Sebelipase alfa for treating Wolman disease [ID3995]

Part 1: For PUBLIC – contains noACIC information

Highly Specialised Technologies committee 2nd meeting [13 July 2023]

Chair: Peter Jackson

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Company: Alexion Pharmaceuticals

Key issues

Sebelipase alfa and HSCT uptake

- Does the committee still consider that up to 50% of patients on SA would have HSCT (early at 2 years old and late at 30 years)?
    - If not, will all patients have HSCT? What proportion would have early vs late HSCT?
    - At what age would children have early HSCT? At [redacted], [redacted] years or at 3 to 4 years?
    - At what age would people have late HSCT? [redacted] or 30 or [redacted] years?

Sebelipase alfa use after HSCT

- Does the committee still consider that 40% of people will reduce their dose of SA after HSCT, up to 40% will stop SA after HSCT over 2 to 2.5 years and 20% will continue on same SA dose for lifetime?
    - If not, what proportion are likely to reduce SA dose after HSCT at 12 months? [redacted] or [redacted]?
    - When are people likely to stop SA after HSCT? 2, 2.5 or 3 years?
    - What proportion of people are likely to stop SA after HSCT? 40%, [redacted] or [redacted]?

Health-related quality of life

- Does the committee still consider that a 20% decrement from the general population quality of life plausibly reflects the quality of life of people on SA ± HSCT?

Discount rate

- Does the committee still consider that a 3.5% discount rate is the most appropriate for this evaluation?

Other considerations

- Are there additional uncaptured benefits of treatment with sebelipase alfa?

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Abbreviations: HSCT, haematopoietic stem cell transplantation; SA, sebelipase alfa

Evaluation history

Preliminary recommendation

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

ECM1

May 2023

DG released

ECM2

July 2023

DG consultation comments

- Company: updated evidence on HSCT uptake and use after SA, revised analyses and PAS
- 2 experts: patient and clinical
- 1 web comment

Abbreviations: ECM, evaluation committee meeting; DG, draft guidance; HSCT, haematopoietic stem cell transplantation; LAL-D, lysosomal acid lipase deficiency; PAS, patient access scheme; SA, sebelipase alfa

Clinical evidence recap

NICE National Institute for Health and Care Excellence

Background

Wolman disease

- Mutation in lipase A lysosomal acid gene
- Decreased or no activity of lysosomal acid lipase enzyme
- Build-up of fats in liver; liver fibrosis and cirrhosis
- Babies/young children: vomiting, diarrhoea, distended abdomen and fat in stools
- Estimated incidence rate ~1 in 350,000 births; [redacted] every other year in England
- If untreated, rapid disease progression: 3.7 months median age at death

Sebelipase alfa (Kanuma, Alexion)

- Enzyme replacement: recombinant human lysosomal acid lipase
- Marketing authorisation (2015): long-term ERT in people with LAL deficiency
- Administration and dose: IV
  - <6 months with rapidly progressive LAL-D: weekly 1 or 3 mg/kg (dose escalation up to 5 mg/kg)
  - People without rapidly progressive LAL-D before 6 months: every other week 1 mg/kg (dose escalation to 3 mg/kg)
- List price: £6,286 per 20 mg vial (revised patient access scheme agreed)

NICE

Abbreviations: ERT, enzyme replacement therapy; IV, intravenous; LAL-D, lysosomal acid lipase deficiency

Treatment pathway: Wolman disease

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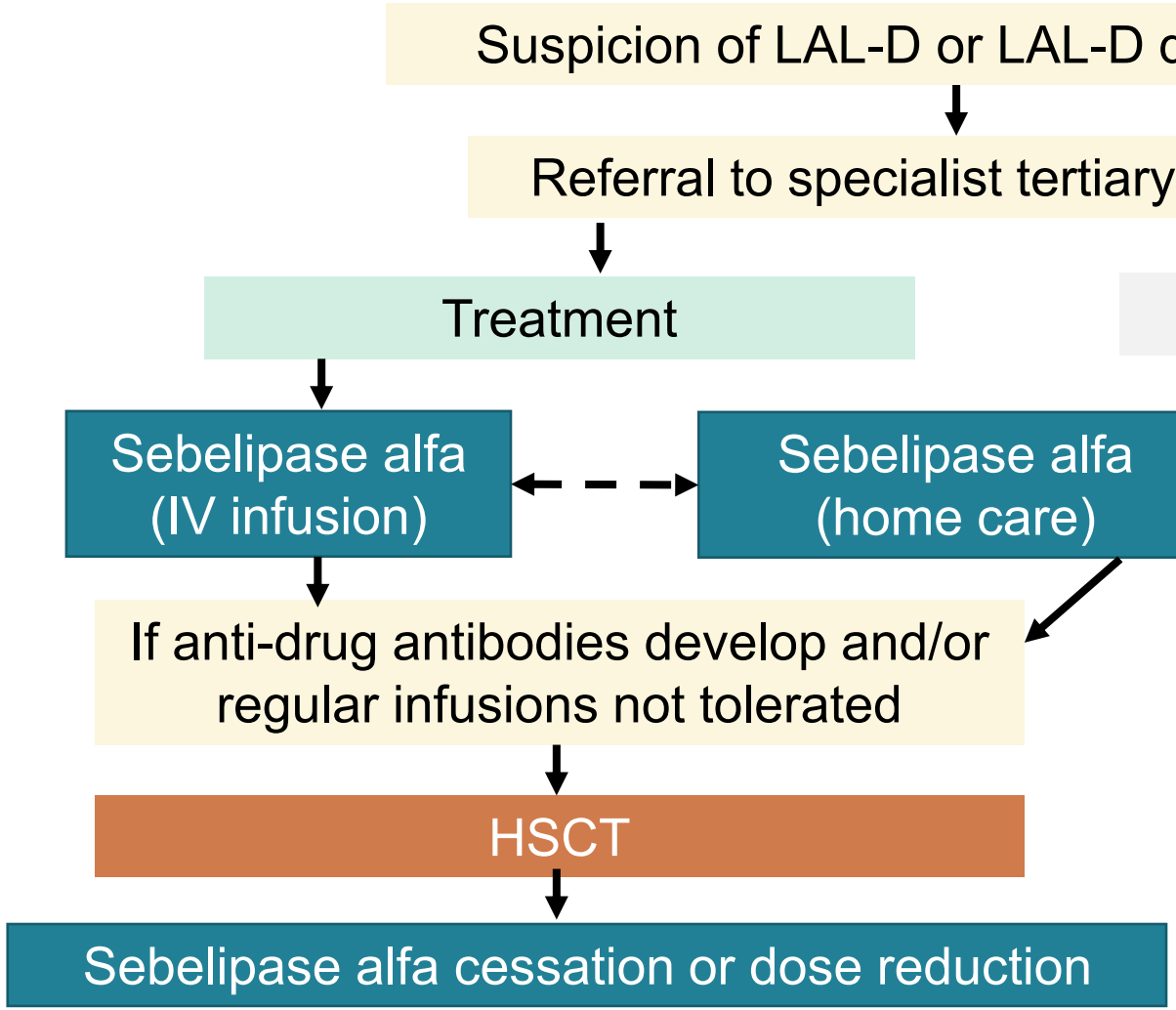
Sebelipase alfa: first-line treatment used alongside nutritional support. May allow HSCT



