Highly Specialised Technology

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

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

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission from Sanofi:**
   a. Initial submission August 2022 (updated marking September 2023)
   b. Addendum February 2023 (updated marking September 2023)

2. **Clarification questions and company responses**
   a. Clarification questions and company responses on initial submission September 2022 (updated marking September 2023)
   b. Clarification questions and company responses on company addendum May 2023 (Updated marking September 2023 version)

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. British Inherited Metabolic Disease Group
   b. Niemann-Pick UK
   c. Patient expert Nominated by Niemann-Pick UK

4. **External Assessment Report – following factual accuracy check**

Post-technical engagement documents

5. **Technical engagement response from company**

6. **Technical engagement responses and statements from experts:**
   a. Clinical expert response, Nominated by Sanofi
   b. Niemann-Pick UK response
   c. Patient expert response, nominated by Niemann-Pick UK
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   e. Patient expert supplementary material, mindmap

7. **External Assessment Group critique of company response to technical engagement** prepared by PenTAG

a. EAG technical engagement response
b. EAG additional technical engagement response to query

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

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

Document B

Company evidence submission

August 2022

Key:
'Commercial in confidence' in turquoise
'Academic in confidence' in yellow

File name	Version	Contains confidential information	Date
HST draft 1.0	**1.0**	**Yes**	**11th August 2022**

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Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASM	Acid sphingomyelinase
ASMD	Acid sphingomyelinase deficiency
AST	Aspartate transaminase
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
BSC	Best supportive care
CCL18	Chemokine ligand 18
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHIT1	Chitotriosidase 1
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CRIM	Cross reactive immunological material
CRS	Cytokine release syndrome
CSR	Clinical study report
CVD	Cardiovascular disease
DET	Data extraction table
DL_{CO}	Lung diffusion of carbon monoxide
ECG	Electrocardiogram
EQ-5D(-5L)	EuroQoL Five Dimensions (Five Levels)
EMA	European Medicines Agency
ERT	Enzyme replacement therapy
ETP	Extension treatment period
FACIT	Functional Assessment of the Chronic Illness Therapy
FDA	Food and Drug Administration
FEV	Forced expiratory volume

FVC	Forced vital capacity
GI	Gastrointestinal
GP	General practitioner
HCP	Healthcare practitioner
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HTD	Highest tolerate dose
IAR	Infusion associated reaction
ICER	Incremental cost-effectiveness ratio
ILD	Interstitial lung disease
IV	Intravenous
IXRS	Interactive Voice Response System/Interactive Web Response System
Kg	Kilogram
KOL	Key opinion leader
LDL	Low-density lipoprotein
LS	Least squares
LSD	Lysosomal storage disease
LYG	Life years gained
mg	Milligram
MHRA	The Medicines and Healthcare products Regulatory Agency
mITT	Modified intention to treat population
MMRM	Mixed effect model repeated measure
MN	Multiples of normal
MRI	Magnetic resonance imaging
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
Nmol	Nanomole
NNPDF	National Niemann-Pick Disease Foundation
NPB-HAQ	Niemann-Pick B – Health Assessment Questionnaire
NPD	Niemann-Pick Disease
OR	Odds ratio

OS	Overall survival
PAP	Primary analysis period
PAS	Patient access scheme
PD	Pharmacodynamic
PFT	Pulmonary function test
PICOS	Population, interventions and comparisons, outcomes, and study design
PK	Pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
Q2W	Once every 2 weeks
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised clinical trial
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	36-item Short Form health survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMPD1	Sphingomyelin phosphodiesterase 1
SMR	Standardised mortality ratio
SRS	Splenomegaly related score
SV	Spleen volume
TEAEs	Treatment emergent adverse events
TLC	Total lung capacity
UK	United Kingdom
ULN	Upper limit of normal
US	United states
WMV	Wilcoxon-Mann-Whitney
WTP	Willingness to pay

