALYs	Cost per QALY gained
Paediatric				
[redacted]	[redacted]	[redacted]	21.76	[redacted]
[redacted]	[redacted]	[redacted]	21.76	£300,000
Adult				
[redacted]	[redacted]	[redacted]	12.07	[redacted]
[redacted]	[redacted]	[redacted]	12.07	£300,000
Combined (approx.)	[redacted]			

Table 4: Scenario 2 – reducing carer disutility in olipudase arm

	Total costs	Total QALYs	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	Cost per QALY gained
Paediatric						
BSC	[redacted]	9.86				
Olipudase alfa	[redacted]	31.16	[redacted]	37.11	21.30	[redacted]
Adult						
BSC	[redacted]	13.77				
Olipudase alfa	[redacted]	25.67	[redacted]	18.97	11.90	[redacted]
50/50 population						
BSC	[redacted]	11.82				
Olipudase alfa	[redacted]	28.41	[redacted]	28.04	16.60	[redacted]

Abbreviations: QALYs, quality adjusted life years; BSC, best supportive care

Table 5: Scenario 2 - Price discount required to achieve ICER of £300,000/QALY

£/20mg vial	% vs list price	Incremental Cost	Incremental QALYs	Cost per QALY gained
Paediatric				
[redacted]	[redacted]	[redacted]	21.30	[redacted]
[redacted]	[redacted]	[redacted]	21.30	£300,000
Adult				
[redacted]	[redacted]	[redacted]	11.90	[redacted]
[redacted]	[redacted]	[redacted]	11.90	£300,000
Combined (approx.)	[redacted]			

Table 6: Scenario 3 – sliding carer disutility in olipudase arm

	Total costs	Total QALYs	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	Cost per QALY gained
Paediatric						
BSC	[redacted]	9.86				
Olipudase alfa	[redacted]	31.06	[redacted]	36.96	21.20	[redacted]
Adult						
BSC	[redacted]	13.77				
Olipudase alfa	[redacted]	25.64	[redacted]	18.93	11.87	[redacted]
Combined						
BSC	[redacted]	11.82				
Olipudase alfa	[redacted]	28.35	[redacted]	27.94	16.54	[redacted]

Abbreviations: QALYs, quality adjusted life years; BSC, best supportive care

Table 7: Scenario 3 - Price discount required to achieve ICER of £300,000/QALY

£/20mg vial	% vs list price	Incremental Cost	Incremental QALYs	Cost per QALY gained
Paediatric				
[redacted]	[redacted]	[redacted]	21.20	[redacted]
[redacted]	[redacted]	[redacted]	21.20	[redacted]
Adult				
[redacted]	[redacted]	[redacted]	11.87	[redacted]
[redacted]	[redacted]	[redacted]	11.87	[redacted]
Combined (approx.)	[redacted]			

3. COMMENTARY

The company selected spleen volume as a proxy for overall disease progression / status in its decision model. The EAG understood that this was an imperfect approximation and does not capture every element of disease progression but nevertheless considered it to be a reasonable assumption.

In general, the EAG considered it axiomatic that the degree of care required by a person with a disease is a function of disease progression and severity: persons with more severe disabilities require more care and assistance than those with less severe disabilities. The EAG noted the point raised by the carer in the appeal decision letter (point 16) which stated that "*the amount of care given is not necessarily directly proportional to the severity of the illness*", and confirms that "*a patient does need the highest level of care at the highest state…but that a patient still needs a significant amount of care in other health states*". The EAG agreed that the care requirements are certainly not zero for the less severe health states and noted that the committee's preferred scenario post AC2 reflects this (see Table 1).

The EAG considered that the driver of carer (and patient) disutility was the health state of the person with the disease, rather than the treatment (pharmaceutical) the person is receiving. Typically, therefore, decision models attach health state utilities to health states, rather than treatments received. However, there are two justifications for deviating from this, and attaching differential utilities to treatment arms. Firstly, where treatment side effect profiles differ, disutilities based on treatment received are applied. Secondly, where the decision model does not capture differences in outcomes with sufficient granularity. The EAG believed this second argument to be relevant to this situation.