- Continue sebelipase alfa until:
  - Lack of clinical response (e.g. anti-drug antibodies develop)
  - Venous access lost from repeated IV

    → Consider HSCT
- After HSCT, sebelipase alfa treatment can continue with reduced dose and may lead to possible treatment discontinuation

Source: Adapted from figure 4, company submission

Abbreviations: HSCT, haematopoietic stem cell transplantation; IV: Intravenous; LAL-D: lysosomal acid lipase deficiency

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Decision problem

	NICE scope	Company	EAG
Population	People with Wolman disease	"Rapidly progressive LAL-D" more current and clinically accurate	Broadly in line with scope – but named differently
Intervention	Sebelipase alfa		Multimodal approach: SA with nutritional support and HSCT
Comparators	Established clinical practice without sebelipase alfa		HSCT used after stabilised with ERT and nutritional support
Outcomes	Mortality, weight/nutrition, haematological, lipids, liver function, liver disease progression, neurological development, cardiovascular, anti-drug antibodies, adverse effects, HRQoL (patients and carers)		Adrenal gland function not included by company (not captured in trials)

Abbreviations: ERT, enzyme replacement therapy; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; LAL-D, lysosomal acid lipase deficiency; SA, sebelipase alfa

Key clinical trials: used in model

Sebelipase alfa improves survival and other outcomes. Substantial uncertainty around long-term effectiveness (development of anti-drug antibodies, compromised venous access, number having HSCT and related timing and outcome)

	LAL-CL08 (n=10) [2014 – 2018]	LAL-CL03 (n=9) [2011 – 2018]
Design	Phase 2, single arm	Phase 2/3, single arm
Population	≤8 months with LAL-D and substantial clinical concerns*	≤2 years with LAL-D and growth failure with onset <6 months
Intervention	Sebelipase alfa	
Primary outcome	Safety and tolerability	Proportion surviving to 12 months
Key secondary outcomes	• Proportion surviving to 12, 18, 24 and 36 months • Growth parameters • Hepatomegaly, splenomegaly, liver function, haematological parameters	As in LAL-CL08 with additional outcomes: • Safety and tolerability • Characterise PK of sebelipase alfa delivered by IV
Locations	UK, USA, Finland, Italy	UK, USA, France, Ireland, Egypt, Turkey

Abbreviations: *enlarged organs, growth failure, family history, anaemia and disturbance of coagulation; HSCT, haematopoietic stem cell transplantation; IV, intravenous; LAL-D, lysosomal acid lipase deficiency, PK: pharmacokinetics

Natural history study: LAL-1-NH01 (used for comparator arm in model)

	LAL-1-NH01 (n=35*)
Design	Retrospective natural history study
Population	Lab confirmed diagnosis of rapidly progressive LAL-D before 2 years
Intervention	Untreated or treated with HSCT and liver transplantation
Duration	Sep 2010 – Mar 2013; Diagnoses between 1985–2012
Primary outcome	Survival and key aspects of clinical course of LAL-D Wolman phenotype
Key secondary outcomes	Historical reference for efficacy studies of ERT in people with LAL-D
Locations	UK, USA, Canada, Egypt, France, and Italy

*data from 21 people untreated with HSCT and liver transplantation with records of early growth failure (matched to LAL-CL03) were used for comparative clinical effectiveness analysis

Abbreviations: ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; LAL-D, lysosomal acid lipase deficiency; n, number

