# Highly Specialised Technology

# Sebelipase alfa for treating Wolman disease [ID3995]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technology**

# Sebelipase alfa for treating Wolman disease [ID3995]

**Contents:**

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Alexion Pharma UK**

2. **Comments on the Draft Guidance from experts:**
   a. Clinical Expert – Nominated by MPS Society
   b. Patient expert – Nominated by MPS Society

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

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

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**Sebelipase alfa for treating Wolman disease [ID3995]**

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**Consultation on the draft guidance document – deadline for comments** 5pm on 23 June 2023. Please submit via NICE Docs.

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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.<br><br>The Evaluation Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>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:<br>• 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;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>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): | **Alexion Pharma 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. |
| | **Revised model base case**<br><br>Following discussion at ACM1 and in response to the Committee's views as laid out in the ACD, Alexion has sought updated patient-level data and using those data, we have updated our economic model and herein present a revised economic base case for sebelipase alfa in rapidly progressing LAL-D.<br><br>Further details of the key assumptions informing the revised model base case are presented in Sections 1-13 of this document and summarised in the bullet points below:<br><br>• **Proportion of patients receiving early HSCT**: [redacted] of patients routed to HSCT (based on pooled experience across treatment centres);<br>• **Timing of early HSCT**: Median age of patients routed to early HSCT is [redacted] years<br>• **Stopping treatment**: Patients not routed to early HSCT stop sebelipase alfa treatment at 30 years (whether due to late HSCT or other reasons, eg introduction of new treatment options such as gene therapy)<br>• **Proportion of patients receiving late HSCT**: the [redacted] of patients not routed to early HSCT receive late HSCT<br>• **Timing to late HSCT**: patients receive late HSCT at 30 years<br>• **Dose reduction post HSCT**: [redacted] of patients reduce their dose of sebelipase alfa at 12 months post transplant |

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| | • **Treatment discontinuation post HSCT**: [redacted] of transplanted patients stop treatment at 24 months post transplant<br>• **Utility:** general population utility assumed<br>• **Discount rate:** 1.5% discount rate assumed<br>• **Vial management:** vial sparing assumed across 2 week doses to minimise vial wastage as per clinical practice<br><br>Based on the above model inputs, and based on a revised PAS [redacted] discount) offered to improve the cost-effectiveness of sebelipase alfa vs BSC, our revised base case results are presented in full in Appendix 2 and summarised below:<br><br>Incremental costs: [redacted]<br>Incremental LYG: [redacted]<br>Incremental QALYs: [redacted]<br>ICER (£/QALY): £275,226<br><br>Scenario analyses varying these key model parameters are presented in Appendix 3.<br><br>In addition to the consideration of the revised model assumptions, we would also like to request that Committee considers the additional benefits of sebelipase alfa not captured in the economic modelling, such as societal and caregiver benefits, as summarised in point 12. |
| 1 | **Overview**<br><br>Rapidly progressing LAL-D is an extremely rare condition with evolving disease management, and as a result, available long-term data (particularly those reflecting expected future management) are limited. It is worth noting, however, that we have presented all data that are currently available for all UK treated patients, as well as long-term follow-up data for patients treated for over 10 years, which is significantly longer-term data than would be expected for HST appraisals (although acknowledging that due to the rarity of the condition, patient numbers are still small).<br><br>In Appendix 1, we have provided a summary table of the most recent detailed patient-level data that we have available for patients treated with sebelipase alfa in order to provide as accurate a reflection as possible of current UK clinical practice.<br><br>Despite the presentation of these data previously in our submission documents, responses to EAG clarification questions and responses to technical engagement, the Committee has made a number of statements throughout the ACD document and within their preferred assumptions that do not reflect these available data. Rather, the Committee appears to have made its recommendation based on either more arbitrary assumptions made by the EAG, or based on clinical input that does not account for differences in terms of relative numbers of patients treated across the different UK |

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| | treatment centres, nor account for any anticipated future evolution of LAL-D patient management in the UK.<br><br>While there is inevitable uncertainty around the evolution of treatment practice and new therapeutic developments, we are concerned that a negative recommendation will prevent the very small number of existing and future UK patients with rapidly progressing LAL-D from accessing sebelipase alfa in the near- to mid-term and thereby preclude them from benefiting from any future developments.<br><br>We anticipate that in addition to the evolution of clinical practice with HSCT, over coming years the development of other novel interventions for LAL-D are likely, such as potentially curative gene therapy which is already being investigated in pre-clinical studies. With these developments, we envisage the need for exogenous enzyme replacement therapy with sebelipase alfa in LAL-D patients will likely diminish over coming decades. In this regard, the use of sebelipase alfa in LAL-D could be considered a bridging option to these alternative and potentially curative future management options. We kindly request that NICE considers this potential when making its final recommendation.<br><br>In our comments below (2-7), we will summarise our overall responses to key issues raised in the ACD, and in subsequent comments we will provide responses to specific points, as well as more minor corrections and clarifications that may be important to consider. We have also provided our suggestions for updates to the model base case, alongside the committee's preferred assumptions, to account for the data that are currently available. |
| 2 | **Early HSCT**<br><br>What has become apparent throughout this process, is that there are currently two different approaches to the management of patients with rapidly-progressive LAL-D in the UK, primarily based around the incorporation of early HSCT into the treatment pathway:<br><br>1. The multi-modal approach that includes the use of HSCT, as required, for patients whose disease has previously been stabilised on sebelipase alfa treatment (based on the experience in Manchester);<br><br>2. The approach where HSCT has not yet been clinically required for patients (based on the experience in Birmingham).<br><br>It is also worth noting that in addition to Manchester and Birmingham, there are treatment centres at Great Ormond Street Hospital (GOSH) and Evelina Children's Hospital in London and at Leeds General Infirmary, which have so far treated a limited number of patients, but which have also consulted with and/or referred patients to Manchester for HSCT.<br><br>Alexion has been advised that of the [redacted] LAL-D patients diagnosed since 2011 in the UK & Ireland (including [redacted] paediatric patients), [redacted] have been treated by the Manchester |

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| | centre, [redacted] have been managed in Birmingham, [redacted] have been managed in London (GOSH, Evelina) and [redacted] in Leeds. Of these patients, [redacted] have died.<br><br>Of the rapidly-progressive LAL-D patients who were stabilised on sebelipase alfa, [redacted] have been under the care of Manchester and [redacted] under the care of Birmingham. Of the Birmingham patients, none has yet required HSCT and all [redacted] remain on licensed doses of sebelipase alfa. In contrast, of the [redacted] Manchester patients, [redacted] remains on sebelipase alfa treatment while [redacted] ([redacted]%) have received HSCT; of these, [redacted] patient died, [redacted] have stopped treatment with sebelipase post HSCT and [redacted] are currently receiving reduced doses of sebelipase, [redacted] of whom have been transplanted within the past 12 months and have the potential to stop treatment over the coming 12-18 months.<br><br>It is likely necessary that a treatment paradigm closer to Manchester's innovative multi-modal approach is adopted if patient access to sebelipase alfa is to be secured in the UK given the combination of: 1) NICE's framework for assessing medicines with its emphasis on cost-effectiveness as well as clinical effectiveness; and 2) the high unit manufacturing costs of sebelipase alfa.<br><br>Our original submitted model and base case reflected the Manchester experience of early HSCT, with [redacted]% of patients in the model routed to early HSCT. The most recent data from the Manchester centre indicate that [redacted]% of patients treated there have been routed to HSCT. If the pooled experience across the English centres is considered, based on [redacted] of [redacted] patients routed to HSCT, the corresponding figure would be [redacted]%. We believe it is more appropriate to reflect this value in the model, based on observed practice across the UK.<br><br>We are concerned that the Committee's preferred approach, which assumes only [redacted]% of patients receive early HSCT, hasn't accounted for the most up-to-date available data on proportions of patients receiving early HSCT.<br><br>In addition to the proportion of patients routed to HSCT, the timing of routing is also an important model input. Based on the ACD, Committee noted a preference for early HSCT to occur between 3 to 4 years of age. Having reviewed the data, we observe that the actual median age of patients receiving early HSCT is [redacted] years (range [redacted]years). We therefore maintain that it would be more appropriate to model the observed median of [redacted] years and have incorporated into our base case analysis accordingly. |
| 3 | **Stopping treatment with sebelipase alfa**<br><br>Besides early HSCT and subsequent treatment cessation, there are a number of other reasons why patients may come off sebelipase treatment in the longer-term, including: late HSCT (see below), further evolution in treatment practice as experience in treated patients grows, the introduction of future cell and gene therapies, and the introduction of biosimilar medicines into the market. Although there is also uncertainty around these, when combined with the very small patient numbers remaining on sebelipase treatment, along with the likely need for late HSCT, we believe that it is reasonable to assume that all patients will have come off treatment by 30 years. |
| 4 | **Late HSCT** |