The EAG did not consider scenario 1 to be a plausible scenario. This implied that patients in the olipudase arm in the least severe disease stage (approximated by a spleen volume of 1-6 times normal) required no carer assistance whilst those in the BSC arm did. This may be plausible on the grounds that the model does not capture all relevant benefits attributable to olipudase, but the EAG noted this contradicts the patient testimony from point 16 in the appeal decision letter, cited above. However, the scenario also assumed that patients in the most severe disease state (represented by spleen volume >15 times normal) receiving olipudase also required no caring assistance, whilst those in the same health state but receiving BSC required more intensive caring. The EAG considered this assumption to lack face validity.

The EAG considered scenarios 2 and 3 to be plausible only if the company's model is judged sufficiently lacking in granularity that it has failed to credibly capture the impact of treatment on patient health status and thus carers, and that there is evidence to support a difference in carer quality of life by treatment arm *over and above that related to disease status/progression already captured by the model*. The EAG was not aware of any data to support this and was not able to consult with clinical experts within the timeframe for this analysis. Understanding that all models are approximations and considering that there may be uncaptured benefits from olipudase over and above those related to disease progression, the EAG considered scenario 3 to represent a plausible compromise analysis, yielding a combined ICER of [redacted] per QALY gained.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID 3913]

Addendum to company evidence submission

October 2024

Version 1.0

File name	Version	Contains confidential information	Date
Addendum B	1.0	Yes	16th October 2024

1. Objective

The aim of this addendum is to present

1. The long-term efficacy and safety data on olipudase alfa in adult and paediatric patients with acid sphingomyelinase deficiency (ASMD) that was collected in the ASCEND (DFI12712) and LTS13632 studies (1, 2)
2. Evidence on the impact of rare, progressive, life-limiting, paediatric conditions, such as ASMD, on informal carers health-related quality of life (HRQoL) and the challenges associated with including carer HRQoL data in economic models for HTA submissions (3, 4)

2. Clinical efficacy and safety data on olipudase alfa

Methodology

ASCEND and ASCEND-Peds were the pivotal studies presented in the company submission (CS). As the extension phase of ASCEND and the LTS13632 study were still ongoing at time of the original submission, interim data were presented for both trials.

Full details on study design and methodology for both ASCEND and LTS13632 studies were provided in the CS (Sections B.2.3 and B.2.11) (5). Patient demographic and baseline characteristics for ASCEND and the parent studies of LTS13632 (DFI13803 [ASCEND-Peds] and DFI13412) were also reported in the CS (Section B.2.3.4 and Appendix M) (5).

ASCEND

The ASCEND phase II/III study was completed on 19 October 2023 (last participant visit), with a final database lock date of 12 January 2024 (1). As the results for the primary analysis period (PAP) have been presented in the CS, the cumulative efficacy results for the PAP and the extended treatment period (PAP+ETP) are presented here (1, 5).

Patient disposition and exposure to olipudase alfa

In total, [redacted] participants completed the PAP and enrolled in the ETP: [redacted] in the placebo/olipudase alfa group and [redacted] in the olipudase alfa/olipudase alfa group. [redacted] ([redacted]%) and [redacted] ([redacted] %) participants in the placebo/olipudase and the olipudase alfa/olipudase alfa groups, respectively, completed the ETP (Table 1). [redacted] discontinued the study and [redacted] ([redacted]%) patients in the placebo/olipudase alfa group discontinued treatment (see Safety results section) (1). [redacted] ([redacted]%) participants in the placebo/olipudase alfa group and [redacted] ([redacted] %) in the olipudase alfa/olipudase alfa group did not complete the ETP due to withdrawal of consent, other reasons related to COVID-19 ([redacted] for each reason in both groups), adverse event or poor compliance to protocol ([redacted] for each in the placebo/olipudase alfa group).

The median cumulative duration of exposure in the PAP+ETP was [redacted] weeks for the placebo/olipudase alfa group and [redacted] weeks for the olipudase alfa/olipudase alfa group (Table 1). [redacted] ([redacted]%) participants received treatment with olipudase alfa for ≥156 weeks to <208 weeks in the placebo/olipudase alfa group. In the olipudase alfa/olipudase alfa group, [redacted] ([redacted]%) participants received treatment for ≥208 weeks (1).

Table 1: Cumulative duration on olipudase alfa in PAP+ETP – mITT population

	Placebo/olipudase alfa N=[redacted]	Olipudase alfa/olipudase alfa N=[redacted]	All patients treated with olipudase alfa N=[redacted]
Number of patients with value	[redacted]	[redacted]	[redacted]
Mean (SD), weeks	[redacted]	[redacted]	[redacted]
Median (min, max), weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ETP, extended treatment period; mITT, modified intent-to-treat; PAP, primary analysis period; SD, standard deviation.
Source: ASCEND (DFI12712) CSR. 24 April 2024 (1).