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

The decision problem is outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with acid sphingomyelinase deficiency (also known as Niemann-Pick disease type B or A/B)	As per scope	N/A
Intervention	Olipudase alfa	As per scope	N/A
Comparator(s)	Best supportive care	As per scope	N/A
Outcomes	The outcome measures to be considered include: • Change in spleen volume • Change in lung function • Change in liver function and volume • Change in physical observations (including observations or measurements from examination of the skin, head, eyes, ears, nose and throat; lymph nodes; heart, vital signs, lungs and abdomen; bone marrow; extremities and joints) • Change in weight, height and onset of puberty in children and young people • Change in neurological observations (including observations or measurements from examination of coordination; cranial nerves; extrapyramidal features; fundoscopy; gait; motor skills; peripheral nervous system; reflexes; sensory nervous system; strength and mental status) • Change in biomarkers (including high sensitivity c-reactive protein; ceramide; iron; cardiac troponin I; ferritin; CCL18 levels; lysosphingomyelin, oxysterols, lipid profile, interleukin-6; interlukin-8 and calcitonin) • Change in fatigue and exercise tolerance	As per scope	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	• Mortality • Adverse effects of treatment • Health-related quality of life • Carer quality of life		
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	As per scope	N/A

Abbreviations: CCL18, chemokine ligand 18; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence

B.1.2 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Olipudase alfa (Xenpozyme)
Mechanism of action	Olipudase alfa is a recombinant human acid sphingomyelinase that reduces sphingomyelin (SM) accumulation in organs of patients with Acid Sphingomyelinase Deficiency (ASMD) (1).
Marketing authorisation/CE mark status	As of 1st August 2022, Sanofi received MHRA MA approval via the MHRA European Commission Decision Reliance Procedure (ECDRP) (PLGB 04425/0901). Regulatory approval for olipudase alfa was granted via the EMA centralised procedure on the 24th of June. The licensed indication for olipudase alfa is enzyme replacement therapy for the treatment of non-CNS manifestations of ASMD in paediatric and adult patients with type B or type A/B.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Olipudase alfa is indicated as an enzyme replacement therapy for the treatment of non-CNS manifestations of ASMD in paediatric and adult patients with type B or type A/B.
Method of administration and dosage	• Olipudase alfa is administered as an IV infusion every 2 weeks. Adult and paediatric patients will receive olipudase alfa at 3 mg/kg following a dose escalation regimen
Additional tests or investigations	• Dose monitoring and liver function tests during dose escalation phase
List price and average cost of a course of treatment	[redacted]
Patient access scheme (if applicable)	[redacted]

Abbreviations: ASM, acid sphingomyelinase; ASMD, acid sphingomyelinase deficiency; CHMP, Committee for Medicinal Products for Human Use; CNS, central nervous system; EMA, European Medicines Agency; IV, intravenous; kg, kilogram; mg, milligram; MA, marketing authorisation; MHRA, The Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PAS, patient access scheme

B.1.3 *Health condition and position of the technology in the treatment pathway*

- Acid Sphingomyelinase Deficiency (ASMD) is a progressive, life-limiting lysosomal storage disease (LSD), characterised by the build-up of sphingomyelin causing widespread multi-organ damage (2).
- ASMD is a very rare disease with approximately 40–50 prevalent patients currently estimated in the UK (3, 4). Of the patients in the UK with ASMD, the majority have type B and type A/B, with currently only 2–3 patients with type A (3).
- Both ASMD type B and A/B are associated with life-threatening complications, often leading to pulmonary dysfunction, splenomegaly, hepatomegaly, and haematologic symptoms. Additional symptoms and complications also include fatigue, bleeding, bruising, heart disease, orthopaedic issues, peripheral neuropathy, reduced motor skills, gastrointestinal (GI) discomfort, and subnormal growth (in children) (2, 5).
- The symptoms associated with ASMD result in notable morbidity and mortality for patients, with age at death varying significantly, ranging from 2 to 72 years dependent on the subtype, age range of patients, and length of follow up (5-8).
- The clinical manifestations of ASMD have a significant impact on patients' quality of life (QoL). Many patients with ASMD are unable to care for themselves, perform common daily activities, and take part in social activities (2, 5, 9). There is also a profound impact on a patient's self-esteem and mental health, with patients frequently suffering with anxiety and depression. Children with ASMD experience poor growth and development, which can result in delayed puberty, and increased risk of bone fracture (10).
- Families and caregivers of patients with ASMD face a substantial QoL burden (9, 11-13). They have to deal with the worry and grief due to the disease progressing and their loved one deteriorating or dying (12). They struggle to maintain relationships, and attend social activities (11). In addition, they face a substantial financial burden due to time spent caregiving, the inability to work and reliance on social services support (9).
- There are currently no treatments that address the underlying pathology of ASMD or alter its rate of progression (2). Only symptomatic care and palliative/supportive measures are currently available (2, 14). Due to the lack of a disease-specific treatment, patients with ASMD continue to deteriorate, and there is an urgent need for a treatment targeting the underlying pathology of the disease.
- Olipudase alfa (recombinant human acid sphingomyelinase) is an enzyme replacement therapy (ERT) indicated for the treatment of non-central nervous system (CNS) manifestations of ASMD in paediatric and adult patients with type B or type A/B. Olipudase alfa specifically targets the underlying pathology of ASMD, reversing the accumulation of sphingomyelin. As the first and only disease-

