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NICE National Institute for Health and Care Excellence

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

Chair's presentation

2nd evaluation committee meeting

Highly Specialised Technologies committee

Chair: Peter Jackson

ERG: Peninsula Technology Assessment Group (PenTAG)

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

Company: Sanofi

December 2023

Key issues

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

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

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

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

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

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

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

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

MAA: Is olipudase alfa suitable for managed access?

Abbreviations: MAA: managed access agreement

Olipudase alfa not recommended

Committee noted uncertainties and requested further analyses:

Key conclusions, clinical:

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

Key conclusions, economic:

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

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Key conclusions:

Economic (continued):

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

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

Further analyses requested:

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

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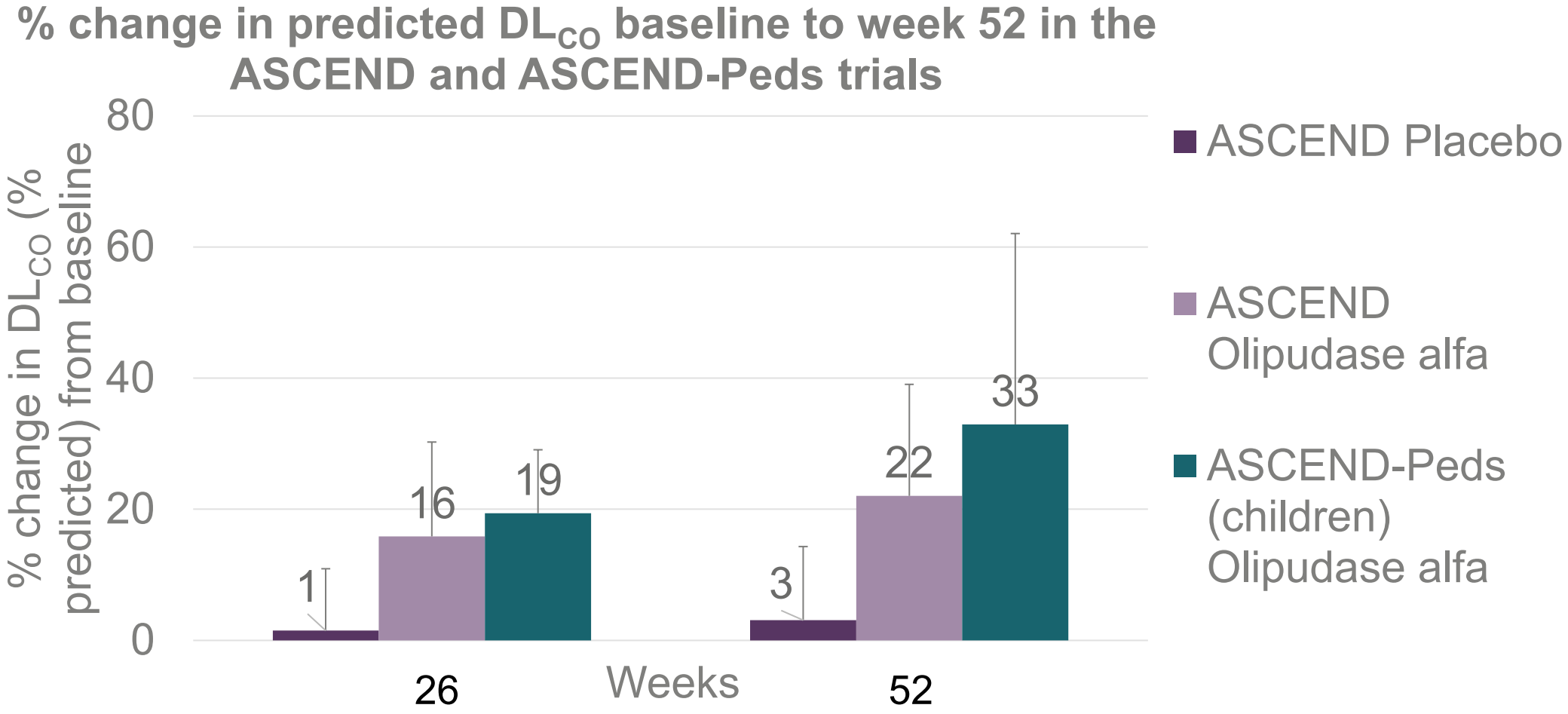
Abbreviations: MAA: managed access agreement; QALY: Quality-adjusted life years; TE, technical engagement

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

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



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

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

Recap: Clinical trial results, change in Spleen volume

DG: Spleen volume still enlarged after taking olipudase alfa

Month 12 ASCEND:

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

Overview of consultation responses

Company: in response to draft guidance,

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

Responses and comments from:

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

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Abbreviations: NPUK: Niemann-Pick UK

Key issue: Long-term treatment effect

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

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

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

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

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

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

Key issue: Long-term treatment effect

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

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

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

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

Clinical expert consultation comments:

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

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

Abbreviations: QoL: Quality of life

Key issue: Modelling mortality

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

What was said at ECM1

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

Company approach post ECM1 – used modified parametric approach

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

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

Key issue: Modelling mortality

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

Limitations with parametric approach still exist

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

Issues with data in Chart review study

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

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

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

Key issue: Discount rate

Was the biggest driver of cost-effectiveness at ECM1

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

What was said at ECM1, draft guidance

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

Company approach post ECM1 – 1.5% discount rate appropriate

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

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Does the committee consider 1.5% discounting to be suitable?

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

Consultation comments: treatment effect

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

Patient expert/professional group

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

Clinical expert

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

Abbreviations: QoL: Quality of life

Key issue: Discount rates

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

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

Key issue: Carer utilities

Disutility for mortality was a biggest ICER driver at ECM1

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

Company response to consultation:

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

New carer disutilities in company base-case

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

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

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

Key issue: Carer utilities

Patient experts:

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

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

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

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

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

Uncaptured benefits

ECM1: there might be benefits not fully captured but uncertain

Company approach post ECM1 –

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

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

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

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

Abbreviations: ECM1: Evaluation committee meeting 1

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

Incident patient subgroup

Company submit subgroup evidence for patients recently diagnosed

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

Additional amendments for subgroup analysis

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

Patient expert

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

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

Should a separate recommendation be considered for this subgroup?

Abbreviations: ECM1: Evaluation committee meeting 1

Company updated and EAG base case assumptions

Assumptions in updated company and EAG-base cases

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

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

Committee preferred assumptions from ECM1

Preferred assumptions

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

Committee conclusion on cost-effectiveness:

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

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

Factors affecting the guidance

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

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

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

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Thank you.

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Back up information

Recap: Nature of condition

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

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

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

Incidence & prevalence:

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

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

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

Consultation comments: Uncaptured benefits of treatment with Olipudase Alfa

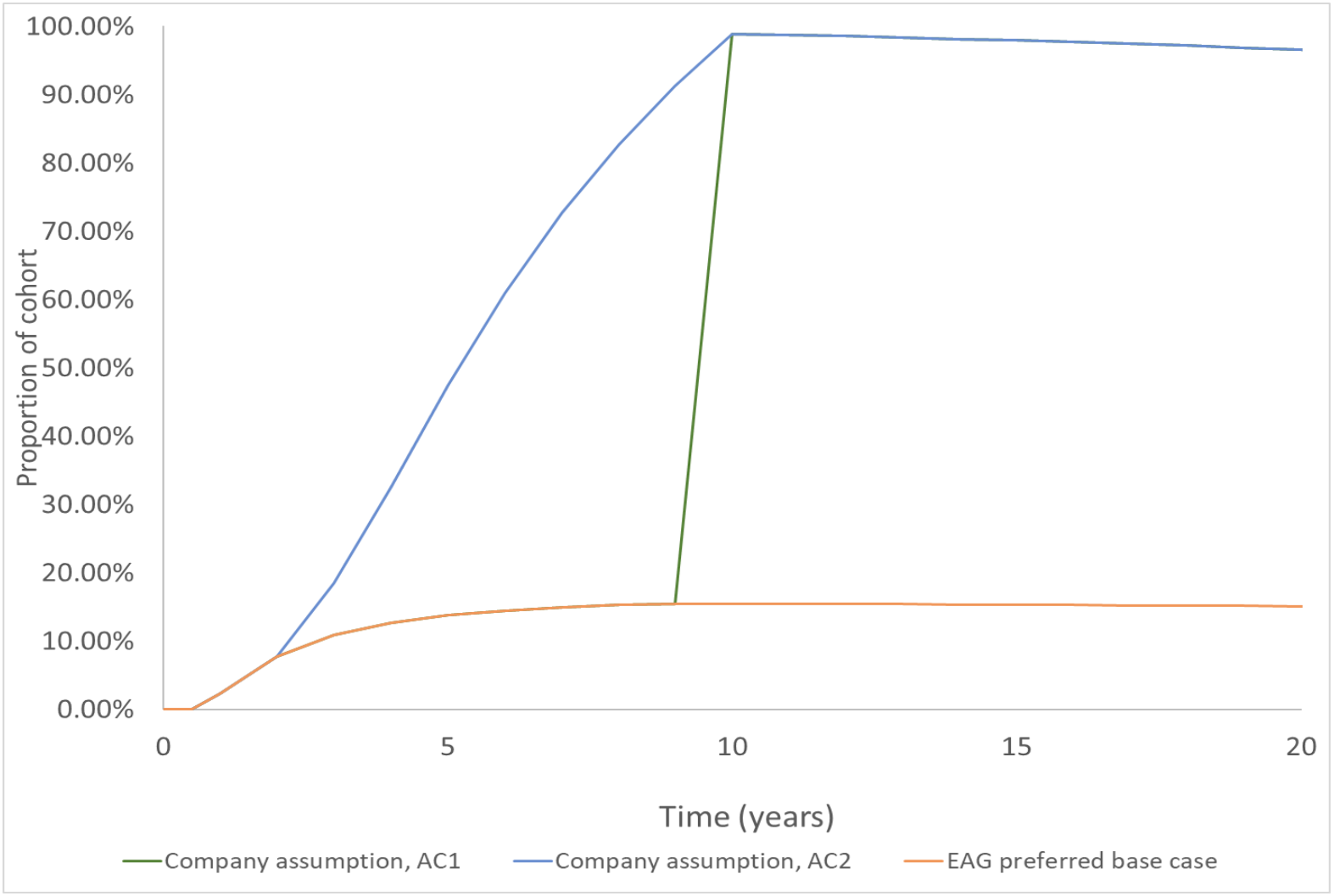
Patient experts/professional group

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

ECD; evaluation consultation document

Key issue: Long-term treatment effect

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



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

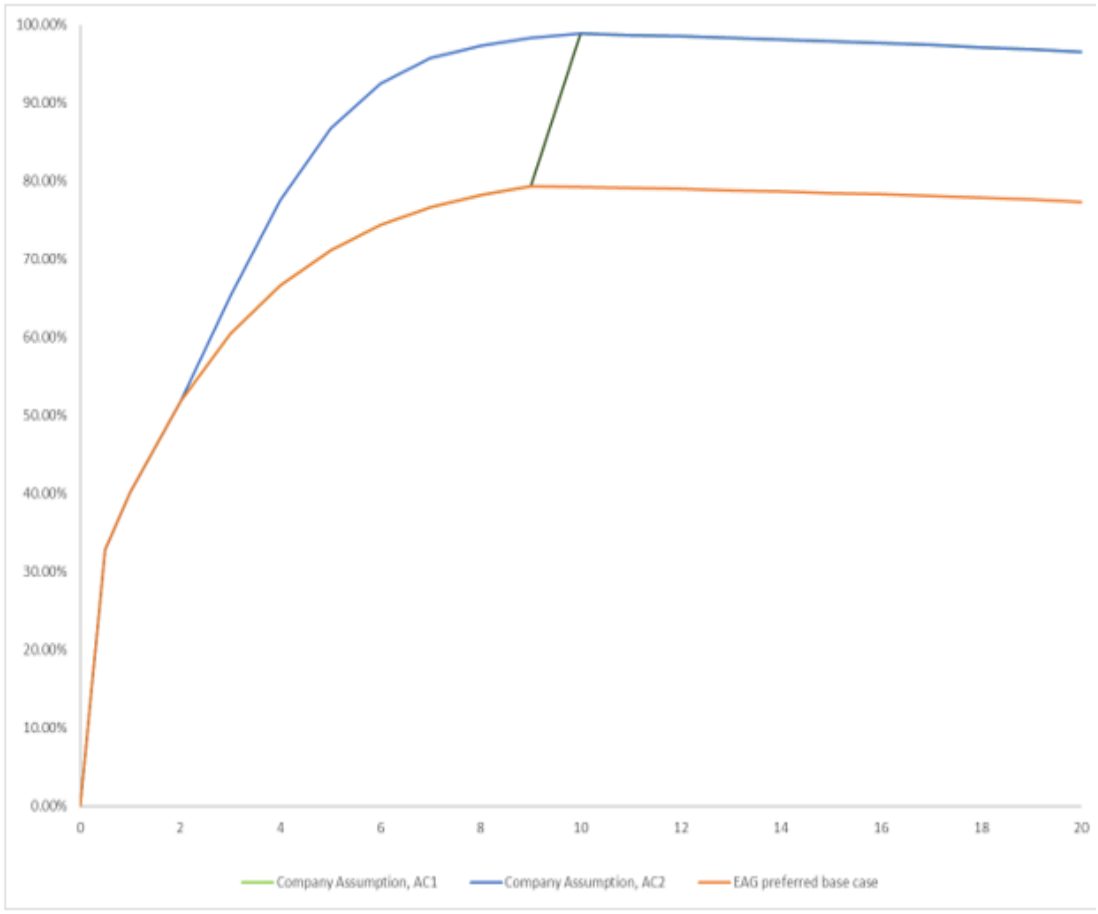
EAG's preferred scenario: implied a continued increase in effect with a declining rate from year 2; proportion in best health stabilises around year 5 or 6 (with a slight decline due to mortality effect)

