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

For committee – contains ACIC information

Highly Specialized Technology Appraisal Committee [05 October 2023]

Chair: Peter Jackson

Lead team: Shehla Mohammed, Stuart Mealing, Jonathan Ives

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Technical team: Tom Jarratt, Yelan Guo, Richard Diaz

Company: Sanofi

Key issues, clinical

Population representativeness:

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

Long term treatment effect:

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

Key issues: economic

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

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

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

Carer's disutilities:

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

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

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

Others:

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

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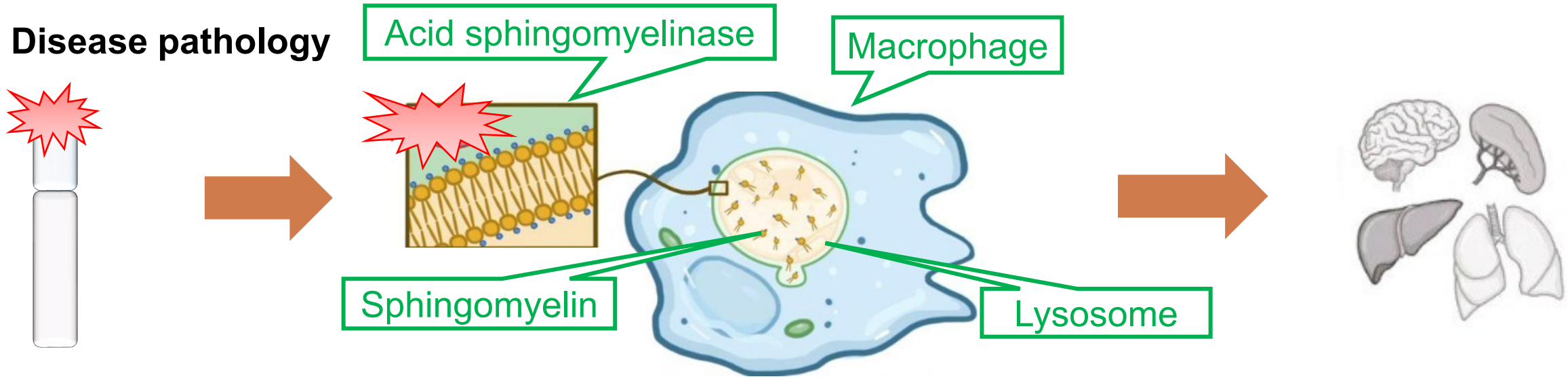
Background: Niemann-Pick (NP) types B and A/B

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

Disease pathology



Mutation in SMPD1 gene

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

Build-up in other cells throughout body, causing damage

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

Background:

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

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

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

Incidence & prevalence:

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

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

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

Abbreviations: ASMD, acid sphingomyelinase deficiency

Signs and symptoms

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

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

Olipudase alfa will not impact on neurological manifesta-tions

Abbreviations: ASMD, acid sphingomyelinase deficiency

Patient perspectives:

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

Submissions from Niemann-Pick UK (NPUK)

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

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

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

Patient perspectives: pathway and intervention

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

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

Benefit of olipudase alfa:

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

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

NICE

Abbreviations: ASMD, acid sphingomyelinase deficiency

Patient perspectives: Impact on carers and families

Impact on carers

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

Impact on siblings:

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

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

Clinical perspectives

Submissions from British Inherited Metabolic Disease Group

Aims of treatment:

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

Diagnosis and management

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

Experience with olipudase alfa:

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

Technology (Olipudase alfa, Xenpozyme)

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

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

Decision problem

Company's decision problem generally consistent with scope

Population, intervention, comparators and outcomes from the scope

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

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

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Baseline population characteristics in trials

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

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

EAG:

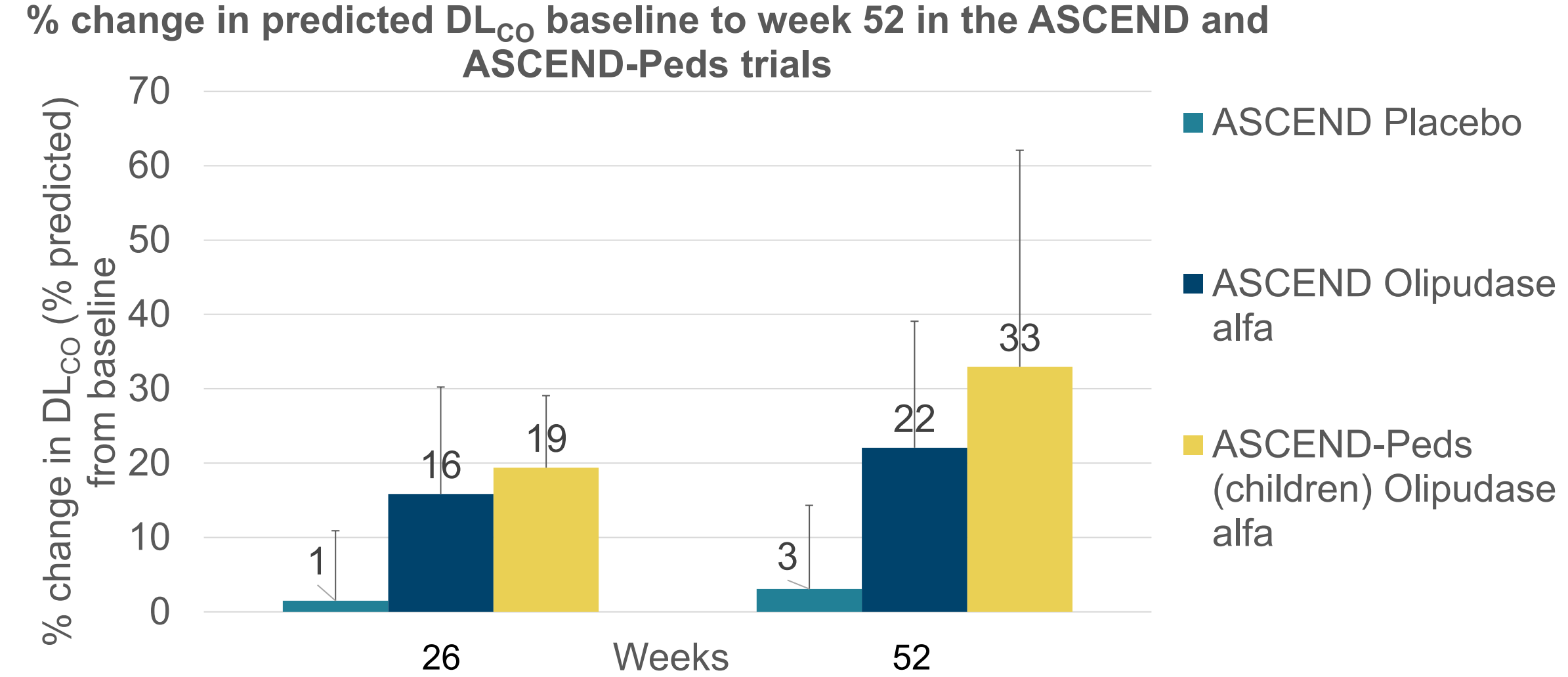
Weight: Baseline weight lower than expected in UK. Expert advice: some people may be smaller with ASMD but unlikely to see difference across population.

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

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

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

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



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

Clinical trial results: % change in predicted DLco

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

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

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

EAG

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

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

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

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

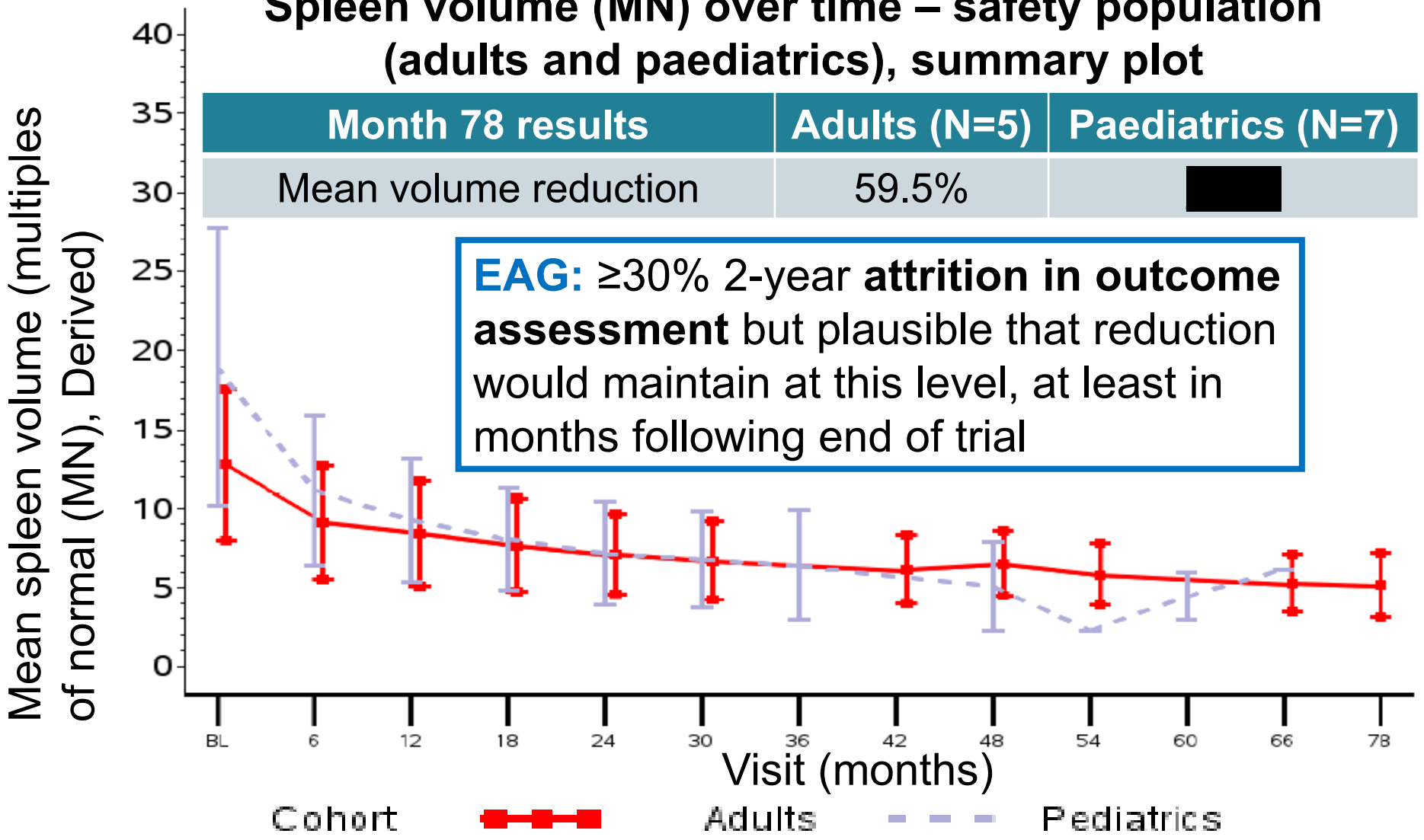
Results, primary outcome: % change in Spleen volume