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| | In addition to the consideration of early HSCT, Committee pointed to uncertainty around the potential use of late HSCT for patients in the longer term. As data are currently not available for patients beyond 11 years (with the patient with the longest follow-up data being the patient having recently undergone an elective HSCT), we had to estimate this based on our best understanding and with clinical input.<br><br>Our assumption was that within 30 years all patients would have experienced issues with venous access and therefore been routed to HSCT and would therefore ultimately wean off treatment (based on current data). It is also worth noting that the EAG received input that this could be expected to happen as early as after 20 years of treatment.<br><br>Further, loss of venous access may not be the only reason for patients having late HSCT – they may elect to have HSCT or some patients could develop ADAs in the longer-term and experience diminishing sebelipase alfa efficacy, which could also require HSCT. It is also worth noting that based on current pooled experience across the treated patient population in the UK, between [redacted] of patients received early HSCT (as described in Section 2 above), and therefore, late HSCT will only be a consideration for the remaining proportion [redacted] of an already small patient population. |
| 5 | **<u>Treatment post-HSCT</u>**<br><br>An additional area of uncertainty relates to sebelipase alfa dose reduction and ultimate treatment discontinuation post-HSCT.<br><br>Committee has indicated that its preferred assumptions are that approximately 40% of people would stop sebelipase alfa after HSCT and it would take 2-2.5 years after transplant to do so. Analysis of the most recent data, however, indicates that these assumptions are out of date. We believe it would be more appropriate to include the updated data in the economic model.<br><br>Our understanding, based on data for current UK patients and clinical input from the Manchester treatment centre, is that post-HSCT, patients initially receive sebelipase alfa at their preceding dose while they stabilise following HSCT and thereafter begin to reduce their dose. Experience to date demonstrates that patients can start reducing their dose from [redacted] months after HSCT, with additional decreases thereafter and when clinically indicated, they may discontinue treatment (by 24-36 months).<br><br>Data from the Manchester centre show that to date, of the [redacted] patients who have had sufficient time to stop treatment post transplant (ie>2 years), [redacted] ([redacted]) have been able to stop treatment; the remaining patient has also been able to reduce their sebelipase dose and the frequency of dosing. The [redacted] further patients received their transplants within the past 6 months so have not yet had sufficient time post-transplant to be assessed for treatment discontinuation. However, [redacted] have already reduced their dose of sebelipase and have the potential to stop treatment over the coming 12-18 months. Should these patients also stop treatment, this would represent [redacted] of post-transplant patients stopping sebelipase. |

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| | Based on the observed data, we believe that the appropriate model inputs should reflect that at least [redacted] (and up to [redacted]) of surviving patients will stop treatment (likely within 2-2.5 years of transplant), while [redacted] of patients are able to reduce their treatment dose and frequency of dosing by 12 months post transplant. |
| 6 | **Health-related quality of life**<br><br>We acknowledge that there is some uncertainty around the health-related quality of life (HRQL) for patients with rapidly progressing LAL-D receiving treatment with sebelipase alfa. However, there is some evidence available for these patients, which needs to be considered rather than disregarded. This includes the retrospective cohort study by Demaret et al. (2021), which included 5 people with Wolman disease who had sebelipase alfa treatment in France, with up to 10 years of follow up. This information was provided within the appraisal and mentioned within the ACD (page 15), and provides a clear demonstration that patients undergoing treatment with sebelipase alfa experienced HRQL at or near the same levels as healthy patients, with normal cognitive development.<br><br>During the committee meeting, the clinical experts and patient representatives also noted that although patients experienced some challenges, mainly around the restrictive diets they are often required to follow, they were generally able to adapt to these restrictions and they were not thought to diminish their quality of life by the 20% reduction explored by the EAG. Further, as part of our responses to technical engagement, we also provided evidence for paediatric quality of life in a number of chronic conditions (including cancer, peanut allergy, and for those receiving IV compared to oral therapy) to attempt to put the impact on patients receiving sepelipase alfa into context. The impact on paediatric HRQL for cancer was indicated at approximately 10% reduction in utility, while most other conditions were found to impact utility by 5–10%.<br><br>Despite the available evidence and clinician and patient testimony, Committee has indicated its preference to incorporate the arbitrary 20% reduction in utility. We do not believe this is appropriate and would suggest general population utility is most appropriate, with scenario analyses exploring a 5-10% reduction in utility to account for the small number of patients who may experience diminished HRQL; this would appear to be more reflective of the available evidence and patient/clinician testimony. |
| 7 | **1.5% versus 3.5% discount rate**<br><br>On page 17, the ACD states: “The committee highlighted that it is unknown if the benefits of sebelipase alfa are sustained over a long period, given the limited longer-term evidence.” This is the reason for rejecting the use of the 1.5% discount rate.<br><br>Currently available evidence, along with clinical and patient input, supports the points that patients would otherwise die and that they are restored to full or near-full health. The ACD itself uses the ongoing efficacy of sebelipase treatment to support arguments for lifelong treatment with sebelipase alfa rather than assuming that patients would require late HSCT or would come off treatment with sebelipase alfa. |

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| | Given the rarity of the condition, with fewer than 10 patients on sebelipase alfa treatment in the UK, data for this appraisal were always going to be limited. Nonetheless, as Alexion has been providing sebelipase alfa to patients under an ongoing global access to medicines programme for the past 8 years, we have been able to provide over 10 years of treatment data for these patients, demonstrating ongoing, long-term efficacy of sebelipase treatment – this is significantly longer-term data than would be expected for most technology appraisals, particularly those being assessed through the HST programme.<br><br>While we acknowledge that patients may require late HSCT in future, this would not be expected to relate to reduced long-term efficacy of the drug, but rather venous access issues. Moreover, this is accounted for within our assumption of all patients stopping treatment by 30 years.<br><br>We would therefore kindly ask the Committee to re-consider its rejection of the use of the 1.5% discount rate, based on the criteria suggested by NICE. |
| **Other comments, and minor corrections and clarifications** | |
| 8 | On Page 7, the ACD states: “The company stated that sebelipase alfa is a first-line treatment option for people with Wolman disease, with best supportive care as the alternative option (which results in early death).”<br><br>In order to put the severity of the condition into context and provide an appropriate description of what is meant by “early death”, it is important to clarify that in the absence of treatment with sebelipase alfa death usually occurs within the first 6 months of life, with a median age of death at 3.0 months. |
| 9 | On page 13, the ACD states that: “The EAG noted that while the Kaplan–Meier curves had the best estimates of expected survival during the trial follow up, it considered that the estimated overall survival over a lifetime was too optimistic and highly uncertain because of the limited data and long-term assumptions.”<br><br>We acknowledge that there is uncertainty around the long-term survival for patients with rapidly progressing LAL-D; however, given both the data that are available and the input from clinical experts, assuming long-term general population mortality is the most reasonable assumption at this point. It should be noted that we have incorporated increased mortality risks at various points in the model, to reflect the available data on the patient experience so far, including the initial risk of mortality when first presenting with the disease and starting treatment with sebelipase alfa, and also when undergoing HSCT, and have modelled our understanding of the long-term clinical expectations for these patients. |
| 10 | On page 15, the ACD states: “The committee recognised that in clinical practice, doses are managed to minimise vial wastage and agreed to consider this scenario in its decision-making.” However, this has not been included in the committee’s preferred base case assumptions. As the committee agrees that dose modulation is used in UK clinical practice to minimise vial wastage, we have included this approach in the updated model base case. |