LTS13632

The LTS13632 phase II study enrolled all five participants from the DFI13412 Phase Ib adult study and all 20 participants from the ASCEND-Peds (DFI13803) Phase I/II paediatric study. Here we present the data up to the last participant last visit (06 September 2023), with a database lock date of 12 October 2023 (2).

Patient disposition and exposure to olipudase alfa

[redacted] patients enrolled in the study completed the treatment and follow-up periods, with [redacted] reported (2).

The median exposure to olipudase alfa was [redacted] weeks in the overall safety population, with minimum and maximum exposures of [redacted] weeks and [redacted] weeks, respectively (Table 2). All paediatric participants were treated in LTS13632 for [redacted] years (2).

Table 2: Cumulative duration on olipudase alfa – Safety population

	Paediatric patients from ASCEND-Peds N=[redacted]	Adult patients from DFI13412 N=[redacted]	All patients N=[redacted]
Number of patients with value	[redacted]	[redacted]	[redacted]
Mean (SD), weeks	[redacted]	[redacted]	[redacted]
Median (min, max), weeks	[redacted]	[redacted]	[redacted]

Abbreviation: SD, standard deviation.
Source: LTS13632 CSR. 26 January 2024 (2).

Efficacy results

Percentage change in spleen volume

The percentage of change in spleen volume was a primary endpoint in ASCEND, and a secondary endpoint in LTS13632, as there were no primary efficacy endpoints in the long-term extension study (1, 2).

ASCEND

The mean spleen volume (multiples of normal [MN]) at study baseline was presented in the CS for both the placebo and the olipudase alfa groups, as were the percentage changes in spleen volume during the PAP (Section B.2.6.1.1) (5).

During the ETP, treatment with olipudase alfa was associated with a continuous reduction in spleen volume up to Week [redacted] in both groups (Figure 1). At Week [redacted], the LS mean percentage reduction from baseline in spleen volume was [redacted]% in the

placebo/olipudase alfa group (n=[redacted]) and [redacted]% in the olipudase alfa/olipudase alfa group (n=[redacted]) (1).

Figure 1: Mean spleen volume (MN) over time in PAP+ETP - mITT population

Notes: After Week 52 all participants received olipudase alfa. The vertical bars represent standard deviations. The baseline is the last non-missing value prior to the first infusion of study treatment.
Abbreviations: ETP, extended treatment period; mITT, modified intent-to-treat; MN, multiple of normal; PAP, primary analysis period.
Source: ASCEND (DFI12712) CSR. 24 April 2024 (1).

LTS13632

In the safety population, a reduction in spleen volume (MN) was observed at all timepoints starting as early as Month 6 and up to Month [redacted] and [redacted] for paediatric and adult participants, respectively (Figure 2) (2).

For paediatric patients, mean spleen volume (MN) was [redacted] (standard deviation [SD]= [redacted], range: [redacted]), indicating [redacted]. The percentage reductions from baseline up to Month 48 were reported in the CS (Section B.2.11.2.1) (5). By Month [redacted], the mean percent reduction from baseline was [redacted]% (SD=[redacted], range: [redacted] [redacted]) based on data from [redacted] paediatric participants ([redacted]) (2).

For adult patients, mean spleen volume (MN) at baseline was [redacted] (SD=[redacted], range: [redacted]), indicating [redacted]. Percentage reductions from baseline up to Month 78 were reported in the CS (Section B.2.11.2.1) (5). At Month [redacted], the mean percentage reduction from baseline was [redacted]% (SD=[redacted], range: [redacted]) for the [redacted] adult participants ([redacted]) (2).

Figure 2: Mean spleen volume (MN) over time in adult and paediatric patients - Safety population

Note: The vertical bars represent standard deviations.
Abbreviation: MN, multiple of normal.
Source: LTS13632 CSR. 26 January 2024 (2).

Percentage change in liver volume

The percentage change in liver volume was a secondary efficacy endpoint in both studies (1, 2).

ASCEND

The mean liver volume (MN) at study baseline was presented in the CS for both the placebo and the olipudase alfa groups, as were the percentage change in liver volume during the PAP (Section B.2.6.1.2) (5).