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

Spleen volume (MN) over time – safety population (adults and paediatrics), summary plot

Month 78 results	Adults (N=5)	Paediatrics (N=7)
Mean volume reduction	59.5%	[redacted]

EAG: ≥30% 2-year **attrition in outcome assessment** but plausible that reduction would maintain at this level, at least in months following end of trial



Month 12 ASCEND:

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

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

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

Results: HRQoL

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

ASCEND

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

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

ASCEND-Peds

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

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

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

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

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key issues identified by EAG

Key issues all have large impact on ICER

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

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

Modelling long-term treatment effect

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

Background

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

Company after TE

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

EAG

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

Experts

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

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

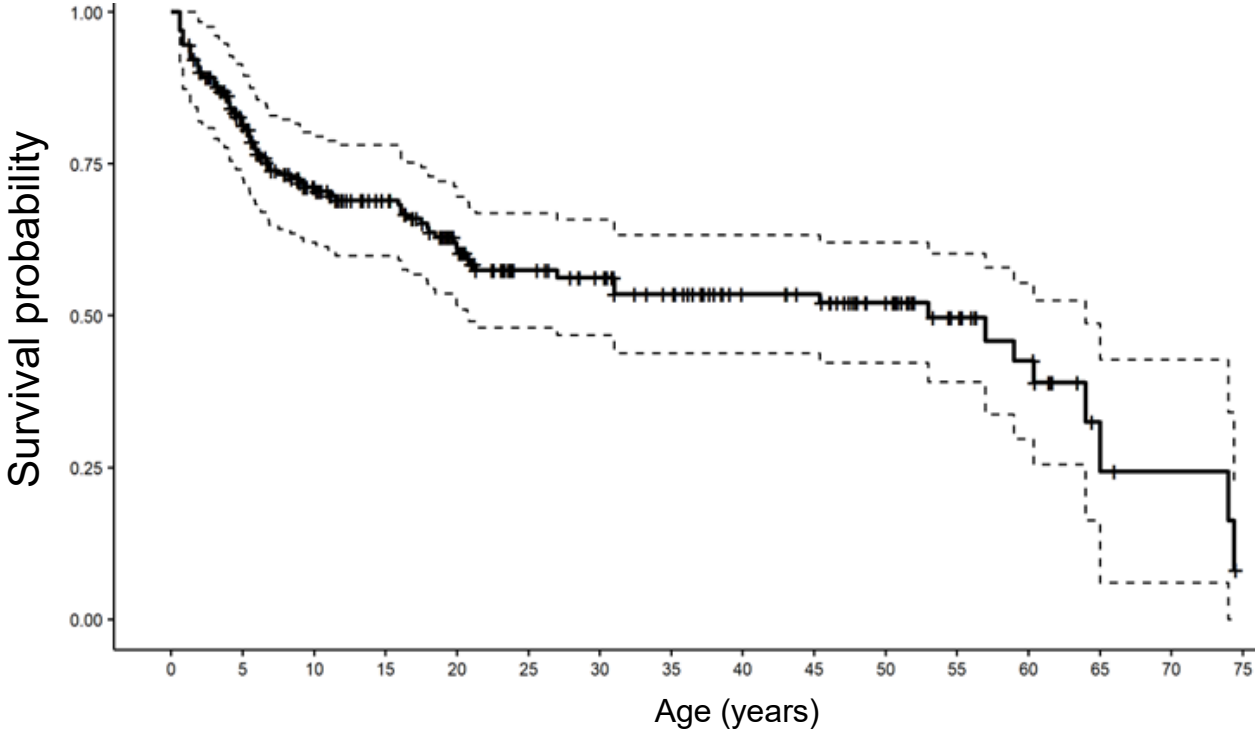
Modelling mortality:

Company and EAG had different approaches to modelling mortality

Company post TE:

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

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



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

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

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

Modelling mortality:

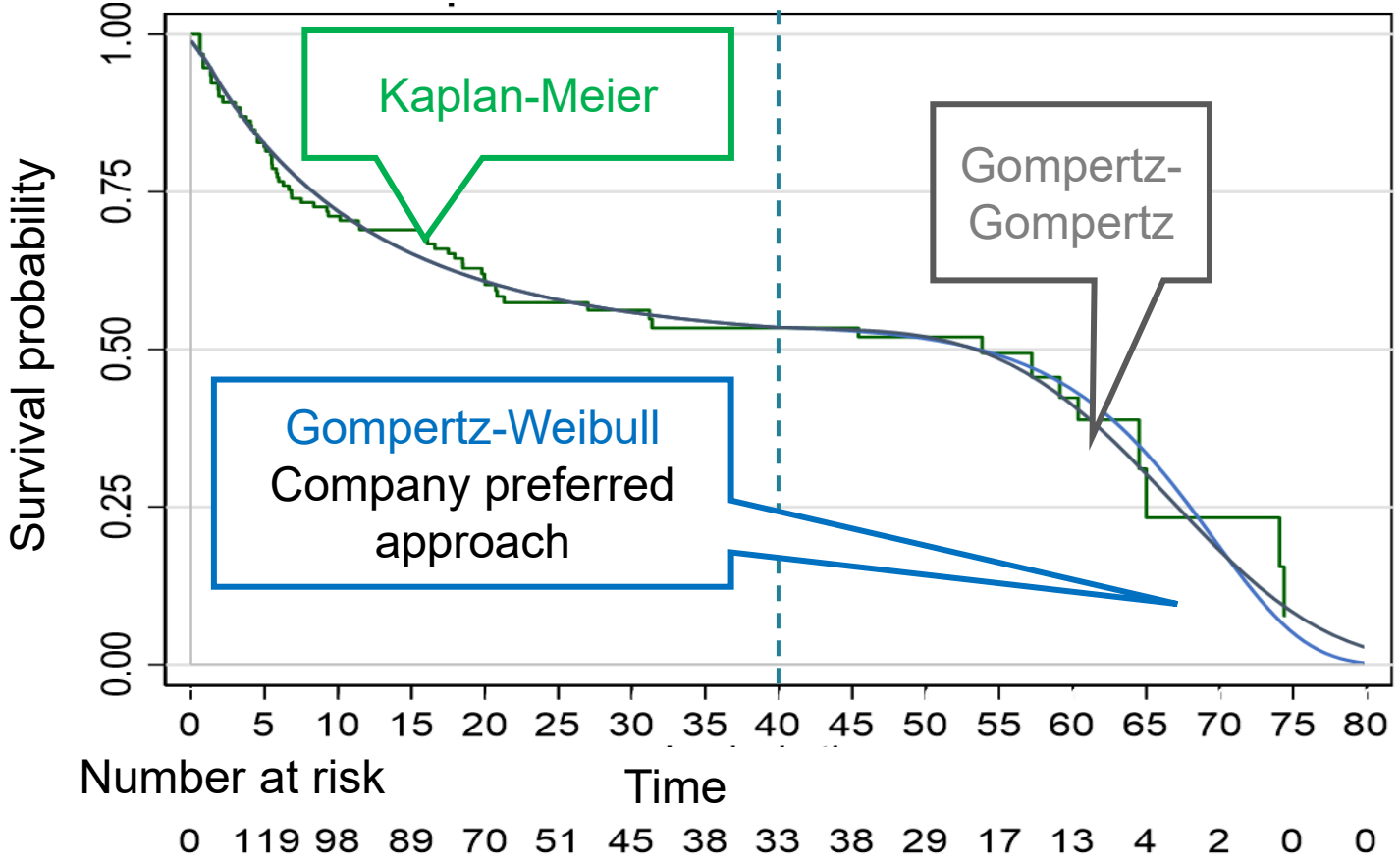
EAG: maintained its original approach as severe limitations in company's revised analysis post-TE;

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

EAG final base-case:

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

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



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

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

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

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

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

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

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

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

Key issue: Carer disutilities (1)

EAG: uncertainty surrounding several assumptions on carer's disutilities

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

Company and EAG base-case assumptions

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

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

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

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

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

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

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

Additional issues: Patient weight and severe subgroup

EAG assumes higher patient weight than company

Company and EAG base-case approaches to modelling weight

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

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

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

EAG

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

Which method of modelling patient weight does the committee prefer?

Other considerations

Equality issues

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

Benefits not fully captured:

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

Managed access

- Company proposed managed access

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

Factors affecting the guidance

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

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

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

QALY weighting

EAG: does not consider appropriate to apply QALY weighting

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

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

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

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

NICE

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

Company and EAG base case assumptions

Assumptions in company and EAG base case

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

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

Company base case and EAG's exploratory analysis

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

Long term treatment effect:

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

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

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

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

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

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

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

What are committee's preferred assumptions?

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

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

Key issues: economic

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

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

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

Carer's disutilities:

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

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

QALY weighting: Does QALY weighting apply?

Others:

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

33

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

NICE National Institute for Health and Care Excellence

Thank you.