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| 11 | On page 17, the ACD states: "The committee also considered that the company model significantly underestimated uncertainty in clinical outcomes including the company's probabilistic sensitivity analysis, which did not vary key model parameters." We would note that the PSA varied over 100 parameters. Committee did not, however, provide information on the key model parameters it wanted to see varied. If Committee can clarify, we would be happy to explore the feasibility of varying further parameters in the PSA. | |
| 12 | The ACD states that the committee "did not identify additional benefits of sebelipase alfa not captured in the economic modelling."<br><br>We would like to point to the following additional benefits of sebelipase alfa treatment that have not been captured in either the Company's or EAG's base case analyses, and do not appear to have been considered by the Committee:<br><br>1. significant societal benefits of treatment with sebelipase alfa, as a result of preventing infant death<br>2. significant disutility associated with parental bereavement (a scenario can be run to capture the bereavement disutility and we would therefore kindly request that Committee explore this scenario in its deliberations)<br>3. substantial economic productivity impacts associated with parents losing their child and of the lost economic potential from the child themselves.<br><br>We would kindly request that the Committee considers these broader benefits in its deliberations. | |
| **13** | **The committee's preferred assumptions** | **The company's suggested assumptions** |
| | The company and EAG base-case analysis included the same key assumptions apart from the choice of discount rate used for cost and benefits (see section 3.12). The committee recalled that the base-case analysis from the company and EAG did not include its preferred assumptions, which were:<br><br>• assuming that up to 50% of people would have haematopoietic stem cell | Based on the arguments provided above, the company do not believe that the committee's preferred assumptions appropriately account for data that are currently available for UK patients and therefore suggests the following model inputs are more appropriate:<br><br>• [redacted]% (based on pooled experience across treatment centres) to [redacted]% (based on Manchester experience) of |

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| | transplant after sebelipase alfa treatment (see section 3.7)<br><br>• people with Wolman disease who have an early haematopoietic stem cell transplant after sebelipase alfa would, on average, have this between 3 to 4 years of age (see section 3.8)<br>• people with Wolman disease who have a late haematopoietic stem cell transplant after sebelipase alfa are likely to have this after 30 years of age (see section 3.8)<br>• 40% of people with Wolman disease would likely stop sebelipase alfa after haematopoietic stem cell transplant and would take between 2 and 2.5 years after the transplant to stop treatment (see section 3.10)<br>• not everyone with Wolman disease would reduce their dose of sebelipase alfa after haematopoietic stem cell transplant (see section 3.10)<br><br>• the EAG's scenario analysis applying a 0.8 weighting to general population utility values was more plausible than assumed general population utility values, but the committee would prefer to see analysis that more accurately captured the quality-of-life changes over the lifetime of the model (see | people would have early HSCT after sebelipase treatment<br>• people with Wolman disease who have an early HSCT after sebelipase alfa would, have this around 2 years of age<br>• people with Wolman disease who have not had an early HSCT would require a late HSCT due to loss of venous access at 30 years of age<br>• Based on current evidence for patients who have had sufficient time post HSCT to step down and stop treatment, at least [redacted]% (and up to [redacted]%) of patients with Wolman disease would stop sebelipase treatment after HSCT at 2 years after the transplant<br>• Based on the current experience of post-HSCT patients, [redacted] of patients would reduce their dose (potentially multiple times) within the first 12 months following HSCT<br><br>• we do not believe that an arbitrary allocation of a 0.8 weighting to general population utility values is appropriate as it neither aligns with current published data nor with clinical/patient representative opinion. Based on the evidence presented in Demaret et al. (2021), we believe the use of general population utilities would be more appropriate and aligns with presented |

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| | section 3.12)<br><br>• applying discount rate of 3.5% to costs and benefits (see section 3.13)<br>• applying a QALY weighting of 3 (see section 3.14). | evidence, with consideration of the scenarios applying a 0.95 and 0.90 weighting to general population utilities to account for the small number of patients that may experience diminished HRQL.<br><br>• applying discount rate of 1.5% to costs and benefits<br>• applying a QALY weighting of 3<br><br>Additional points:<br>• application of vial management to minimise vial wastage, as per clinical practice.<br><br>When these positions are taken forward into the cost-effectiveness model, with a revised PAS, the deterministic ICER is £275.226. See Appendix 2 for further detail of the base case outcomes. |

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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. 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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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- 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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**Appendices**

**Appendix 1: Currently available detailed patient-level data for Wolman disease patients treated with sebelipase alfa in England**

| Patient ID | Previous trial? | Treatment start | Current age | Current dose | HSCT (yes/no) | Status | Comments |
|---|---|---|---|---|---|---|---|
| Manchester (including patients referred to Manchester) | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
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|---|---|---|---|---|---|---|---|
| **Evelina Children's Hospital, London** | | | | | | | |
| [redacted] | | | | | | | |
| **Birmingham** | | | | | | | |
| [redacted] | | | | | | | |
| **Leeds** | | | | | | | |
| [redacted] | | | | | | | |
| **Great Ormond Street, London** | | | | | | | |
| [redacted] | | | | | | | |

**Notes:** [redacted]

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**Appendix 2: Base case results based on updated model**

Base case – deterministic

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|---|---|
| BSC | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Sebelipase alfa | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £275,226 |

**Key:** ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
**Note:** Costs and QALYs are discounted at 1.5% per annum.

Base case – probabilistic (using expanded parameter inclusion)

| Technologies | Total costs (£) [95% CI] | Total QALYs [95% CI] | Incremental costs (£) [95% CI] | Incremental QALYs [95% CI] | ICER versus baseline (£/QALY) [95% CI] |
|---|---|---|---|---|---|
| BSC | [redacted] | [redacted] | - | - | - |
| Sebelipase alfa | [redacted] | [redacted] | [redacted] | [redacted] | £274,682<br>[£268,617 to £282,161] |

**Key:** ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
**Note:** Costs and QALYs are discounted at 1.5% per annum.

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**Sebelipase alfa for treating Wolman disease [ID3995]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on 23 June 2023. Please submit via NICE Docs.