Up to Week [redacted], treatment with olipudase alfa was associated with a continuous reduction in liver volume over time in both placebo/olipudase alfa and olipudase alfa/olipudase alfa groups (Figure 3). At Week [redacted], a reduction of [redacted]% in liver volume was observed in the placebo/olipudase alfa group (n=[redacted]) and of [redacted]% in the olipudase alfa/olipudase alfa group (n=[redacted]) (1).

Figure 3: Mean liver volume (MN) over time in PAP+ETP - mITT population

Notes: After Week 52 all participants received olipudase alfa. The vertical bars represent standard deviations. The baseline is the last non-missing value prior to the first infusion of study treatment.
Abbreviations: ETP, extended treatment period; mITT, modified intent-to-treat; MN, multiple of normal; PAP, primary analysis period.
Source: ASCEND (DFI12712) CSR. 24 April 2024 (1)

LTS13632

In the safety population, a reduction in liver volume (MN) was observed at all timepoints starting as early as Month 6 and up to Month [redacted] and [redacted] for paediatric and adult participants, respectively (Figure 4) (2).

For paediatric patients, mean liver volume (MN) was [redacted] (SD=[redacted], range: [redacted]), indicating [redacted]. The percentage reductions from baseline up to Month 48 are reported in the CS (Section B.2.11.2.2) (5). By Month [redacted], the mean percentage reduction from baseline was [redacted]% (SD=[redacted], range: [redacted]) in [redacted] paediatric participants ([redacted]) (2).

For adult patients, mean liver volume (MN) at baseline was [redacted] (SD=[redacted], range: [redacted]), indicating [redacted]. Percentage reductions from baseline up to Month 78 are reported in the CS (Section B.2.11.2.2) (5). At Month [redacted], the mean percentage reduction from baseline was [redacted]% (SD=[redacted], range: [redacted]) for the [redacted] adult participants ([redacted]) (2).

Figure 4: Mean liver volume (MN) over time in adult and paediatric patients - Safety population

Note: The vertical bars represent standard deviations.
Abbreviation: MN, multiple of normal.
Source: LTS13632 CSR. 26 January 2024 (2).

Percentage change in DLco (% predicted)

The percentage change in diffusing capacity of the lung for carbon monoxide (DLco) was the independent primary endpoint in ASCEND and was not included in the outcomes assessed in LTS13632 (1, 2).

ASCEND

The mean % predicted DLco at study baseline in the placebo and the olipudase alfa groups was presented in the CS for both the placebo and the olipudase alfa groups, as were the percentage changes in % predicted DLco (Section B.2.6.2.1) (5).

During the ETP, participants in the placebo/olipudase alfa group showed improvement in % predicted DLco from Week 52 onwards and participants in the olipudase alfa/olipudase alfa group demonstrated further improvement from baseline compared with Week 52 of the PAP. In both groups, % predicted DLco improved up to Week [redacted] then remained stable up to Week [redacted], with the LS mean percentage change from baseline in DLco (% predicted) at Week [redacted] improving by [redacted]% and [redacted]% in the placebo/olipudase alfa (n=[redacted]) and the olipudase alfa/olipudase alfa (n=[redacted]) groups, respectively (1).

Figure 5: Mean DLco (% predicted) over time in PAP+ETP - mITT population

Notes: After Week 52 all participants received olipudase alfa. The vertical bars represent standard deviations. The baseline is the last non-missing value prior to the first infusion of study treatment.
Abbreviations: DLco, diffusing capacity of the lung for carbon monoxide; ETP, extended treatment period; Hb, haemoglobin; mITT, modified intent-to-treat; MN, multiple of normal; PAP, primary analysis period.
Source: ASCEND (DFI12712) CSR. 24 April 2024 (1).

Safety results

ASCEND

The safety data in Tables 3 and 4 include all adverse events (AEs) that started on or after the first infusion of olipudase alfa during PAP+ETP. The safety data for participants in the placebo/olipudase alfa group while they were treated with placebo during PAP were presented in the CS (Section B.2.10) and are not included here (5).

Overall, olipudase alfa was well tolerated during PAP+ETP. [redacted] participants treated with olipudase alfa ([redacted]) experienced ≥1 treatment-emergent adverse event [TEAE] and [redacted] ([redacted]%) participants experienced ≥1 TEAE potentially related to the study intervention. The percentage of participants with TEAEs related to the study intervention was similar between the placebo/olipudase alfa and the olipudase alfa/olipudase alfa groups. Overall, the majority of the TEAEs were mild or moderate in severity; severe TEAEs were experienced by [redacted] participants in the placebo/olipudase alfa group ([redacted] events) and [redacted] participants in the olipudase alfa/olipudase alfa group ([redacted] events) (Table 3) (1).