NICE National Institute for Health and Care Excellence

Back-up slides

Treatment pathway

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

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

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

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

Clinical trials and studies

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

Key: Ongoing trial; Completed trial; Additional data

Olipudase alfa

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

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

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

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

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

Informs mortality in main analysis post TE

SPHINGO-100
Survey study of 30 children and 29 adults

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

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

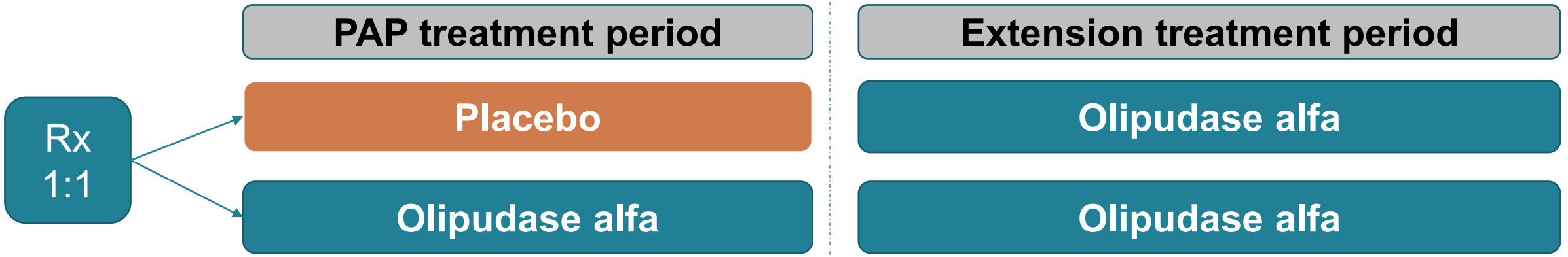
Informs mortality in scenario analysis for severe subgroup