**Appendix 3: Scenario analyses based updated model**

| Scenario and sensitivity | ICER | Change | % |
|---|---|---|---|
| Basecase | £275.23K | - | - |
| [redacted] | [redacted] | [redacted] | [redacted] |

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| Scenario and sensitivity | ICER | Change | % |
|---|---|---|---|
| Basecase | £275.23K | - | - |
| [redacted] | [redacted] | [redacted] | [redacted] |

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Manchester University NHS Foundation Trust; lead responder [redacted] consultant paediatric inherited metabolic disease. |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | While I have no links to the tobacco industry (?) I have acted as a consultant and trial investigator to Alexion. |

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| **Name of commentator person completing form:** | [redacted] |
|---|---|

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>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 | I have grave concerns regarding this process, which has carried on for over 7 years. The decision which clearly could have been reached after the 1st appraisal was that a funding agreement could have been reached on funding infantile onset LALD but not later-onset disease. This was resisted by the company at the time. The same conclusion however was not able to be reached on this occasion, despite much longer term evidence of benefit and a significant cost reduction by the current use of HSCT, not reflected at all in the first appraisal. This suggests a serious inconsistency in the 2 processes. In the process of the last nearly10 years since this product was licensed, the company have provided free/compassionate use Sebelipase to all post-trial or newly diagnosed infantile onset patients. To deny any reference to this vast cost saving (£15-20 million) to the NHS by this protracted process (well beyond any timescales in the NICE description of the HST) seems to be wilfully difficult and an incentive for further procrastination. |
| 2 | The cost effectiveness modelling process which is central to the NICE decision has little to do with efficacy of the product. That this is the most effective enzyme replacement therapy the LSD community has seen in 20 years seems to be irrelevant to the process. In fact the perverse situation when the longer these children survive as adults the less cost effective the treatment becomes illustrates just how unsuitable the modelling process is for rare condition therapies. At the very first NICE meeting relating to this drug I remember a health economist approaching me afterwards to ask about the comparator group (ie palliative care and rapid death) and stated that they did not know how to model this and that he didn't really understand it. It seems that this has not changed in the intervening 7 years. I (as a clinical expert) am asked in the model to suggest what will happen to use of sebelipase and HSCT over the next 50-60 years of a patient's life. Despite having seen more of these infants than any other Doctor I am aware of I have no idea how to do this and to make me suggest answers and numbers is simply magical thinking. I am then however not allowed to suggest that any of these patients would have another (new) treatment in this vast timeframe, despite our gene therapy for LALD being 12 months from clinical trials. |

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| | |
|---|---|
| 3 | Decision to transplant: I include a slide reviewing treatment of all infants diagnosed or treated with Wolman disease in the UK in the last 12 years. This includes trial patients treated here initially then repatriated. This reflects the best evidence available globally on current treatment trends in this exceptionally rare disease. As can be seen almost 50% of children have received HSCT in the first 10 years of life, suggesting this number may increase over the next 10 years. While the mean age at HSCT was 3.3 years the median was 2 years, with 1 patient having HSCT at 10 years of age. While early transplants as defined by the committee are indeed happening before the age of 4 in most, later transplants start from the age of 10 years and more are likely in the second decade in our expectation. |
| 4 | Quality of life: As can be seen from research conducted by the MPS society in their consultation responses the families with Wolman disease view their quality of life very highly. If we use a subjective assessment of QOL the family perception is of a much higher QOL than perceived by healthcare professionals as they view every day in the context of their child having a 'fatal' childhood disease. QOL is perceived through expectations not just experience. Via this lens and the data provided by the MPS society I think it is reasonable to assume the health related QOL of children and families with Wolman disease is greater than 80% of a healthy person. |
| 5 | Dosing of Sebelipase post HSCT: as can be seen from the data provided 50% of surviving transplanted patients have stopped ERT. The 50% still on ERT are on reducing doses. We have reviewed the dosing history of our patients treated so far and, while individually managed, the average doses are:<br>5mg/kg weekly in first year after HSCT<br>1mg/kg alternate weekly 1-3 years post HSCT<br>No ERT by 3 years post HSCT |
| | |

Insert extra rows as needed

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**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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. 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.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- 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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| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Evaluation Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>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:<br>• 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;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>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): | The MPS Society |

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| | |
|---|---|
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments<br><br>Insert each comment in a new row.<br>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 | Although the cohort of early onset LAL D patients is small, the life survival and demonstrated long-term benefits of treatment is undeniable compared to the alternative, which is death. |
| 2 | To address the committee's uncertainties around how quality of life compares to people without the condition we were able to conduct a further survey during the two-week consultation period. The survey explored how the level of functioning and quality of life of children with LAL D, compared to children without the condition.<br>We received 15 responses from people between the ages of 6-12 years (current age range of known people with LAL D in England) 33% of responses were from people with LAL D. The data demonstrated that people with LAL D are achieving good to normal developmental gains. Whilst there are more medicalisation and delayed skills in people with LAL D aged 1-3 yrs, review of current data suggests that people with LAL D are improving with age and becoming closer to the healthy population in terms of abilities and quality of life. Our oldest LAL D child in the 6-8yr group met all endpoints under each category. Our LAL D child in the 9-12 yr group met more endpoints than non-affected children in two out of three categories and equalled in the other.<br>[redacted]<br><br>Outcomes outlined above are consistent with evidence previously submitted to NICE. In 2017 we provided the committee with evidence that the company presented at WORLD 2017. This data reflected the social and developmental outcomes of five clinical trial patients all who were over the age of 3 years. Reported outcomes demonstrated that all were developing well and within normal range with four out of five children |

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**Sebelipase alfa for treating Wolman disease [ID3995]**

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| | |
|---|---|
| | attending nursery or school. At this time we also presented case examples demonstrating the improved clinical and daily lives of children with LAL D, all of whom were thriving with development within the good to normal range.<br><br>In March 2023 further data and outcomes presented showed that children were achieving developmental gains with some excelling in areas such as reading and writing. All children were active with good social opportunities appropriate to their age.<br><br>[redacted] |
| 2 | There is an overwhelming concern from the clinical and patient community that the lifesaving / normalisation ability of ERT, is being nullified by cost.<br><br>The UK is unrivalled in its treatment of early onset LALD with over 22 people treated in the UK.<br><br>Sebelipase alfa is one of the most effective ERT's seen for many years. The clinical outcomes and lifesaving benefits seen in patient responses is transformational, demonstrating that sebelipase alfa has real world clinical benefit regardless of whether patients subsequently require or elect to have a HSCT. |
| | Despite the idiosyncratic nature of this appraisal, the prolonged delay has given 6 more years of additional data and clinical understanding and has further validated that children's level of functioning and quality of life improves, as they get older and is comparable to children without the condition.<br><br>We now have over 11 years of excellent data, similar to recently approved gene therapies. Insisting on moving the bar on how much long term data is needed not only undervalues this treatment but discriminates against both existing patients and any newly diagnosed families with LAL D.<br><br>We therefore feel that unreasonable emphasis has been placed on uncertainty of outcomes and the committee have failed to proportionately attribute reasonable value to the longevity of the outcomes in treated children. |
| 3 | We are concerned that the inference of the below statement, implies that it is the condition that prevents the child for being able to do certain activities. To be clear, it is not the condition but their port-a-cath devices or gastrostomies that prevent them for participating in activities such as contact sports for example.<br><br>3.2 *'One patient expert explained that having sebelipase alfa means that, apart from restrictions in diet and not being able to do certain activities, their child is able to go to school and participate in most activities with their peers many years after diagnosis'* |
| 4 | We do not feel the below statement is reflective of the full population. Whilst ERT in general can restrict holidays abroad for periods of longer than a week. If holidaying in the UK, it is more achievable as homecare nurses can be provided if planned and available. The time missed from school is minimal for most patients as treatment can be planned to prevent this. Many children in receipt of ERT (not just with LAL D) now have their treatment at school to limit this further. |