During the ETP, [redacted] in the placebo/olipudase alfa group had a serious adverse event (SAE) of extrasystoles which was considered possibly related to the study intervention by the Investigator. [redacted] underlying comorbidities (pre-existing

cardiomyopathy) and ASMD diagnosis provide an alternative explanation for the [redacted], and the company did not consider [redacted] to be treatment-related.

No deaths were reported during the PAP+ETP. There were [redacted] that led to study withdrawal. [redacted] ([redacted]%) participants in the placebo/olipudase alfa group had a TEAE that led to treatment withdrawal (a rash in [redacted] and pregnancy in the [redacted]) (1).

Table 3: Overview of TEAEs in PAP+ETP – Safety population

Adverse reactions	Placebo/olipudase alfa (N=[redacted])		Olipudase alfa/olipudase alfa (N=[redacted])		All patients treated with olipudase alfa (N=[redacted])	
	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAEs[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs potentially related to study drug[‡]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs by severity	[redacted]		[redacted]		[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAEs potentially related to study drug[§]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to treatment withdrawn	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to study withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to study treatment interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any protocol-defined infusion-associated reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any algorithm-defined infusion-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse reactions	Placebo/olipudase alfa (N=[redacted])		Olipudase alfa/olipudase alfa (N=[redacted])		All patients treated with olipudase alfa (N=[redacted])	
	n (%)	Events	n (%)	Events	n (%)	Events
associated reactions						
Any treatment-emergent pregnancies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs considered symptomatic overdose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs for dose limiting toxicity criteria met		[redacted]		[redacted]		[redacted]
DLT1¶	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLT2††	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLT 3‡‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Includes all AEs that started on or after the first infusion of olipudase alfa. If due to incomplete date/time, this determination could not be made unambiguously, the AE is assumed to be treatment-emergent;
‡ Includes TEAEs that started on or after the first infusion of olipudase alfa and were identified by the investigator as related or possibly related to the study treatment; § Includes serious TEAEs that were identified by the investigator as related or possibly related to the study treatment; ¶ Any increase in AST, ALT, total bilirubin, or AP >3x baseline (prior to olipudase alfa therapy) and > the upper limit of normal range >2x ULN; †† Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT above the normal range >2x ULN; ‡‡ Any increase in ALT or AST >3x ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>ULN).
MedDRA version 23.1 has been used for coding the adverse events.
Abbreviations: AE, adverse event; ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; DLT, dose limiting toxicity; ETP, extended treatment period; PAP, primary analysis period; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
Source: ASCEND (DFI12712) CSR. 24 April 2024 (1).

Overall, the most common TEAEs were observed in the system organ class (SOC) of 'Infections and infestations': [redacted] and [redacted] patients in the placebo/olipudase alfa and olipudase alfa/olipudase alfa groups, respectively. The most frequent TEAE was headache: [redacted] events in [redacted] ([redacted]%) participants in the placebo/olipudase alfa group and [redacted] events in [redacted] ([redacted]%) participants in the olipudase alfa/olipudase alfa group (Table 4) (1).

Table 4: Summary of the most common treatment-emergent adverse events by SOC and PT in PAP+ETP - Safety population

Primary SOC Preferred Term (PT)	Placebo/olipudase alfa (N=[redacted])		Olipudase alfa/olipudase alfa (N=[redacted])		All patients treated with olipudase alfa (N=[redacted])	
	n (%)	Events	n (%)	Events	n (%)	Events
Any class†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Primary SOC Preferred Term (PT)	Placebo/olipudase alfa (N=[redacted])		Olipudase alfa/olipudase alfa (N=[redacted])		All patients treated with olipudase alfa (N=[redacted])	
	n (%)	Events	n (%)	Events	n (%)	Events
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Includes TEAEs with percentages of events ≥2% and number of participants ≥2 in the ' All treated patients' group.
Abbreviations: ETP, extended treatment period; PAP, primary analysis period; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Source: ASCEND (DFI12712) CSR. 24 April 2024 (1).

LTS13632

The safety of olipudase alfa in participants with ASMD who are exposed to long-term treatment with olipudase alfa was the primary endpoint of the LTS13632 study. The cumulative data from LTS13632 and the respective parent study (DFI13803 for the paediatric participants DFI13412 for the adult participants) are presented in Table 5.