Abbreviations: BSC, best supportive care

ASCEND clinical trial study design

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

True treatment crossover for placebo, mock crossover for active arm



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

Key clinical trial designs and populations

Key: Ongoing | Completed

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

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

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

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

Key clinical trials: designs and outcomes

Key: Ongoing | Completed

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

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

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

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

Key clinical trial baseline characteristics

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

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

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

Key clinical trial baseline characteristics

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

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

EAG comment

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

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

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

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

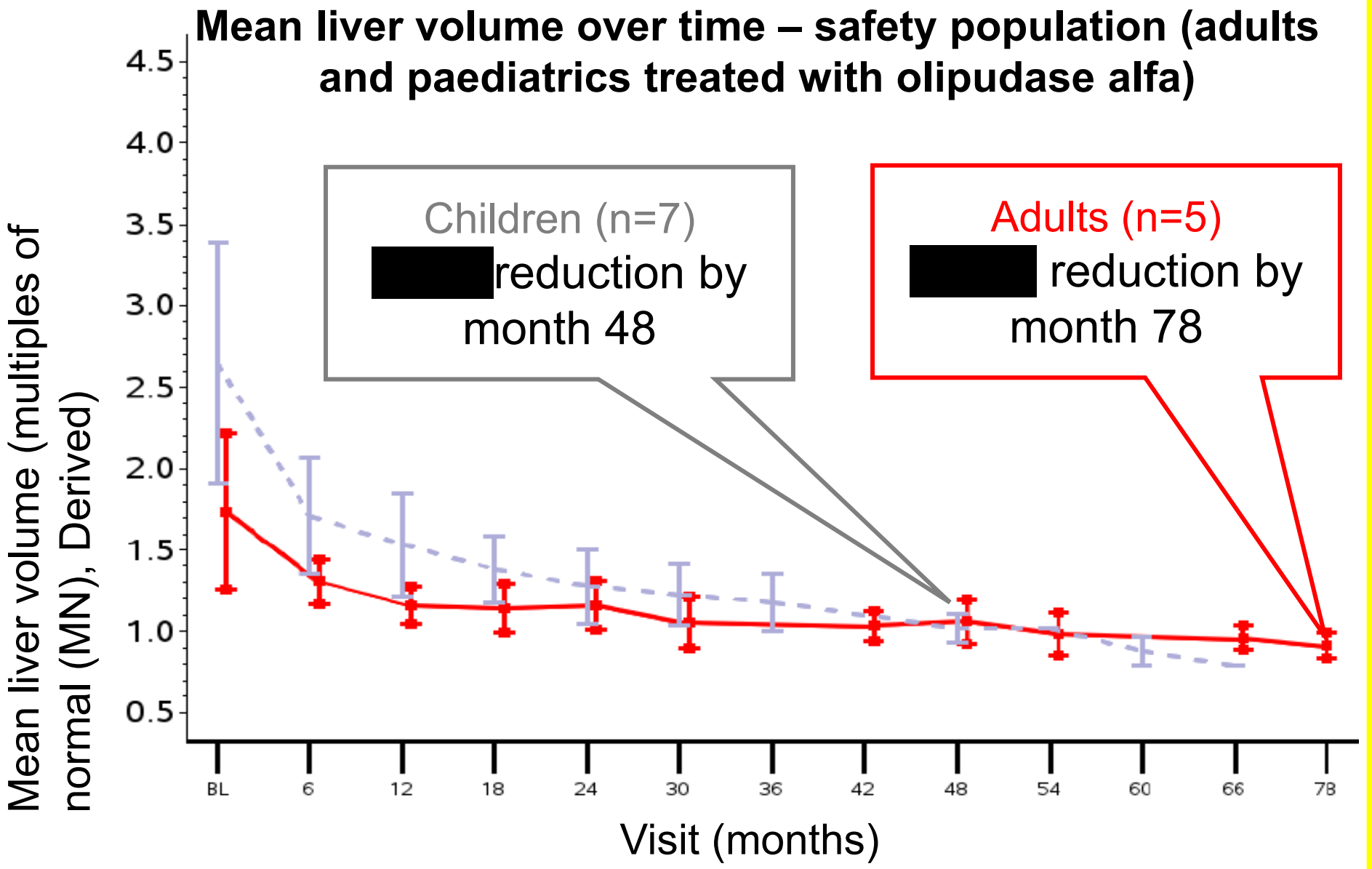
EAG comments

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

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

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

Results, secondary outcome: % change in Liver volume



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

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

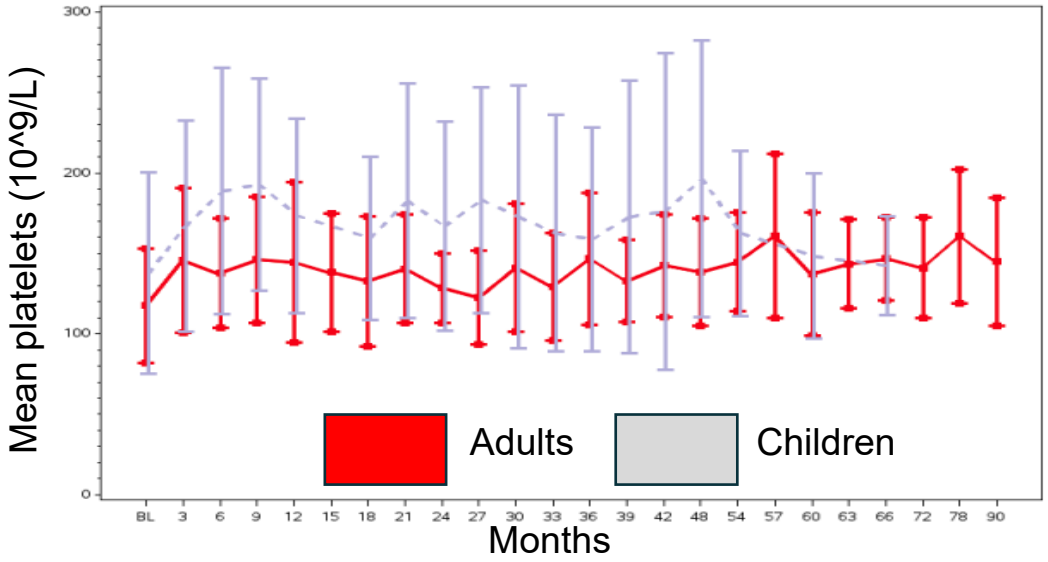
Results: Other efficacy outcomes

Improvement largely seen in other efficacy outcomes

Platelet counts

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

Platelet counts in LTS13632



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

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

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

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

Adverse events

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

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

Key issues, clinical

Population representativeness:

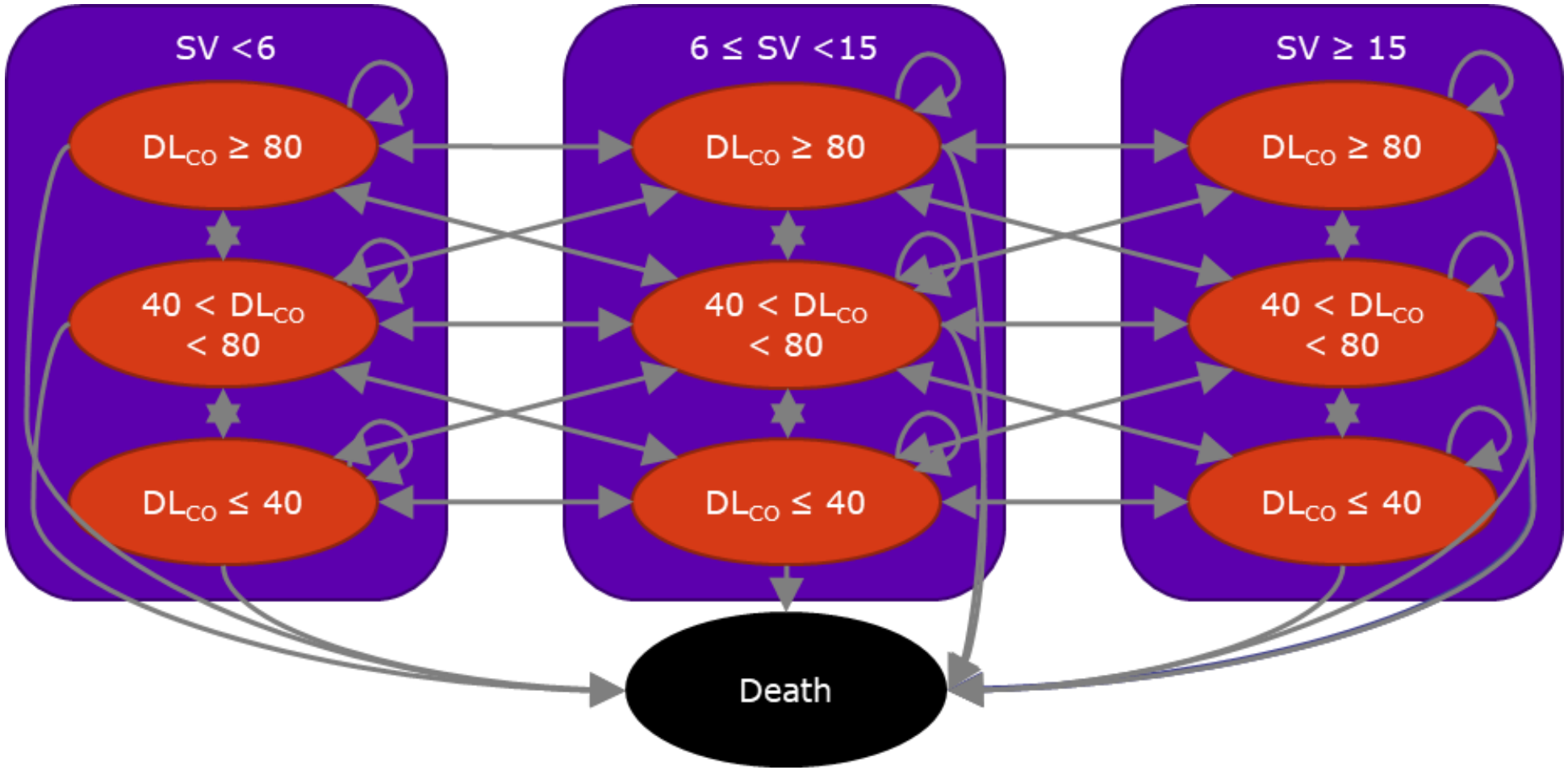
- Does the committee consider that the population in trials represent those seen in the UK in terms of ASMD type, severity, and baseline characteristics including age and weight?