modifying treatment for ASMD, olipudase alfa represents a major step-change in the management of this condition.

- Olipudase alfa addresses a substantial unmet need among patients who have an increased risk of mortality and reduced QoL due to non-CNS manifestations of ASMD, including splenomegaly, respiratory and liver failure.

B.1.3.1 *Disease overview*

Acid sphingomyelinase deficiency (ASMD) (also known as Niemann-Pick Disease [NPD] type A, type B, and B-variant corresponding to type A/B) is a very rare disorder. ASMD is progressive and impairs the functioning of multiple organs including the lungs, liver and spleen. ASMD often leads to premature death, particularly in cases of childhood onset of symptoms (7). The condition has a profound impact on the quality of life (QoL) of both patients and their families, and caregivers (9, 12).

ASMD belongs to a group of inherited metabolic disorders, known as lysosomal storage diseases (LSDs) caused by enzyme deficiencies within the lysosome, ultimately resulting in the accumulation of undegraded substrate. ASMD is caused by pathogenic variants of the *SMPD1* gene encoding acid sphingomyelinase (ASM), resulting in the expression of defective ASM (2, 15, 16). ASM is responsible for the degradation of sphingomyelin, a lipid commonly found in cell membranes and nerve cell axons, to ceramide and phosphocholine (2, 15, 16). Therefore, reduced ASM activity results in progressive lysosomal accumulation of sphingomyelin, particularly in reticuloendothelial tissues in the spleen, liver, lung, bone marrow, and lymph nodes (2, 17, 18). In patients with severe disease, neurons may also be affected (2, 17, 18). The build-up of sphingomyelin causes widespread multi-organ damage (2).

Age of diagnosis for patients with ASMD is varied, ranging from birth to late adulthood, with a more severe phenotype associated with earlier diagnosis (19). Diagnosis of ASMD type A is usually made before the child reaches one year of age (20). Patients with ASMD types A/B or type B are often diagnosed in childhood due to evident organomegaly, or in some cases, interstitial lung disease (ILD) or reduced platelet counts (21). However, some patients are diagnosed in adulthood due to later development of symptoms and years of misdiagnoses (21, 22).

Patients with ASMD may exhibit varied disease severity, typically ranging from most severe in patients with ASMD type A, to varied severity in patients with ASMD type B, as presented in Table 3. ASMD presents as a spectrum of phenotypes, which are often defined based on the presence and severity of neurological manifestations (2, 17):

- ASMD type A (infantile neurovisceral ASMD), is the early onset (diagnosis usually made before the child reaches 1 year of age) and acute neuropathic form of ASMD which is associated with rapidly progressive neurological degeneration and death, usually before the age of 3 years