Cost-effectiveness evidence recap

NICE National Institute for Health and Care Excellence

Company model structure

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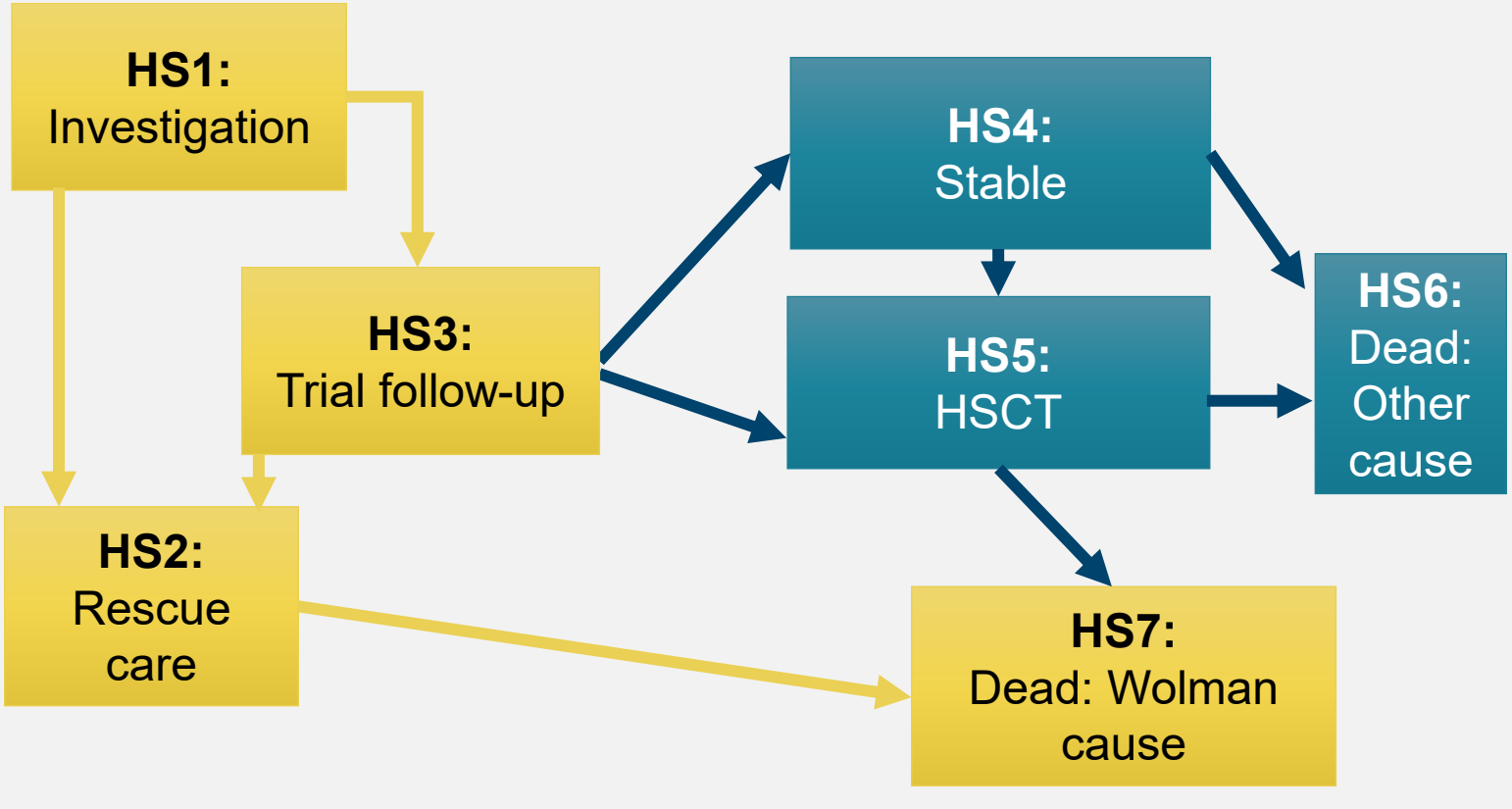
Model structured around clinical trials period (short-term) and pre- and post-HSCT (longer-term)



Model overview:

- Short term (HS1, HS2 and HS3) informed by clinical trial data (and natural history study for BSC)
- HS4, HS5 informed by clinical expert opinion (HSCT use – early and late)
- One-off risk of death applied to HSCT, then UK general population mortality after 5 years

Abbreviations: BSC, best supportive care; HS, health state; HSCT, haematopoietic stem cell transplantation

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Company model health states description

	Representation	Use of sebelipase alfa
HS1 Investigation	Hospital-based neonatal care including IV parenteral nutrition Trial-based, Wolman-related mortality risk	from birth, hospital setting
HS2 Rescue care	1-month neonatal critical care before LAL-D death	until death, hospital setting
HS3 Trial follow-up	Physician and dietician monitoring up to 5 years. Include specialist nutrition. LAL-D related mortality risk from trials unless transition to HSCT	Alexion home care service
HS4 Stable	Physician and dietician monitoring at 5 years until loss of venous access and transition to HSCT as rescue (late HSCT). Include specialist nutrition. No LAL-D related mortality	Alexion homecare service
HS5 HSCT	Initial immunomodulation and HSCT and remaining natural life. Entry via early or late HSCT, both carry mortality risk from procedure. Physician and dietician monitoring continues post HSCT. Include specialist nutrition	Stopped 18 months after HSCT
HS6/HS7 Dead	Mortality from Wolman-related, HSCT-related, or other cause	Not relevant