[redacted] experienced TEAEs during both parent and extension studies, with [redacted] (40%) paediatric patients experiencing [redacted] severe AEs and [redacted] ([redacted] %) adult patients experiencing [redacted] severe AEs (Table 5). The TEAEs related to study intervention and reported in [redacted] participants ([redacted]%) were: pyrexia, urticaria, headache, nausea, vomiting, abdominal pain, abdominal pain upper, rash and C-reactive protein increase.

[redacted] adult [redacted] experienced [redacted] treatment-emergent SAEs during LTS13632, none of which were treatment-related. [redacted] paediatric participants experienced overall [redacted] treatment-emergent SAEs, including [redacted] paediatric participants who experienced [redacted] SAEs related to study intervention. In [redacted] of the paediatric participants, the treatment-related SAEs were reported in the parent study, while the [redacted] experienced [redacted] hypersensitivity events during LTS13632.

[redacted] led to study or treatment withdrawal. [redacted] was reported during the study period.

Table 5: Overview of TEAEs – Safety Population

Adverse reactions	Paediatric patients from DFI13803 (N=[redacted])		Adult patients from DFI13412 (N=[redacted])		All patients (N=[redacted])	
	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAEs†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs potentially related to study drug‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs by severity	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAEs potentially related to study drug§	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to treatment withdrawn	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to study withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to study treatment interruption¶	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any protocol-defined infusion-associated reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any algorithm-defined infusion-associated reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-emergent pregnancies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs considered	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse reactions	Paediatric patients from DFI13803 (N=[redacted])		Adult patients from DFI13412 (N=[redacted])		All patients (N=[redacted])	
	n (%)	Events	n (%)	Events	n (%)	Events
symptomatic overdose						
Any TEAEs for dose limiting toxicity criteria met						
DLT1††	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLT2‡‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLT 3§§	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Includes all AEs that started during the on-treatment period. If due to incomplete date/time, this determination could not be made unambiguously, the AE is assumed to be treatment-emergent; ‡ Includes TEAEs that were identified by the investigator as related or possibly related to the study treatment; § Includes serious TEAEs that were identified by the investigator as related or possibly related to the study treatment; ¶ Any TEAE leading to treatment interruption is based on AE eCRF page where "Action Taken=Drug Interrupted" from DFI13412 and LTS13632, as well as "Action Taken = Drug Interrupted or Drug withdrawn" from DFI13803; †† Any increase in AST, ALT, total bilirubin, or AP >3x baseline (prior to olipudase alfa therapy) and > the upper limit of normal range >2x ULN; ‡‡ Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT above the normal range >2x ULN; §§ Any increase in ALT or AST >3x ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>ULN).
MedDRA version 23.1 has been used for coding the adverse events.
Abbreviations: AE, adverse event; ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; DLT, dose limiting toxicity; eCFR, electronic Case Report Form; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
Source: LTS13632 CSR. 26 January 2024 (2).

Conclusions

The results from both the ASCEND and LTS 13632 studies support the long-term efficacy and tolerability of olipudase alfa in patients with ASMD.

In the ASCEND study, the clinical benefit of olipudase alfa demonstrated in the PAP was further substantiated during the ETP, with improvements in % predicted DLco and spleen and liver volumes reductions. Participants treated with placebo during the PAP showed improvement in all three outcomes after switching to treatment with olipudase alfa, while participants in the olipudase alfa/olipudase alfa group demonstrated continued and sustained improvements over time.

Paediatric and adult participants treated with olipudase alfa in the long-term extension study LTS13632 showed sustained improvement over time, with [redacted] reductions in both spleen and liver volumes.

Treatment with olipudase alfa was well tolerated in both studies and showed a favourable long-term safety profile in LTS13632.

Patients with ASMD require substantial caregiver support at every stage of the disease (6). As noted by the clinical experts in the comments to the draft guidance, due to its long-term efficacy, olipudase alfa reverses disease and leads to substantial health improvements that restore patients to near normal quality of life (7). Thus, olipudase alfa is likely to considerably reduce the need for caregiver support.

In conclusion, the data presented here highlight the long-lasting clinical benefits of olipudase alfa for both paediatric and adult patients with ASMD and reduce the uncertainties associated with the clinical assumptions in the company's long-term model.