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| | |
|---|---|
| | *3.2 -'However, the experts also highlighted that the treatment can affect the ability to have family holidays and can result in the need for additional support for children who miss some school time'* |
| 6 | To the point below. We felt that it was wholly inappropriate to try and force clinicians to give a hypothesis on the proportion of patients who would have a transplant at the meeting. It would be very challenging for any clinician to give a view on something they have not experienced or had to consider within their clinical practice.<br><br>Despite this, evidence does indicate that 43% of surviving patients so far have had HSCT.<br><br>*3.7 'Also, there was a difference in views between clinical experts about the use of haematopoietic stem cell transplant. One of the clinical experts estimated that up to 50% of people with Wolman disease would have a haematopoietic stem cell transplant. Another clinical expert had stated that none of the people with Wolman disease in their practice had a transplant after sebelipase alfa'.* |
| | In response to the below statements - Current experience of HSCT bar one is a result of ERT no longer being viable.<br><br>All people who had received HSCT due to ERT no longer being viable stated that at the time, if they had a choice, they would not have opted for it. Some of the reasons shared included; high mortality risks, uncertainties, family members being donors and prolonged hospital stays.<br><br>For those people tolerating and responding to ERT, HSCT may also not be a consideration or even known about. This is a fair view, as most people given the choice would opt for a treatment that presents the least risk. We have seen this in MPS VI, where transplants are rarely carried out since ERT was approved.<br><br>However, whilst the long-term benefits of HSCT are still uncertain, it is showing better correction overall, including improved GI symptoms resulting in people being able to tolerate a normal diet without fat restrictions and being able to stop ERT.<br><br>One parent has spoken very positively on the additional benefits of HSCT<br><br>*"Yes, it's made a huge difference. He's eating. So, after the transplant, he's a completely different child. He's had no vomiting issues, unless he has a bug or he has a high temperature, sometimes he might vomit. Diarrhoea, he doesn't have anything like that."*<br><br>*He's completely fine now. It's done everything, to be honest, we didn't expect. The way he is in himself talking, moving about, eating, growing. He's a completely different child."*<br><br>As more is known and outcomes more widely talked about, HSCT may become a consideration for more people, even if ERT is well tolerated. As in, the most recent case discussed at committee. |

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| | |
|---|---|
| | ***3.2/3.7****-'The patient experts explained that the decision to have a hematopoietic stem cell transplant is a difficult one and most parents and people with Wolman disease would only choose to have a transplant if sebelipase alfa was not providing adequate benefits'*<br><br>*3.7 A patient expert explained that because of the mortality risks with transplant, long hospital stays, being in isolation, and the uncertain long-term benefits, most people with Wolman disease and their carers would prefer to continue sebelipase alfa until the treatment becomes ineffective.* |
| | In response to the below statement. Given current outcomes of HSCT, I believe that some clinical centres would now discuss HSCT as an early treatment option after a period of stability on ERT.<br><br>*3.8 The committee concluded that some people have haematopoietic stem cell transplant early, but the proportion of early transplants is uncertain and early transplant would likely occur, on average, after 3 to 4 years.* |
| | In response to the below; I believe it is anticipated that all patients will stop ERT after a period of stabilisation following HSCT. However, this will be determined by clinical response, level of engraftment and response to ERT being reduced and withdrawn.<br><br>Currently 50% of transplanted people have now stopped ERT<br><br>*3.8 One clinical expert explained that out of 5 people having sebelipase alfa, 1 had continued with the standard dose, 2 were on a reduced dose, and 2 stopped sebelipase alfa treatment within 2 to 2.5 years after haematopoietic stem cell transplant. The committee considered that the assumptions around sebelipase alfa dosing over a lifetime was highly uncertain. The committee concluded that up to 40% of people with Wolman disease would stop sebelipase alfa after haematopoietic stem cell transplant.* |
| | Evidence in other conditions treated with ERT contradicts the EAG's view below. In a recent publication on the role of elusolfase alfa it was determined that; *'long-term treatment with elosulfase alfa slows down the progressive deterioration in endurance associated with the disease, has a positive impact on pulmonary function and patients' ability to perform ADL and lessens their need for caregiver assistance. While ERT is not expected to result in normalisation of clinical parameters, appropriate continued therapy leads to clinically meaningful improvements in some parameters and a slower progression of this progressive debilitating disease overall'* ***Cleary et al. Orphanet J Rare Dis (2021)***<br><br>*3.12 The EAG reported that frequent infusion with sebelipase alfa may affect quality of life, as seen in other conditions that need enzyme replacement therapies* |
| | NHS England prides itself on having a fair and just system and we acknowledge that part of this system is ensuring value for money and cost effectiveness, but how can this be true when less effective and expensive therapies are approved over a treatment that has shown lifesaving properties and disease reversal.<br><br>*"Davis 1994 concluded "unless the child is in the process of dying, continued survival is always on balance a benefit to the child, so that if treatment is not burdensome it should always be given"* ***(quoted by Sarah Elliston 2007; The best interests of the child in Healthcare)*** |

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Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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# Health Technology Evaluation

# Sebelipase alfa for treating Wolman disease [ID3995]

### Comments on the DG received from the public through the NICE Website

| **Name** | [redacted] |
|---|---|
| **Comments on the DG:** | |

**Recommendation 1.1**
This recommendation is totally unfair and it is not based on clinical experience. Sebelipase alfa is working well and satisfactory in Wolman cases as it has been demonstrated in countries like Spain and USA. On the other hand, Wolman patients don´t have many options to survive without this type of ERT (enzymatic replacement therapy) treatment. This recommendation is attacking to the right of the life.

**Recommendation 1.2 But it is not clear how much longer people will live or how their quality of life compares with people without the condition.**
Sebelipase alfa is using in some countries from 2015 in Wolman cases (Spain & USA for instance). These patients still alive with better life quality than others. It is not a question of "how much" is a question about live or die.

**Recommendation 1.2 Because of the clinical uncertainties and uncertainties around the likely treatment pathway when sebelipase alfa is used, the cost-effectiveness estimates are highly uncertain.**
This text about certainty is totally wrong. There is several scientific publications about the great results of treatment. Please have a look to these papers:
https://pubmed.ncbi.nlm.nih.gov/33407676/
https://pubmed.ncbi.nlm.nih.gov/37222260/
https://pubmed.ncbi.nlm.nih.gov/36133901/

**Paragraph 3.18**
Totally unfair under the patient´s point of view and against of WHO recommendations.

**Paragraph 3.5**
Maybe we can find several reasons for this uncertainty because there still does not have enough studies about long term safety but this therapy is the only option to survive with life´s quality

**Paragraph 3.15**
As representative of patients (AE LALD: www.aelald.org) the cost- effectiveness of the treatment is not the reason to deny the patient´s rights. NICE should negotiate with the company but at the same time must provide the best treatment to Wolman patients.
Please have a look:
https://www.who.int/news-room/fact-sheets/detail/human-rights-and-health

**Paragraph 3.16**

Please, do you have any report or publication or paper about this information?. Russia, Spain and USA are the countries with the major quantity of diagnosed cases. Any of these countries are not Asian countries.

# Sebelipase alfa for treating Wolman disease (rapidly progressive LAL-D) [ID3995]

## EAG response to company draft guidance consultation response


**Produced by** Newcastle University

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**Date completed** 11th July 2023

Please note all confidential information is both underlined and separately highlighted and may include information that is submitted under 'commercial in confidence' in turquoise, information submitted under 'academic in confidence' in yellow, and information submitted under 'depersonalised data' in pink.