Abbreviations: HS, health state; HSCT, haematopoietic stem cell transplantation; IV, intravenous; LAL-D, lysosomal acid lipase deficiency

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Company model overview

Key model drivers are associated with HSCT assumptions

- Technology affects **costs** by:
  - Different dosage of sebelipase alfa across lifetime
  - Bridging to HSCT

- Technology affects **QALYs** by:
  - Increasing survival
  - Increasing HRQoL with sebelipase alfa and later management with HSCT

- Assumptions with greatest ICER effect:
  - Proportion and age receiving HSCT
  - Proportion with dose reduction and stopping after early HSCT
  - Discount rate
  - Using general population life expectancy and utility for both sebelipase alfa and HSCT
  - Extrapolation approach for survival

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Abbreviations: HRQoL, health related quality of life; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Overview of economic modelling: company revised base case

Clinical trial period (0 to 5 years)

Clinical trial data

CL-003
- (n=9; 5 alive at 5 years)

CL-008
- (n=10; 8 alive at 3 years)

Company model assumes survival of [redacted]) from clinical trial period

Post-clinical trial period (5 years onwards)

Company assumptions

- All treated with SA have general population mortality
- All will have HSCT
- One-off mortality risk for early and late HSCT (20% based on Potter 2021)
- General population utilities throughout model (one-off decrements for events e.g. HSCT)

[redacted]

Early HSCT (at [redacted] years)

[redacted]

Late HSCT (at 30 years)

SA use after HSCT:
- [redacted] reduce dose
- [redacted] stop SA after HSCT at 2 years

Abbreviations: HSCT, haematopoietic stem cell transplantation; KM, Kaplan-Meier; n, number; SA, sebelipase alfa

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Key issue 1: HSCT uptake after sebelipase alfa (1)

Uncertainty around timing and uptake of early and late HSCT after SA

Background (ECM1 committee considerations)

HSCT uptake after SA

- % difficult to predict (small population, oldest treated person ~10 years). Company assumed everyone has HSCT after SA. Patient experts suggest HSCT is last resort

Early HSCT

- Result of ADA. Clinical experts differed in views (0% or 50%). Company assumed [redacted]. Committee preferred assumption up to 50%. EAG scenarios: 0%, 50%, 100%

Timeframe for early HSCT

- Company assumed HSCT at 2 years old. Committee considered likely to happen after 3 to 4

Late HSCT

- Multiple considerations: response to ERT (decreases by 3 to 4 years old), treatment for ADA, adherence to strict diet, venous access (other options when no access; maintain over lifetime; risk of thrombosis)
- Company assumed HSCT at 30 years old. Committee considered likely after 30. EAG scenario: HSCT at 20 and 40 years, venous access not lost (no late HSCT over lifetime)

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Abbreviations: %, proportion; ADA, anti-drug antibodies; ECM, evaluation committee meeting; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; SA, sebelipase alfa

HSCT uptake after sebelipase alfa (2)

Company revised base case: early HSCT inputs based on current UK data

Company

- Emphasises evolving management of LAL-D. SA likely to be bridging option as novel interventions develop (e.g. curative gene therapy in pre-clinical studies)
- Provides **updated evidence on early HSCT from UK cohort**
  - Revised base case early HSCT: [redacted] at [redacted] years old
  - Scenarios: early HSCT [redacted] at [redacted] years old; [redacted] at [redacted] and [redacted] years old
- Long-term follow-up up to ~11 years after SA: limited data on expected future management
  - Late HSCT: result of ADA, reduced efficacy of SA, no venous access
  - Revised base case late HSCT: [redacted] at 30 years of SA
  - Scenarios: late HSCT [redacted] at 30 years; [redacted] at [redacted] and [redacted] years of SA
    - EAG clinical input suggest no venous access could be as early as 20 years of SA

New

Clinical expert (based on same UK data as company)

- Early HSCT: [redacted], likely by 4 years
  - Mean age [redacted] years (median [redacted] years; [redacted] had HSCT at 10 years)
- Late HSCT: start from 10 years

Abbreviations: ADA, anti-drug antibodies; HSCT, haematopoietic stem cell transplantation; LAL-D, lysosomal acid lipase deficiency; SA, sebelipase alfa

HSCT uptake after sebelipase alfa (3)

HSCT may be promoted as an early option because of improved outcomes

MPS Society

- Emphasises that HSCT is usually a last resort after SA no longer viable
  - HSCT: high mortality risks, uncertainties, family members are donors, long hospital stays
- People likely opt for treatment with lowest risk
  - Long-term benefits of HSCT uncertain, but
    - Improved GI symptoms; tolerate normal diet without fat restrictions; can stop SA
    - Given HSCT outcomes, early HSCT may be an acceptable option after SA stability

EAG comments

- Consider [redacted] may be indicative of UK clinical practice
  - [redacted] patient elected to have HSCT at 10 years old, so may be considered as late HSCT
    - [redacted] ([redacted]) have early HSCT
- Reasons 5 patients in Manchester had early HSCT:
  - 3 ADAs with clinical and laboratory features of deterioration
  - 1 anaphylaxis to ERT
  - 1 ongoing haemophagocytic lymphohistiocytosis
- Late HSCT inputs: considerable uncertainty