3. Health-related quality of life in caregivers of children with rare, progressive, life-limiting conditions

Introduction

[redacted]

Methodology

[redacted]

Results of the workshop

[redacted]

[redacted]

Future research priorities

[redacted]

Conclusions

[redacted]

4. References

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Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID3913]

A Highly Specialised Technology Appraisal

Critique of evidence submission from company post-appeal

October 2024

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Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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1. INTRODUCTION

Following the appeal decision for olipudase alfa for treating acid sphingomyelinase deficiency published 24th July 2024, the company submitted additional evidence which was received by the External Assessment Group (EAG) in full on 17th October 2024 prior to appraisal committee 3, scheduled for 7th November 2024. The evidence comprised an addendum presenting long term efficacy and safety data on olipudase alfa from the ASCEND (DFI12712) and LTS13632 studies, and evidence on the impact of rare, progressive and life-limiting paediatric conditions on informal carers' HRQoL as well as challenges associated with including HRQoL data in decision models for HTA. No further economic analysis was submitted by the company. This report summarises the EAG's critique of the submission.

2. REVIEW

1 Long term efficacy and safety data

In the original company submission (CS), the company presented evidence from three trials with unique populations: ASCEND (a double-blind RCT with adults), ASCEND-Peds (an open-label, single-arm trial with children, and DFI13412 (an open-label single arm trial with adults). An open-label, long-term extension study, LTS13632, combining participants from ASCEND-Peds and DFI13412 was also reported in the CS though with minimal participants remaining at the longer follow-up timepoints. In its addendum, the company presented final follow-up data for ASCEND and LTS13632, which had become available since the original CS. The EAG critique of the original study designs is provided in its previous report.

2.1. Participant attrition

The EAG had previously raised concerns about the reliability of long-term follow-up data reported in the CS due to high numbers of missing participants at the longer follow-up timepoints. There was also differential attrition in ASCEND at 2-years according to different clinical outcomes (e.g. attrition ≥30% in the olipudase alfa arm at year 2 for spleen volume, DLco, liver volume and platelet count; attrition 50% for DLco).

In ASCEND, the company reported that [redacted] of 36 participants randomised completed the initial primary analysis period (PAP) and enrolled in the extension period (ETP): [redacted] in both arms. Of those [redacted], the company reported that [redacted] participants ([redacted]%) completed the ETP; [redacted] ([redacted]%) in the placebo/olipudase arm and [redacted] ([redacted]%) in the olipudase/olipudase arm. Reasons for discontinuing the study varied and included withdrawal of consent (reasons not reported), COVID-19, adverse events ([redacted] the company stated were considered to be related to treatment), and poor compliance to protocol (reasons not reported). However, further attrition was noted at final follow-up for each clinical outcome. For example, [redacted] ([redacted]%) and [redacted] ([redacted]%) participants in the placebo/olipudase and olipudase/olipudase arms, respectively, were available for spleen and liver volume outcomes, and [redacted] ([redacted]%) and [redacted] ([redacted]%) participants were available for DLco. In its addendum, the company did not provide any explanation for the additional missing participants at the final follow-up timepoint, and at how long into the ETP the missing participants had dropped out. At the rate described at the final follow-up, the EAG considered that the rate of attrition had the potential to meaningfully influence the results. In the original CS, the company stated that data were missing for some outcomes due to participant non-attendance or technical

faults with certain assessments. The EAG considered it plausible that the same issues continued throughout the trial. It was unclear to what extent missingness of data was at random, however the lack of detail about the reasons for missingness and the high level of missingness across the key outcomes meant that the EAG considered the new data from ASCEND to be at a high risk of bias.

Conversely, all participants originally enrolled in ASCEND-Peds (20) and DFI13412 (5) entered LTS13632 and were stated to have completed the final follow-up.

2.2. Length of follow-up

In its original report, the EAG raised an uncertainty in the plausible long-term treatment effect of olipudase alfa for people with ASMD. Clinical expert advice to the EAG was that stable, long-term efficacy is plausible for enzyme-replacement therapies (ERTs), and this has been shown for Gaucher disease, another lysosomal storage disorder. However, not all ERTs have shown long-term efficacy, and clinical advisors expressed a concern that there may be treatment waning in severe patients due to antibody resistance.

The duration of treatment in ASCEND was reported in the mITT population only, and therefore was not specific to the populations who were included in the clinical outcome data (i.e. the length of follow-includes people who dropped out of the study). This may mean that the median/mean duration of treatment relevant to the clinical data is longer that that reported in the company addendum, depending on when the attrition happened, although this is not guaranteed since some participants may have dropped out towards the end of the study period.