# 1 Introduction

In May 2023, the National Institute for Health and Care Excellence (NICE) issued a Draft Guidance Consultation (DGC) for sebelipase alfa for treating Wolman disease.[1] The DGC states sebelipase alfa is not recommended, within its marketing authorisation, for treating Wolman disease (rapidly progressive lysosomal acid lipase deficiency [LAL-D]) in people who are 2 years or younger when treatment starts.[1] The DGC states that because of the clinical uncertainties and uncertainties around the likely treatment pathway when sebelipase alfa is used, the cost-effectiveness estimates are highly uncertain.[1] They go on to state that even when considering the condition's severity, and the effect of sebelipase alfa on quality and length of life, the most likely cost-effectiveness estimates are much higher than what NICE considers an acceptable use of NHS resources.[1]

## *1.1 Overview of the company's DGC response*

In June 2023, the company submitted a response to the NICE DGC.[2] The company's response includes a written document, a revised economic model, and an updated base case analysis. The company's response document provides additional discussion around five key issues which are discussed in the next section below with updated analyses presented as appropriate.[2]

The uncertainty in the current evidence base is anticipated given the very small number of existing and future UK patients and the company acknowledge the uncertainty around the evolution or treatment practice in the UK and the potential for new therapeutic developments. The key issues are summarised in Table 1, which presents the NICE Appraisal Committee's preferred economic model assumptions, alongside the company's suggested assumptions. This is done in order to highlight how the two differ, for all except the application of a QALY weight of 3.

The EAG conducted cost-effectiveness analysis using the revised company economic model for all the preferred assumptions put forth by both the NICE Appraisal Committee and the company. The EAG checked the base case analysis presented by the company which produced a base-case ICER of £275,226. This base-case analysis utilised a discount rate of 1.5% for future benefits and costs. It also assumed that [redacted] of patients would undergo haematopoietic stem cell transplant (HSCT) after sebelipase alfa treatment, and [redacted] of patients would discontinue sebelipase alfa after [redacted] years of HSCT. The analysis further assumed that the quality of life for patients with Wolman disease would remain consistent with that of the general UK population. Using the same approach with the Appraisal committee's preferred assumptions the EAG provided the committee analysis which produced a base-case ICER of £608,675. This base-case analysis utilised a discount rate of 3.5% for future benefits and costs. It also assumed that that 50% of patients would undergo HSCT following 3 years of sebelipase alfa treatment. After 2 years of HSCT, it was estimated that 80% of patients would discontinue sebelipase alfa, with 40% stopping the treatment altogether. The committee base-case analysis also considered a 20% decrease in the quality of life for patients with Wolman disease compared to the general UK population. To minimise vial wastage, the committee assumed vial sharing across two-week doses.

Additionally, the EAG explored different ICERs based on the committee's base-case assumptions. In the committee's base-case scenario, a discount rate of 1.5% was applied to future benefits and costs, resulting in an ICER of £501,499. Another scenario assumed that patients would undergo HSCT after 4 years of sebelipase alfa treatment, with 40% discontinuing the treatment over 2.5 years of HSCT. This alternative scenario yielded ICERs of £613,011 and £505,421 for discount rates of 3.5% and 1.5% for future benefits and costs, respectively.

The EAG conducted further analyses on the ICER which are described below, and the summarised results are presented in Table 2. All scenarios are presented using QALY weightings of 1 (equivalent to no weight) and 3 (as requested by both the company and the committee).

**Table 1: Summary of committee's and company's preferred assumptions**

| The committee's preferred assumptions | The company's preferred assumptions |
|---|---|
| Assuming that up to 50% of people would have haematopoietic stem cell transplant after sebelipase alfa treatment (see section 3.7 of DGC). | [redacted] (based on pooled experience across treatment centres) to [redacted] (based on Manchester experience) of people would have early HSCT after sebelipase treatment. |
| People with Wolman disease who have an early HSCT after sebelipase alfa would, on average, have this between 3 to 4 years of age (see section 3.8 of DGC). | People with Wolman disease who have an early HSCT after sebelipase alfa would, have this around 2 years of age. |
| People with Wolman disease who have a late HSCT after sebelipase alfa are likely to have this after 30 years of age (see section 3.8 of DGC). | People with Wolman disease who have not had an early HSCT would require a late HSCT due to loss of venous access at 30 years of age. |
| 40% of people with Wolman disease would likely stop sebelipase alfa after HSCT and would take between 2 and 2.5 years after the transplant to stop treatment (see section 3.10 of DGC). | Based on current evidence for patients who have had sufficient time post HSCT to step down and stop treatment, at least [redacted] (and up to [redacted]) of patients with Wolman disease would stop sebelipase treatment after HSCT at 2 years after the transplant. |
| Not everyone with Wolman disease would reduce their dose of sebelipase alfa after HSCT (see section 3.10 of DGC). | Based on the current experience of post-HSCT patients, [redacted] of patients would reduce their dose (potentially multiple times) within the first 12 months following HSCT. |
| The EAG's scenario analysis applying a 0.8 weighting to general population utility values was more plausible than assumed general population utility values, but the committee would prefer to see analysis that more accurately captured the quality-of-life changes over the lifetime of the model (see section 3.12 of DGC). | The company argue that they do not believe that an arbitrary allocation of a 0.8 weighting to general population utility values is appropriate as it neither aligns with current published data nor with clinical/patient representative opinion. Based on the evidence presented in Demaret et al. (2021),[3] the company believe the use of general population utilities would be more appropriate and aligns with presented evidence, with consideration of the scenarios applying a 0.95 and 0.90 weighting to general population utilities to account for the small number of patients that may experience diminished HRQoL. |
| Applying discount rate of 3.5% to costs and benefits (see section 3.13 of DGC). | Applying discount rate of 1.5% to costs and benefits. |

| The committee's preferred assumptions | The company's preferred assumptions |
|---|---|
| Applying a QALY weighting of 3 (see section 3.14 of DGC). | Applying a QALY weighting of 3. |
| Abbreviations: EAG, evidence assessment group, DGC, Draft Guidance Consultation; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplant; QALY, quality adjusted life year. | |

### *1.2 EAG brief description of and response to the individual comments raised in the company's DGC stakeholder response*

#### 1.2.1 Key issue 1: Early HSCT

The first key issue raised by the company are the two different approaches to the management of patients with rapidly-progressive LAL-D in the UK: (1) the multimodal approach that includes the use of HSCT as required for patients whose disease has previously been stabilised on enzyme replacement therapy (ERT) treatment (based on the experience of Manchester); and (2) the approach where HSCT has not been clinically required for patients (based on the experience of Birmingham).[4] Other centres have also consulted with/referred patients to Manchester for HSCT, including [redacted] children who were referred from the Republic of Ireland ([redacted] undergone HSCT).[4]

The company provides patient-level data for patients treated with sebelipase alfa in the UK (Appendix 1).[4] Although the age that an individual patient which had HSCT is not provided, new analysis by the company suggests that, using data from Manchester, [redacted] of patients are routed to early HSCT.[4] Across all English centres, the corresponding figure is [redacted].[4] The EAG's approach, which was also the preferred Committee approach was 50%.[1] The EAG welcome the additional data, although given the small patient population, are unclear why only 11 patients are included, and not 21 (who were treated with sebelipase alfa) or 15 (those treated with sebelipase alfa who survived). The proportion of patients undergoing HSCT would therefore be either [redacted]. Therefore, the [redacted] proposed by the company may still overestimate the patients likely to have HSCT.