Abbreviations: ERT, enzyme replacement therapy; GI, gastrointestinal; HSCT, haematopoietic stem cell transplantation; SA, sebelipase alfa

UK: Sebelipase alfa and HSCT

New

Since 2011 (UK and Ireland) [redacted] **LAL-D**
([redacted] Manchester, [redacted] Birmingham, [redacted] London, [redacted] Leeds)

[redacted] **SA treated**
([redacted] Manchester, [redacted] Birmingham)

Deaths

[redacted] **continued SA** 3-5mg/kg
([redacted] Manchester, [redacted] Birmingham)

[redacted] **HSCT**
([redacted] Manchester; [redacted] last 12 months)

[redacted] **stopped SA**

[redacted] **continued SA**
(reduced dose)

Company
- **MAN:** multimodal, reflects early HSCT
- **BIRM:** HSCT not yet needed
- **Early HSCT** (MAN/BIRM): [redacted]
- **Median age early HSCT:** [redacted] years (range [redacted] years); [redacted] patient elected at 10 years
- **Late HSCT:** [redacted] by 30 years

Clinical expert
- **Early HSCT:** [redacted]
  - Mean age [redacted] but median [redacted] years ([redacted] had HSCT at 10 years)
  - Early HSCT by 4 years
- **Late HSCT:** start from 10 years

- Does the committee still consider that up to 50% of patients on SA would have HSCT (early at 2 years old and late at 30 years)?
- If not, will all patients have HSCT? What proportion would have early vs late HSCT?
- At what age would children have early HSCT? At [redacted], [redacted] years or at 3 to 4 years?
- At what age would people likely have late HSCT? [redacted] or 30 or [redacted] years?

*Discrepancy between company ([redacted]) and clinical expert ([redacted]) data; **Discrepancy between company ([redacted]) and clinical expert ([redacted]) data

Abbreviations: BIRM, Birmingham; HSCT, haematopoietic stem cell transplantation; LAL-D, lysosomal acid lipase deficiency; MAN, Manchester; SA, sebelipase alfa

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Key issue 2: Sebelipase alfa use after HSCT (1)

Inputs about SA dose uncertain

Background (ECM1 committee considerations)

- Company assumed that after HSCT, SA dose is reduced and stops after 18 months
- EAG considered inputs highly uncertain and noted limited data to model % on different SA doses. Provided scenarios: 50% reduce dose, 50% stop
- Clinical experts: of 5 people after HSCT, 1 had same SA dose, 2 reduced dose, 2 stopped after 2 to 2.5 years (3 of 4 people were stable on 3mg/kg)
- Committee considered:
  - SA dose over lifetime highly uncertain
  - 40% of people will reduce their dose of SA after HSCT
  - Up to 40% will stop SA after HSCT over 2 to 2.5 years
  - 20% will continue on same SA dose for lifetime

Abbreviations: ECM, evaluation committee meeting; HSCT, haematopoietic stem cell transplantation; SA, sebelipase alfa

Sebelipase alfa use after HSCT (2)

Company

- Used data from Manchester centre: after HSCT, continue SA at same dose until stable, then reduced (can start from 3 months and may stop by 2 to 3 years)
  - Of [redacted] people >2.5 years after HSCT: [redacted] stopped ([redacted]), [redacted] reduced dose
  - Further [redacted] who had HSCT in past 6 months have reduced dose
  - Company revised base case:
    - [redacted] stop SA at 2 years after HSCT
    - [redacted] reduce SA dose at 12 months after HSCT
    - [redacted] reduced dose by 18 years old
  - Scenarios:
    - [redacted] stop SA at 3 years after HSCT
    - if additional [redacted] patients stop, [redacted] ([redacted]) stop SA after 2 years HSCT
    - [redacted] reduce SA dose at 12 months after HSCT
    - [redacted] reduced dose by 18 years old
    - People who do not have HSCT (and no ADAs), increase SA to 5mg/kg
    - 100% SA compliance (vs 96%)
- SA likely stopped within 30 years: no venous access, late HSCT, evolution in treatment practice, introduction of future cell and gene therapies, and biosimilars
  - Input to EAG: ERT may stop as early as 20 years of treatment

New

Abbreviations: ADA, anti-drug antibodies; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; SA, sebelipase alfa

Sebelipase alfa use after HSCT (3)

Clinical expert

- From Manchester centre, data on average doses of SA:
  - 5 mg/kg weekly in 1st year after HSCT
  - 1 mg/kg alternate weekly: 1–3 years after HSCT
  - No SA by 3 years after HSCT

EAG scenarios

- 40% stop SA at 2 and 2.5 years after HSCT (committee preferred assumption)
- [redacted] stop SA at 2.5 years after HSCT (company revised base case proportion)
- No one (0%) will reduce SA dose after HSCT

- Does the committee still consider that 40% of people will reduce their dose of SA after HSCT, up to 40% will stop SA after HSCT over 2 to 2.5 years and 20% will continue on same SA dose for lifetime?
- If not, what proportion are likely to reduce SA dose after HSCT at 12 months? [redacted] or [redacted]?
- When are people likely to stop SA after HSCT? [redacted], 2.5 or 3 years?
- What proportion of people are likely to stop SA after HSCT? 40%, [redacted] or [redacted]?