In ASCEND, the duration of treatment with olipudase alfa in the PAP and ETP ranged between [redacted] weeks to [redacted] weeks and between [redacted] weeks to [redacted] weeks in the placebo/olipudase and olipudase/olipudase arms, respectively. The company reported that approximately [redacted]% of participants in the placebo/olipudase arm received treatment for between 3 to 4 years and [redacted]% of participants in the olipudase/olipudase arm received treatment for more than 4 years.

In LTS13632, there was also significant variation in the duration of treatment with olipudase: paediatric treatment with olipudase alfa ranged from [redacted] to [redacted] weeks and adults were treated for between [redacted] and [redacted] weeks. This means that all paediatric participants were treated for more than [redacted] years and all adults were treated for more than [redacted] years.

2.3. Results

The EAG considered the key consideration with the new results to be whether clinical outcomes with olipudase alfa remained stable at the new longer follow-up timepoints. To this point, the EAG considered the new evidence to demonstrate just this: outcomes for spleen and liver volume (ASCEND and LTS13632), and DLco (ASCEND), were all consistent with previous data cut-offs and there was no evidence of treatment waning. The company did not report participants' outcomes on the SF-36 measure of health-related quality of life (HRQoL) at the final follow-up: these data were assessed, but the trial clinical study report (CSR) provided by the company did not include the data tables that contained these data.

In terms of safety outcomes reported by the company, the EAG did not consider there to be a notable increase in safety risk in comparison with the earlier PAP data reported in the original CS. There was a high risk of treatment-emergent advice events (TEAEs) in both studies. A breakdown of adverse events in the original and extension periods were not presented for either study, though the company reported that all participants experienced at least one TEAE in both phases of LTS13632. A sizeable minority of participants ([redacted]% in ASCEND and [redacted]% in LTS13632) experienced a serious TEAE. In [redacted]% and [redacted]% of cases, respectively, these serious TEAEs were considered to be potentially related to olipudase alfa. There were no deaths. In ASCEND, [redacted]% of participants had treatment withdrawn due to a TEAE, [redacted]. Approximately [redacted]% of participants in both studies required a dose reduction due to a TEAE.

2.4. Conclusions on the additional clinical and safety data

Overall, the EAG considered that the additional results provided evidence that the treatment effect of olipudase alfa can remain stable on key clinical outcomes for between [redacted] to [redacted] years. A substantial portion of data was missing from ASCEND at the final follow-up for those outcomes, which does add uncertainty as to whether this stability would be experienced by all people with ASMD who receive treatment. However, the majority of participants received treatment with olipudase alfa for several years, and there is some confidence from the facts that data from LTS13632 were also stable, and there was no clear evidence that the missing data from ASCEND were related to participants' outcomes. In the original EAG report, the EAG noted that improvements in key clinical outcomes were not matched with meaningful improvements in participants HRQoL. As no data were presented by the company for HRQoL, it's unclear whether this was still the case at these later timepoints. During its original assessment, clinical

experts advised the EAG that the clinical outcomes with olipudase alfa would represent a meaningful benefit to the lives and functioning of people with ASMD. Clinical experts also advised that rates of AEs may improve over time with more experience with administering olipdase alfa at a slower rate. The safety data provided for the longer-term follow-up did not show a meaningful tapering in the risk of adverse events over time, though this was difficult to determine from the data presented.

3. IMPACT OF PROGRESSIVE CONDITIONS IN CHILDREN ON CARER HRQOL & CHALLENGES OF MEASUREMENT AND VALUATION

[redacted]

The EAG accepts that quantifying and valuing care-giver burden is an under-researched area. In the original EAG report, the EAG noted the company was conducting a prospective/retrospective cohort study to map disease course, disease burden, HRQoL, resource use, and to validate patient-reported outcome measures (PROs) in ASMD, which was expected to complete in April 2023 [NCT04106544]. The company did not mention this study in its addendum, and the EAG was therefore unsure if results were yet available.

The key issue for the committee is how and whether this issue should be incorporated into decision analysis. If a reduction in care-giver burden is included in the benefits of the treatment in question, then to ensure a fair comparison, the consequent *increases* in care-giver burden from the reallocation of resources required to pay for it must also be included (i.e. the opportunity cost must be modified to account for this). This may be pragmatically implemented by a reduction in the willingness to pay threshold the committee is prepared to accept.