The timing of early HSCT is also an important driver for the cost-effectiveness modelling. The Committee noted a preference for early HSCT to occur between 3-4 years of age as more realistic.[1] The company have reviewed the evidence and suggest an actual median age of [redacted] years (range [redacted] years).[4] Professor Simon Jones further indicates the mean age was 3.3 years.[5] Given the current definition of early HSCT, likely to be 4 and under, there is [redacted]).[2] As this child had elected to the have HSCT after 10 years of age, they may be considered to have had late HSCT (which would fit with the range of [redacted] given by the company for early HSCT).[4] Therefore, the revised English centre data using the latest company patient data would be [redacted] ([redacted] patients had early HSCT, out of [redacted] patients in England who whom were alive and being treated with sebelipase alfa). Using either [redacted] patients treated with sebelipase alfa or the 15 patients treated who had survived, early HSCT accounted for either [redacted] of patients respectively.

The EAG acknowledge that the two lead centres for patients with rapidly progressive LAL-D have different approaches for treatment. Although Manchester treats more patients, and has become a leading centre pioneering new approaches, [redacted] patients (out of [redacted]) have undergone HSCT.[4] Potter et al. 2021[6] summarises the indications for five patients who had HSCT. Three patients who had an initial response to ERT were attenuated by ADAs with clinical and laboratory features of deterioration, one patient developed anaphylaxis to ERT and the last patient had ongoing haemophagocytic lymphohistiocytosis. In Birmingham, [redacted] have not required HSCT and are being treated with ERT (see Appendix 1, company response to DGC).[4] With no clear explanation (aside

from a small patient population) as to why children in Birmingham have been able to tolerate treatment with ERT for longer than those in Manchester, the EAG considers that the English average of [redacted] is more plausible, although the proportion of early HSCT might be lower still, at [redacted] depending on the dominator used.

In the scenario where individuals with Wolman disease undergo an early HSCT after sebelipase alfa treatment, typically between the ages of 3 to 4 years, based on the committee assumption, the EAG conducted separate analyses for ages 3 and 4 years with incremental cost per QALYs gained of £333,756 and £340,730, respectively. When applying a QALY weighting of 3 to both scenarios, the incremental cost per QALY gained was £110,861 and £113,193 for ages 3 and 4 years respectively. The company assumed individuals with Wolman disease undergo an early HSCT after sebelipase alfa treatment at [redacted] years producing an incremental cost per QALYs gained of £275,226. When applying the QALY weighting of 3 the incremental cost per QALY gained is £91,495.

The company assumption of patients undergoing HSCT after receiving sebelipase alfa treatment was [redacted] and [redacted] and the incremental cost per QALY gained of [redacted] and [redacted], respectively. Applying a QALY weighting of 3 in this scenario produces incremental cost per QALYs gained of [redacted] and [redacted], respectively.

### 1.2.2 Key issue 2: Late HSCT

The company assumed that some patients may require a 'late' HSCT up to 30 years of age.[7] The committee recognised the uncertainty in HSCT later in life but concluded that if a transplant later in life is done, it is likely to happen after 30 years.[1] Reasons for late HSCT would include issues with venous access, diminishing sebelipase alfa efficacy arising from ADAs in the longer term or patient choice.

In summary, the EAG, company and committee all agree that there is uncertainty associated with the long-term clinical effectiveness of sebelipase alfa. The oldest patient treated using multi-modal therapy is a single patient aged [redacted] years old,[2] and whilst the EAG acknowledge that this is long-term follow up compared to other rare diseases, there remains considerable uncertainty. Exploration by the EAG of when HSCT is required due to loss of venous access was explored and found to have a moderate impact on the ICER.[8]

Based on the committee's assumption that individuals with Wolman disease who undergo a late HSCT after sebelipase alfa would typically do so after the age of 30 the EAG utilised an age of 40-years for the analysis. The results revealed an incremental cost per QALY gain of £328,032. By applying a QALY weighting of 3, the incremental cost per QALY gain is calculated to be £108,979. For this scenario the company assumption was that individuals with Wolman disease who undergo a late HSCT after sebelipase alfa would do so at 30-years of age and the incremental cost per QALY gain was £275,226. By applying a QALY weighting of 3, the incremental cost per QALY gain is calculated to be £91,495.

### 1.2.3 Key issue 3: Stopping treatments with sebelipase alfa, including treatment post-HSCT

The committee concluded that up to 40% of people with Wolman disease would stop sebelipase alfa after HSCT and that this would likely occur between 2 to 2.5 years following transplantation.[1] In contrast, the company consider that patients can start reducing their dose from 3 months after HSCT, and they may discontinue treatment by 24-36 months.[4] Observed data based on clinical experience from one centre (Manchester) provided by the company indicates that of the [redacted] patients who are >2.5 years post HSCT [redacted] ([redacted]) have discontinued treatment.[2] The company go on to detail the [redacted] further patients who had received HSCT in the last 6 months have [redacted] received their reduced dose, and may stop treatment in 12-18 months (which would represent [redacted] of post-transplant patients stopping

treatment).[4] The EAG consider that the [redacted] patients who had received HSCT recently, are indeed too early to assess for sebelipase alfa discontinuation, and the [redacted] is more appropriate at this stage.

In addition to discontinuation of sebelipase alfa post HSCT, the company asserts there may be other reasons to assume that all patients will come off sebelipase alfa treatment within 30 years.[4] Reasons cited include advances in cell and gene therapies, availability of biosimilars and anticipated requirements for late HSCT. Although plausible, there is understandably great uncertainty surrounding future treatment pathways.

In accordance with the committee's scenario, which suggests that 40% of individuals with Wolman disease would discontinue sebelipase alfa treatment after undergoing HSCT, with the discontinuation occurring within a range of 2 to 2.5 years following the transplant, the EAG conducted separate analyses for both timeframes. The results revealed an incremental cost per QALY gain of £407,704 for the 2-year timeframe and £412,376 for the 2.5-year timeframe. When applying a QALY weighting of 3 to these assumptions, the incremental cost per QALY gained was found to be £135,404 for the 2-year timeframe and £136,956 for the 2.5-year timeframe. The company scenario assumed [redacted] of individuals with Wolman disease would discontinue sebelipase alfa treatment after undergoing a HSCT and the incremental cost per QALY gain of would be £275,226 for the 2-year timeframe and £279,272 for the 2.5-year timeframe. When applying a QALY weighting of 3 to these assumptions, the incremental cost per QALY gain was found to be £91,495 for the 2-year timeframe and £92,840 for the 2.5-year timeframe.

Based on the committee's assumption that not all individuals with Wolman disease would decrease their sebelipase alfa dosage post-HSCT, the EAG conducted an analysis considering this scenario. The results indicated an incremental cost per QALY gain of £710,704. When applying a QALY weighting of 3 the incremental cost per QALY gain is £236,035. The company assumed all individuals with Wolman disease would decrease their sebelipase alfa dosage post-HSCT with the results indicating an incremental cost per QALY gain of £275,226. When applying a QALY weighting of 3 the incremental cost per QALY gain is £91,495.

### 1.2.4 Key issue 4: Health-related quality of life

The committee agreed that applying a 0.8 weighting to the general population utility values is more plausible than assuming general population utility values.[1] The company acknowledged uncertainty around health-related quality of life (HRQoL) for patients with rapidly progressing LAL-D receiving treatment with sebelipase alfa but suggest general population utilities are most appropriate, with scenario analyses exploring a more modest 5-10% reduction in utilities which they felt was more reflective of the available evidence.[4]

Whilst the EAG acknowledges the significant measurement challenges related to HRQoL in neonates and infants there was an absence of proxy HRQoL or utilities available from the LAL-CL-03 and LAL-CL08 clinical trials or uncovered in the company's systematic review of the literature.