Abbreviations: HSCT, haematopoietic stem cell transplantation; SA, sebelipase alfa

RECAP

Key issue 3: Utilities (1)

Uncertainty around health-related quality of life of people on SA and after HSCT

Background (ECM1 committee considerations)

- Company base case: QoL for people on SA (± HSCT) = age-matched UK general population
  - Rationale: retrospective cohort study in France (Demaret 2021, n=5) using Pediatric Quality of Life Inventory questionnaire showed evidence of normal or near normal development and HRQoL in LAL-D patients
  - Scenario: 10% decrease in UK general population QoL
- EAG considered regular IV with SA may affect QoL
  - Scenario: 20% decrease in UK general population QoL
- Disutility
  - Company scenarios: utility decrements for parenteral nutrition, HSCT, family bereavement
  - EAG scenarios: caregiver disutility for ERT
- Committee considered:
  - HRQoL not accurately captured over lifetime
  - French study: small, different results for patients and carers, limited follow up
  - EAG scenario using 20% decrease more plausible
  - Base case should include disutility for HSCT

Abbreviations: ECM, evaluation committee meeting; ERT, enzyme replacement therapy; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; IV, intravenous; LAL-D, lysosomal acid lipase deficiency; n, number; SA, sebelipase alfa

Utilities (2)

Company

- Notes that clinical and patient experts at ECM1 reported challenges around restrictive diets but did not consider this to decrease QoL by 20%
- Reiterates evidence from Demaret (2021) and evidence for paediatric QoL in other chronic conditions e.g. cancer and those having IV therapy indicates 5% to 10% decrease in utility to general population
- Company revised base case: unchanged; general population utilities and HSCT disutility
- Scenarios: 5% and 10% reduction in general population utilities; disutility: family bereavement included, HSCT excluded

Clinical and patient experts

- MPS society HRQoL survey suggests families view their QoL very highly
- Reasonable to assume HRQoL of children and families with Wolman >80% of a healthy person
- Evidence in other conditions treated with ERT (e.g. elusolfase alfa) contradicts EAG's view that frequent infusion with SA may affect QoL: 'long-term treatment with elosulfase alfa … has a positive impact on … patients' ability to perform ADL and lessens their need for caregiver assistance" (Cleary et al. Orphanet J Rare Dis 2021)

Abbreviations: ECM, evaluation committee meeting; ERT, enzyme replacement therapy; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; IV, intravenous; SA, sebelipase alfa

MPS Society HRQoL survey

- ***Study aim:** provide evidence in response to DG consultation within 3-week timeframe; compared function and QoL in 15 children with and without LAL-D (unclear if children with LAL-D had SA only)
- **Method:** Pediatric Quality of Life Inventory not used (lack of access); survey reflect PedsQL themes, based on Pathways (endorsed by American Academy of Pediatric findings), checked by UK clinicians and psychologists. HRQoL used EQ-5D
- Completed online by carers

New

6 – 8 years (n=[redacted])

Proportion meeting all endpoints for:	LAL-D (n=[redacted])	No LAL-D (n=[redacted])
Gross motor skills / fine motor skills /co-ordination	[redacted]	[redacted]
Daily activities	[redacted]	[redacted]
Emotional development / self-expression	[redacted]	[redacted]
Language and understanding	[redacted]	[redacted]
Play and social skills	[redacted]	[redacted]
Thinking and reasoning	[redacted]	[redacted]

9 – 12 years (n=[redacted])

	Proportion meeting endpoints	
	LAL-D (n=[redacted])	No LAL-D (n=[redacted])
Physical and daily activities	[redacted]	[redacted]
Intellectual and cognitive	[redacted]	[redacted]
Social and emotional	[redacted]	[redacted]

*Calculated from data (does not tally with data provided)

Abbreviations: DG, draft guidance; EQ-5D, EuroQol-5 dimensions; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; LAL-D, lysosomal acid lipase deficiency; n, number; SA, sebelipase alfa; *provided by email by MPS Soc 11/07/23

MPS Society EQ-5D results

QoL domain	6-8 year olds		9-12 year olds	
	LAL-D (n=[redacted])	No LAL-D (n=[redacted])	LAL-D (n=[redacted])	No LAL-D (n=[redacted])
Mobility	[redacted] no problems [redacted] slight	[redacted] no problems	[redacted] no problems	[redacted] no problems
Self care	[redacted] no problems [redacted] slight [redacted] severe	[redacted] no problems	[redacted] no problems	[redacted] no problems
Usual activities	[redacted] no problems [redacted] slight	[redacted] no problems	[redacted] no problems	[redacted] no problems
Pain and discomfort	[redacted] no pain or discomfort [redacted] slight	[redacted] no pain or discomfort	[redacted] no pain or discomfort	[redacted] no pain or discomfort
Anxiety / depression	[redacted] not anxious or depressed [redacted] slightly [redacted] moderately	[redacted] not anxious or depressed	[redacted] not anxious or depressed	[redacted] not anxious or depressed [redacted] slightly

NICE **Abbreviations:** LAL-D, lysosomal acid lipase deficiency; QoL, quality of life; n, number

Utilities (3)

EAG comments

- Significant HRQoL measurement challenges in neonates and infants: no proxy utilities from SA clinical trials or literature
- 20% decrease in general population QoL based on literature
  - Simon (2019): 2/18 health states valued using time trade-off in 3 rare diseases were ERT conditions in 8 and ≥18-years old
    - Estimated health utilities: 0.48 (0.42–0.53) for children and 0.67 (0.62–0.72) for adults
    - Published UK mean EQ-5D utilities for nutritional/metabolic conditions in adults: 0.742
  - HSCT SR: greater anxiety/depression in children with HSCT than matched controls
    - Similar to findings in MPS Society survey
- Committee preferred more accurate representation of QoL changes over lifetime of model
  - EAG consider weighting of 0.742 for general population utilities was more plausible but model did not allow a more nuanced approach
- EAG scenarios: 5%, 10%, 20% and 26% decreases in general population utilities

- Does the committee still consider that a 20% decrement from the general population quality of life plausibly reflects the quality of life of people on SA ± HSCT?