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

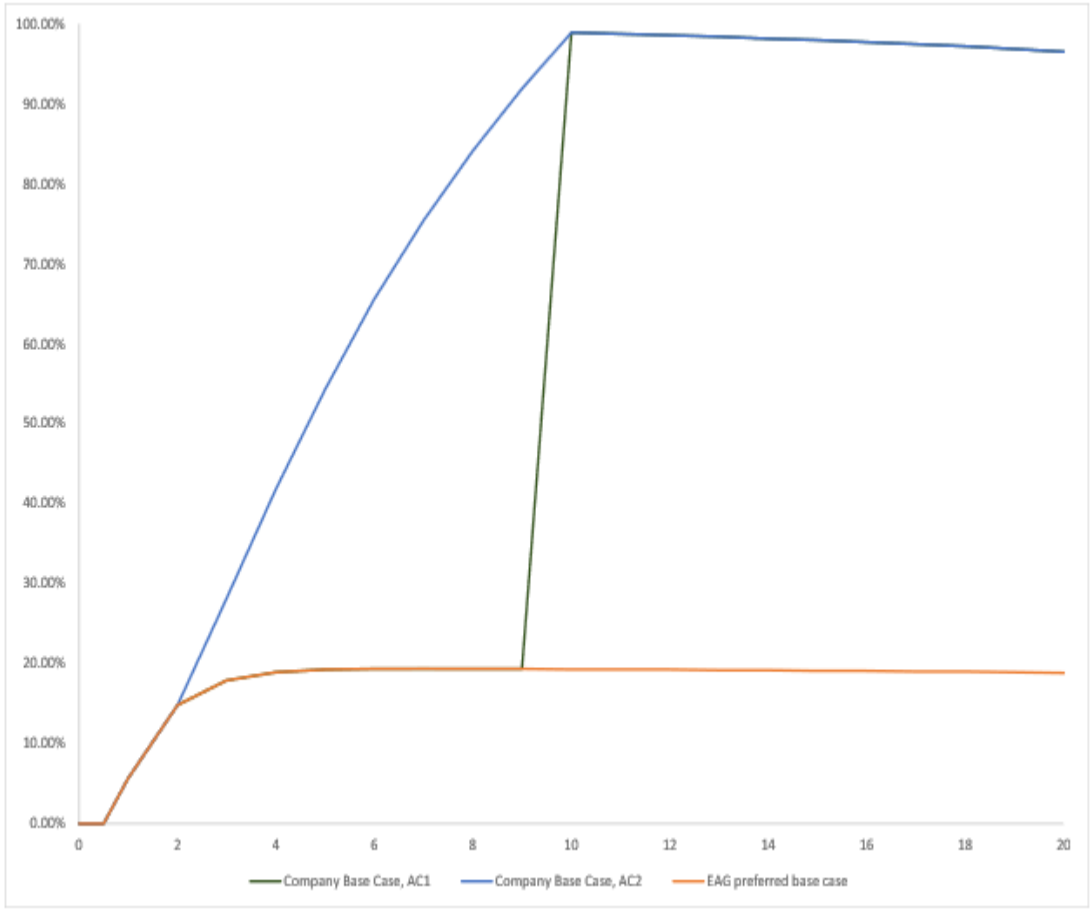
Abbreviations: DLco, diffusing capacity of the lungs for carbon monoxide SV: Spleen volume

Key issue: Long-term treatment effect

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



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



Source: EAG response, figure 2 and 3

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

EAG: Other comments

Trial generalisability

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

Exit interviews with trial participants

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

QALY weighting

EAG: does not consider appropriate to apply QALY weighting

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

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

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

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

Abbreviations: QALY: Quality-adjusted life year

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

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

Abbreviations: MAA: managed access agreement

Managed access

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

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

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

Managed access team: potential candidate for MAA but uncertainties remain

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

Abbreviations: MAA: managed access agreement