The company relies on qualitative narrative evidence provided by the MPS Society,[9] data published in other conditions considered analogous by the company and a retrospective cohort.[3] The retrospective cohort evaluates the bio-clinical follow-up of five patients based in France with rapidly progressive LAL-D who had not received HSCT. HRQoL was evaluated by the Pediatric Quality of Life Inventory questionnaire (PedsQL 4.0) and completed either by proxy (parent, carer) or by the patient when age appropriate. There is ten-year HRQoL follow-up data for one patient, with a median follow-up time of 83 months (min to max 14-120 months). Parents or patients reported acceptable or high HRQoL

globally in all 4 dimensions with one parent scoring 100% in every applicable domain which is much higher than the norm (50 – 80%) for both parent and child reported scores. Cognitive development was reportedly normal, and no patients in this cohort had special educational needs.[3] It should be mentioned that the number of patients in the Demaret *et al*., 2021 study is however very small, responses available for three of 5 children and 5 parents.[3] Two of the child participants were pre-school age and unable to give a response. Parents may not be perfect proxies for their children and in Demaret *et al*., 2021 there were variations between child and parent responses.[3] To illustrate differences in HRQoL decrements the EAGs 20% reduction in QoL explored in the sensitivity analysis was based on different studies which showed lower HRQoL. The study by Simon *et al.*, (2019)[10] investigated health utilities for three rare diseases in childhood and adulthood using the time-trade off approach. Two of the 18 health states valued were ERT conditions in 8 and ≥18-years old. The estimated health utilities for ERT treatment were (0.48, 95% CI: 0.42–0.53) and (0.67, 95% CI: 0.62–0.72), for children and adults, respectively. The results of the Simon et al, (2019)[10] study is in line with recently published UK mean scores for EQ-5D-3L HRQoL utilities for *Endocrine, nutritional and metabolic disease*s, in adults which includes ICD-10 code E75.5 for *other lipid storage disorders,* and suggests mean scores of 0.742 for male and female of all ages.[11]. Both of these studies suggest that assuming that a patient's health is the same as the UK general population could overestimate HRQoL for this condition.[10] Furthermore, a systematic review to examine anxiety and depression in children who have undergone allogenic HSCT compared to age matched normal population, reported that out of the eight eligible studies, four demonstrated higher frequencies of anxiety and one additional study identified significantly higher mild, moderate and severe post-traumatic stress disorder.[12] Similarly for depression, four out of six eligible studies reported depression ranges from 7 to 25% higher in children who received allogenic HSCT compared to age matched population normal values.[12] Survey findings provided by the MPS Society demonstrate [redacted] of respondents aged between 6-8 years with LAL-D reported experiencing slight to moderate symptoms of anxiety and depression compared to [redacted] of unaffected people.[13]

Considering the methodological limitations associated with the HRQoL data submitted in evidence the EAGs position is to present analyses for both a 5-10% decrease (as produced by the company) and a 20% decrease in QoL for consideration by the committee.

The committee raised concerns regarding the plausibility of the EAG's scenario analysis, which applied a 0.8 weighting to general population utility values, stating that a more accurate representation of quality-of-life changes over the lifetime of the model was preferred. In response, the EAG conducted a review of the evidence[11] and determined that a weighting of 0.742 for general population utility values was more plausible but the model did not easily allow a more nuanced approach as preferred by the committee. By utilising this revised weighting, the incremental cost per QALY gained was calculated to be £443,277. Additionally, when applying a QALY weighting of 3 (resulting in an overall weighting of 2.226), the incremental cost per QALY gain is £147,030. Instead, the company suggested using 0.9 weighting to general population utility values and by applying these values the incremental cost per QALY gain was calculated to be £305,944. Additionally, when applying a QALY weighting of 3 (resulting in an overall weighting of 2.226), the incremental cost per QALY gain were £101,676 and [redacted], respectively.

### 1.2.5 Key issue 5: Discount rate

According to NICE, the recommended discount rate for costs and health effects in the reference case is 3.5%. The committee expressed uncertainty regarding the extent to which sebelipase alfa can fully or almost fully restore health in individuals.[1] Additionally, a HSCT could potentially address clinical concerns when sebelipase alfa's effectiveness is diminished and eliminate the requirement for a low-fat

diet, but it carries its own risks. Consequently, the committee determined that sebelipase alfa does not satisfy the criteria for utilising a 1.5% discount rate.[1]

However, the company acknowledges the possibility of patients needing a late HSCT in the future, which is not anticipated to be linked to reduced long-term effectiveness of the drug but rather to issues related to venous access.[4] Furthermore, the company have already factored this into their assumption that all patients will discontinue treatment within 30 years. The company requests the committee to reconsider its rejection of using the 1.5% discount rate, in accordance with the criteria proposed by NICE.

The EAG in the EAR[8] used both a 3.5% discount rate and a 1.5% discount rate to assess the ICER for all scenarios proposed by the committee and the company. Additionally, the EAG incorporated QALY weighting for all scenarios, considering both the 3.5% and 1.5% discount rates in their evaluation and these are all presented in Table 2.

**Table 2: Summary table presenting the ICER values based on the preferred assumptions for both the committee and company across a range of scenarios**

| No | Assumption | The committee's preferred assumptions | ICER (3.5%) | | ICER (1.5 %) | The company's suggested assumptions | ICER (1.5 %) | | ICER (3.5 %) |
|---|---|---|---|---|---|---|---|---|---|
| | | | Weight 1 | Weight 3 | | | Weight 1 | Weight 3 | |
| 1 | Percentage of people would have HSCT after sebelipase alfa treatment | 50% | £378,537 | £125,782 | £319,485 | [redacted] | £275,226 | £91,495 | £328,282 |
| | | | | | | [redacted] | £189,444 | £62,957 | £231,360 |
| 2 | Age of people with Wolman disease who have an early HSCT after sebelipase alfa | Year 3 | £333,756 | £110,861 | £279,131 | Year [redacted] | £275,226 | £91,495 | £328,282 |
| | | Year 4 | £340,730 | £113,193 | £284,124 | | | | |
| 3 | People with Wolman disease who have a late HSCT after sebelipase alfa are likely to have this after 30 years of age | Year 40 | £328,032 | £108,979 | £275,295 | Year 30 | £275,226 | £91,495 | £328,282 |
| 4 | Percentage of people with Wolman disease would likely stop sebelipase alfa after HSCT and would take between 2 and 2.5 years after the transplant to stop treatment | 40% after 2 years | £407,704 | £135,404 | £343,685 | [redacted], after 2 years | £275,226 | £91,495 | £328,282 |
| | | 40% after 2.5 years | £412,376 | £136,956 | £346,728 | [redacted], after 2.5 years | £279,272 | £92,840 | £334,476 |
| 5 | Number of people with Wolman disease would reduce their dose of sebelipase alfa after HSCT | Not everyone | £710,704 | £236,035 | £610,106 | All patients | £275,226 | £91,495 | £328,282 |
| 6 | Adjusting the quality of life of patients with Wolman Disease in comparison with | - | - | - | - | 1 | £275,226 | £91,495 | £328,282 |
| | | 0.8 | £410,918 | £136,346 | £344,380 | 0.95 | £289,773 | £96,317 | £345,660 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | general population utility values by applying a weight to the general population value | 0.742 | £443,277 | £147,030 | £371,447 | 0.90 | £305,944 | £101,676 | £364,981 |
| 7 | Applying discount rate to costs and benefits | 3.5% | £328,282 | £109,027 | - | 1.5% | £275,226 | £91,495 | - |
| 8 | Additional points: application of vial management to minimise vial wastage, as per clinical practice | - | £309,426 | £102,764 | £259,665 | 2-week round-up | £259,665 | £86,322 | £309,426 |

Abbreviations: HSCT, haematopoietic stem cell transplant; No, number; QALY, quality adjusted life year
Footnote: application of vial management to minimise vial wastage, as per clinical practice

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