Abbreviations: EQ-5D, EuroQol-5 dimensions; ERT, enzyme replacement therapy; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; SR, systematic review

RECAP

Key issue 4: Discount rate

Background

- Committee may consider using non-reference-case discount rate of 1.5% per year for costs and health effects, if the following are all met:
  - SA is for people who would otherwise die or have a very severely impaired life
  - SA is likely to restore them to full or near-full health
  - Benefits are likely to be sustained over a very long period
- Committee must take account of plausible long-term health benefits and be confident that it is highly plausible that benefits are maintained over time
- Committee must be satisfied any irrecoverable costs of SA (e.g. acquisition, related service design or delivery) have been appropriately captured in model or mitigated through commercial arrangements (NICE process and methods guide 2022, sections 4.5.3 to 4.5.5)
- Company preferred 1.5%. Committee preferred 3.5%

Company

- Reiterates evidence supports patients die otherwise and are restored to full or near-full health
- Company revised base case: maintain 1.5%. Scenarios: 0%, 3.5%, 5%

- Does the committee still consider that a 3.5% discount rate is the most appropriate for this evaluation?

NICE

Abbreviations: SA, sebelipase alfa

Other considerations: survival modelling

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Background

- In its base case, company applied Wolman-related mortality for SA from trials' KM (5-year)
  - After 5 years, UK general population mortality
- EAG considered over lifetime, OS optimistic and uncertain
  - Provided scenarios of extrapolations to KM curves
- EAG considered limited data on OS after SA and HSCT (based on Potter 2021; n=5 children)
- Clinical experts advised increased mortality risk in 2 years after HSCT but then risk falls substantially
- Committee considered survival estimates after 5 years are uncertain

Company

- Long-term general population mortality assumption most reasonable
- Model includes:
  - increased mortality risks at different points (e.g. presenting with LAL-D, starting SA, HSCT)
  - current understanding of long-term clinical expectations for patients
- Company revised base case: extrapolations using KM from trials
- Scenarios: extrapolations using exponential, Gompertz, Weilbull, log-normal; 0% decrease HRQoL and 10% HR on other cause mortality; 20% HR on other cause mortality

Abbreviations: HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; KM, Kaplan-Meier; LAL-D, lysosomal acid lipase deficiency; n, number; OS, overall survival; SA, sebelipase alfa

Other considerations at ECM1

Issue	Considerations at ECM1	Committee preference	Company DG response
Vial wastage (DG 3.11)	**Company base case:** assumed partly used vial disposed **Company and EAG scenarios:** adjusted vial use over 2 weeks to reduce wastage	Consider clinical practice to minimise vial wastage	Base case: adjusted vial use to reduce wastage
QALY weighting (DG 3.14)		• Despite uncertainty, SA likely to provide QALY gain >30 • Consider QALY weighting of 3	

Abbreviations: DG, draft guidance; ECM, evaluation committee meeting; QALY, quality-adjusted life year; SA, sebelipase alfa

Uncaptured benefits of sebelipase alfa

Company

- Significant societal benefits from preventing infant death
- Significant disutility related to parental bereavement
    - Company scenario: include bereavement disutility
- Substantial economic productivity impacts related to parents losing their child and lost economic potential from child
    - Company scenario: include lost economic productivity

- Are there additional uncaptured benefits of treatment with sebelipase alfa?

Company revised base case assumptions in ECM2 – updated PAS

Assumption	Committee preferred after ECM1	Company revised base case
Early HSCT uptake after SA	Up to 50% after 3 to 4 years old	[redacted] at [redacted] years
Late HSCT uptake after SA	Proportion uncertain, likely after 30 years old	[redacted] at 30 years
Reduce SA dose after HSCT	Not everyone will reduce SA: 80% reduce, 20% do not reduce	[redacted] at 12 months after HSCT
Stop SA after HSCT	Up to 40% stop over 2 to 2.5 years	[redacted] at 24 months after HSCT
Utilities	20% decrease in UK general population QoL	UK general population
Vial management	Vial sparing across 2-week doses to minimise vial wastage	Vial sparing across 2-week doses to minimise vial wastage
Discount rate	3.5%	1.5%
ICERs using 3.5% (and 1.5%) discount rate	• 3 years early HSCT, stop SA at 2 years after HSCT: **£608,675 (£501,499)** • 4 years early HSCT, stop SA at 2.5 years after HSCT: **£613,011 (£505,421)**	**£328,272 (£275,225)** **NB: EAG base case: company's revised assumptions using 3.5% rate**

Abbreviations: ECM, evaluation committee meeting; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; QoL, quality of life; SA, sebelipase alfa

Cost-effectiveness results

Company revised base case results (updated PAS, 1.5% rate)

Deterministic incremental base case results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental LYGs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£275,226**