Long term treatment effect:

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

Company's model overview

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



Disutilities by damage of:

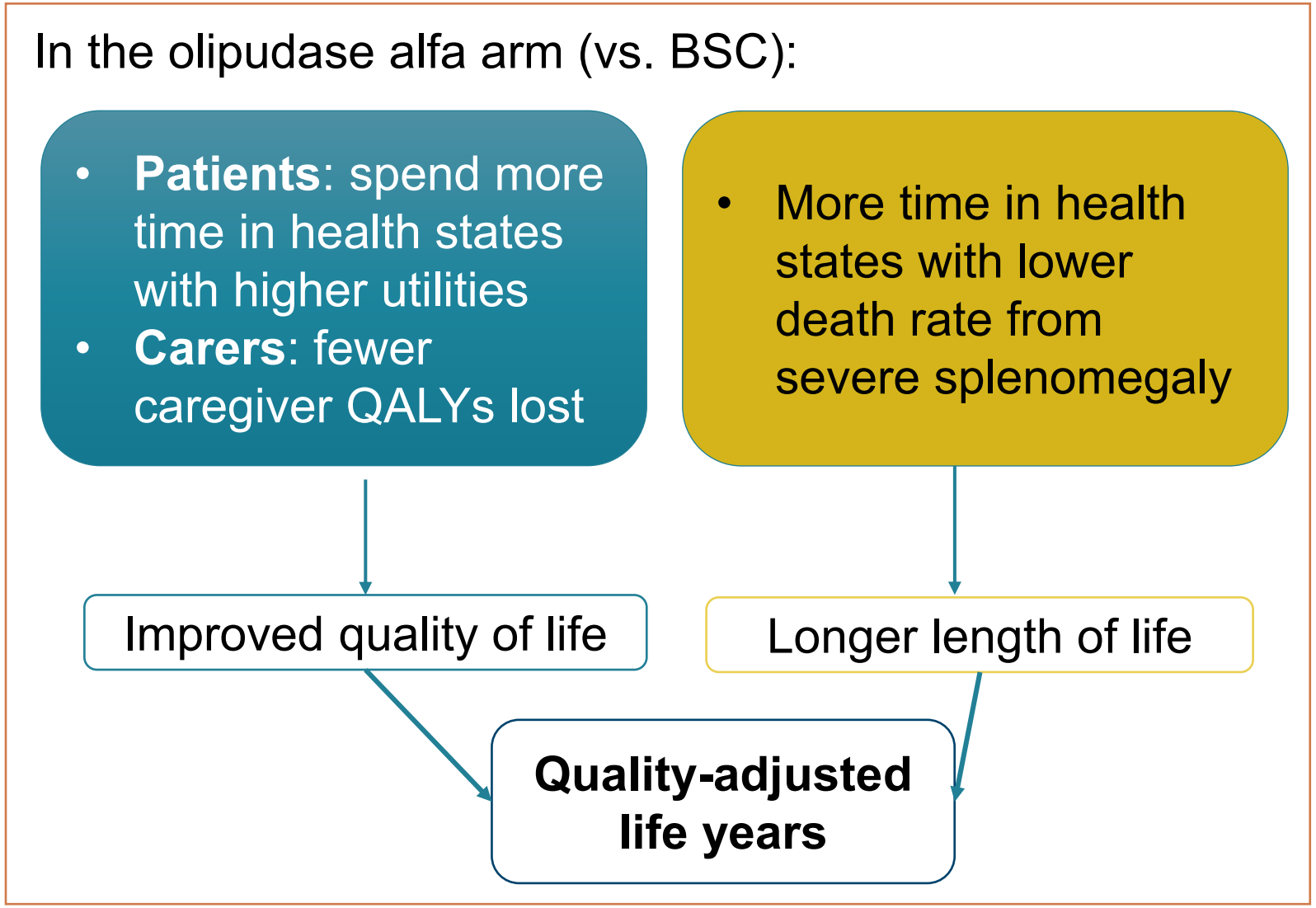
- Liver
- Spleen
- Respiratory
- Cardiovascular
- Major bleeding

Utility decrement for caregivers determined by treatment

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

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

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



Technology affects costs by:

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

Assumptions with greatest ICER effect in company's model:

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

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

How company incorporated evidence into model

Input and evidence sources

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

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

Modelling mortality:

Company and EAG had different approaches to modelling mortality

Background

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

EAG:

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

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

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

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

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

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

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

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

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

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

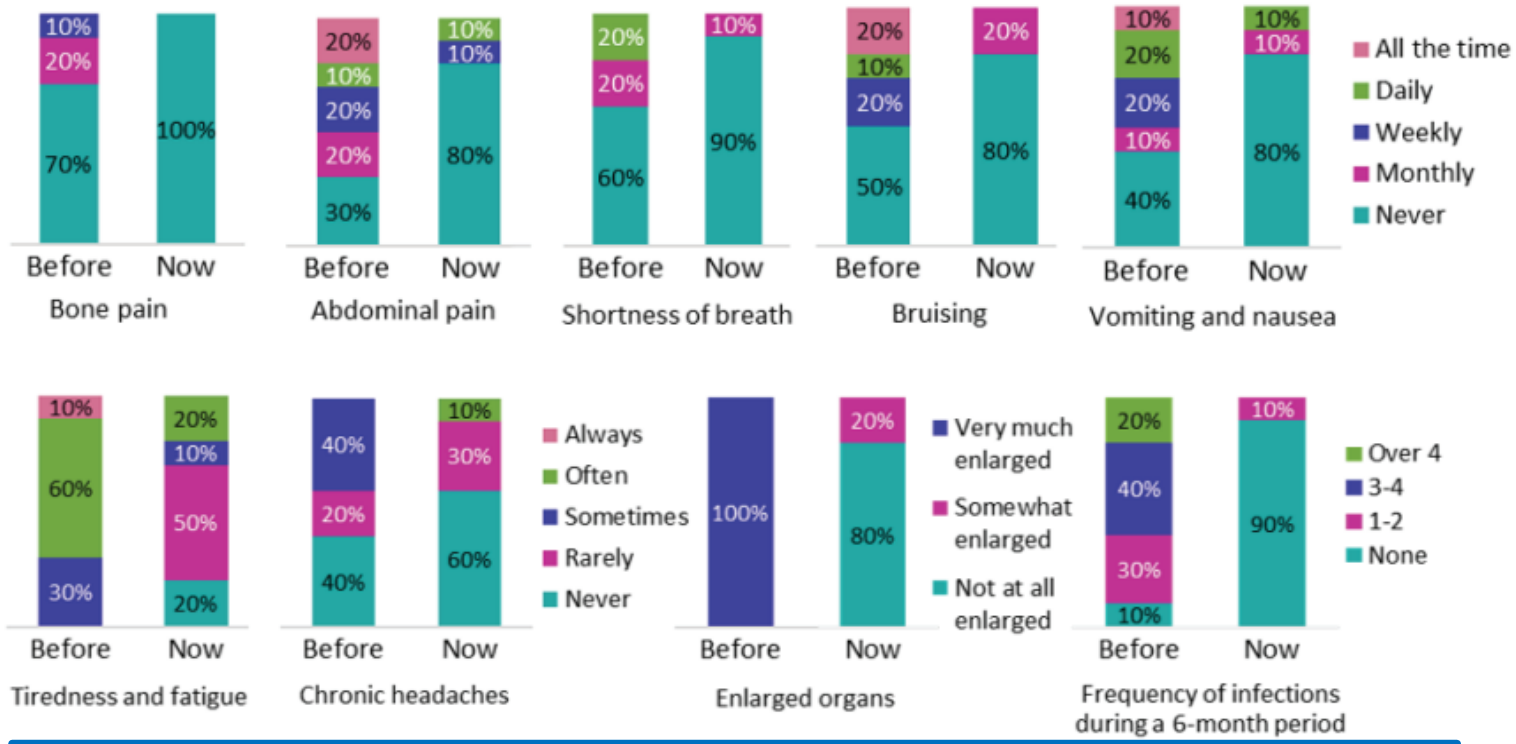
Key issue: Discounting rates 1.5% vs 3.5% (2)

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

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

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

Results of survey of 10 paediatric patients or carer



EAG: lack of robust evidence:

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

Olipudase improved all non-neurological manifestations

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

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

EAG: Lack of evidence on benefits sustained over long time

Company:

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

EAG comments

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

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

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

Abbreviations: ASMD, acid sphingomyelinase deficiency

Utilities (for person with ASMD)

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

Patient utilities for each health-state

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

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

Key issue: Carer disutilities (1)

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

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

Company and EAG base-case assumptions

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

Key issue: Carer disutilities (1)

EAG: applying carer disutility to BSC arm only lacks plausibility

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

Patient expert

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

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

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

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

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

Key issue: carer's disutilities (2)

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

EAG:

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

EAG carer utility values

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

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

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

Abbreviations: MS, multiple sclerosis

Key issue: Modelling patient weight

EAG and company have different preference for modelling weight

Baseline age and weight (company base-case)

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

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

EAG

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

Company following TE

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

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

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

Which method of modelling patient weight does the committee prefer?

Key issue: Subgroup analysis in people with severe disease

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

Background

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

EAG

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

Company following TE

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

Clinical expert

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

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

Company base case and EAG's exploratory analysis

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

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

What are committee's preferred assumptions?

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

Company base case and EAG's exploratory analysis

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

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

What are committee's preferred assumptions?

Company base case and EAG's exploratory analysis

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

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

What are committee's preferred assumptions?