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Sebelipase alfa	[redacted]	[redacted]	[redacted]	[redacted]	**£274,682** (£268,617 to £282,161)

There are no confidential commercial discounts for best supportive care

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG; life year gain; QALY, quality-adjusted life year; PAS, patient access scheme;

Company scenario analyses (1) – updated PAS, 1.5% rate

Scenario and sensitivity	ICER	Change	%
Revised base case	**£275,226**	-	-
Early HSCT (revised base case [redacted] at [redacted] years old)			
[redacted] at [redacted] years	£503,530	£228,305	183%
[redacted] at [redacted] years	£189,444	-£85,782	69%
[redacted] at [redacted] years	£147,922	-£127,303	54%
[redacted] at 3 years	£279,131	£3,906	101%
[redacted] at 4 years	£284,124	£8,898	103%
Late HSCT (revised base case [redacted] at 30 years old)			
[redacted] at 30 years	£475,666	£200,441	173%
[redacted] at 20 years	£169,424	-£105,801	62%
[redacted] at 40 years	£332,865	£57,639	121%
SA use after HSCT (revised base case: after HSCT, [redacted] reduce SA at 12 months; [redacted] stop at 24 months)			
[redacted] reduce SA dose	£341,245	£66,019	124%
[redacted] stop SA after early HSCT at 24 months	£255,815	-£19,410	93%
[redacted] stop SA after early HSCT at 3 years	£277,234	£2,008	101%
[redacted] reduce dose at age 18 (vs [redacted])	£238,353	-£36,872	87%
100% SA compliance (vs 96%)	£285,656	£10,430	104%
Patients who don't receive HSCT (no ADAs) increase to 5mg/kg	£307,473	£32,248	112%

Abbreviations: ADA, anti-drug antibodies; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; SA, sebelipase alfa

Company scenario analyses (2) – updated PAS, 1.5% rate

Scenario and sensitivity	ICER	Change	%
Revised base case	**£275,226**	-	-
Survival extrapolation (revised base case: KM trial)			
Predicted survival – exponential	£367,437	£92,211	134%
Predicted survival – Gompertz	£335,100	£59,874	122%
Predicted survival – Weibull	£325,237	£50,011	118%
Predicted survival – log-normal	£274,719	-£506	100%
20% hazard ratio applied to other cause mortality	£277,696	£2,470	101%
Utilities (revised base case: UK general population)			
5% reduction in UK general population HRQoL, all ages	£289,773	£14,547	105%
10% reduction in UK general population HRQoL, all ages	£305,944	£30,718	111%
HRQoL = EQ-5D VAS (vs EQ-5D TTO)	£273,933	-£1,292	100%
10% decrease HRQoL & 10% HR on other cause mortality	£307,356	£32,130	112%
Disutility			
HSCT procedure and recovery disutility excluded	£273,926	-£1,299	100%
Family bereavement disutility included	£231,457	-£43,768	84%
Vial management (revised base case: 2-week low waste)			
1-week round-up vial consumption	£284,696	£9,470	103%

Abbreviations: EQ-5D, EurQol-5 dimensions; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; PAS, patient access scheme; TTO, time trade off; VAS, visual analogue scale

Company scenario analyses (3) – updated PAS, 1.5% rate

Scenario and sensitivity	ICER	Change	%
Revised base case	**£275,226**	-	-
Other costs			
Lifecycle price – [redacted]	£148,345	-£126,880	54%
[redacted]	£210,026	-£65,200	76%
No homecare service	£278,259	£3,033	101%
Specialist nutrition excluded	£256,823	-£18,402	93%
Cost HSCT 20% higher	£275,734	£508	100%
Discount rate (revised base case: 1.5%)			
0%	£219,389	-£55,837	80%
3.5%	£328,282	£53,056	119%
5%	£350,586	£75,360	127%
Time horizon (revised base case: lifetime)			
6 years	£305,398	£30,172	111%
Uncaptured benefits			
Economic productivity included	£186,329	-£88,896	68%

Abbreviations: HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; SA, sebelipase alfa

EAG scenarios – updated PAS

Parameter	Committee preferred at ECM1	ICER		Company suggested	ICER	
		3.5%	1.5%		3.5%	1.5%
Early HSCT uptake	50%	£378,537	£319,485	[redacted]	£328,282	£275,226
				[redacted]	£231,360	£189,444
Age at early HSCT	Year 3	£333,756	£279,131	Year [redacted]	£328,282	£275,226
	Year 4	£340,730	£284,124			
Age at late HSCT	Year 40	£328,032	£275,295	Year 30	£328,282	£275,226
Stop SA after HSCT	40% after 2 years	£407,704	£343,685	[redacted] after 2 years	£328,282	£275,226
	40% after 2.5 years	£412,376	£346,728	[redacted] after 2.5 years	£334,476	£279,272
Reduce SA after HSCT	No one (0%)	£710,704	£610,106	All patients (100%)	£328,282	£275,226
QoL decrement compared to UK general population (weight applied)	-	-	-	0%	£328,282	£275,226
	20%	£410,918	£344,380	5%	£345,660	£289,773
	26%	£443,277	£371,447	10%	£364,981	£305,944
Vial management	Minimise wastage (2 week)	£309,426	£259,665	Minimise wastage (2 week)	£309,426	£259,665

Abbreviations: ECM, evaluation committee meeting; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QoL, quality of life; SA, sebelipase alfa

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End of Part 1
Thank you