- ASMD type B (chronic visceral ASMD) has a variable age of onset, and diagnosis can range from early childhood to adulthood. Patients with ASMD type B are characterised by slower progression (patients surviving until adulthood), with little or no neurological involvement. Other more variable features include liver dysfunction, pulmonary dysfunction, and delayed growth and puberty. Premature death can occur due to clinical manifestations such as liver and respiratory diseases.
- ASMD type A/B (chronic neurovisceral ASMD) includes patients with disease manifestations intermediate to ASMD type A and type B with variable neurological symptoms. Prolonged survival, and less severe neurological symptoms distinguishes this from ASMD type A, and premature death can occur due to clinical manifestations such as liver and respiratory disease(s)

Patients with ASMD type A are characterised by severe neurodegeneration in the first year with death usually by age 3. On the other hand, patients with ASMD type A/B survive early childhood and have combination of neurological (less severe than type A) and non-neurological symptoms (2). Both ASMD type B and A/B are characterised by severe and progressive somatic multi-systemic manifestations including splenomegaly (present in >90% of patients), hepatomegaly (present in >70% of patients), lung disease (present in >80% of patients), and gastrointestinal (GI) issues (present in >75% of patients) (2, 5).

Table 3: Onset, lifespan and common genotypes of ASMD by subtype

	ASMD type A	ASMD type B	ASMD type A/B
Phenotypic presentation	Infantile onset of severe neurodegeneration with other manifestations, including failure to thrive, hepatosplenomegaly and respiratory infections	Chronic progressive multisystemic disease. Often characterised by severe and progressive somatic multi-systemic manifestations, such as hepatosplenomegaly, ILD, thrombocytopenia, dyslipidaemia, and GI symptoms little or no neurologic involvement	ASMD type B phenotype but also progressive neurologic findings (ataxia, variable degrees of developmental delay and peripheral neuropathy)
Onset	Early infancy	Variable, childhood or adulthood	Variable, generally in childhood
Natural history	Uniform severity and prognosis	Variable manifestations, severity, and rates of disease progression	Variable manifestations, severity, and rates of disease progression[†]
Neurological involvement	Severe neurodegeneration	Little or no neurological involvement	Variable neurological symptoms
Lifespan	Premature death most commonly due to neurological degeneration; death usually before the age of three years	Survival to adulthood is common, with premature death from progressive liver and/or respiratory disease	Premature death from liver and respiratory disease; age at death ranges from childhood to adulthood
Included in the license	No	Yes	Yes

Abbreviations: ASMD, acid sphingomyelinase deficiency; GI, gastrointestinal; HDL, high-density lipoprotein; ILD, interstitial lung disease; LDL, low-density lipoprotein.
Source: Adapted from McGovern et al, 2017a (2); McGovern et al, 2017b (17); and Wasserstein et al, 2019 (14)
[†] Slower rate of progression than ASMD type A, but more severe than ASMD type B

The clinical manifestations of ASMD result in patient symptoms that include respiratory difficulties, fatigue, bleeding, bruising, heart disease, orthopaedic issues, peripheral neuropathy, reduced motor skills, gastrointestinal discomfort, and subnormal growth in affected children (Table 4) (2, 5). With no treatment currently available, organ damage caused by ASMD is currently irreversible, resulting in reduced life expectancy (particularly in patients with paediatric onset) (23, 24).

Table 4: Clinical Manifestations and Complications of ASMD

Disorder	Clinical manifestations and complications	Patient symptom	Patient impact	Frequency†	Source
Cardiopulmonary	• Interstitial lung disease • Respiratory infections, including pneumonia • Cardiac valve disease • Mixed dyslipidaemia with low HDL-C • Early-onset coronary artery disease	Shortness of breath	• Difficulty performing common daily activities • Exacerbated fatigue • Unable to exercise or participate in desired recreational activities, sports, and hobbies • May require supplemental oxygen	42%	McGovern et al, 2008 (25) and Sanofi data on file (22)
		Fatigue	• Difficulty performing common daily activities • Lack of concentration and coordination • Dizziness • Limitations on work/school (e.g. having to stop, limit hours)	69%	Pokrzywinski et al, 2021 (9)
		Cough	-	27%	Sanofi data on file (22)
		Dyslipidaemia: • Low HDL-C • High LDL-C	• Increased risk of coronary artery disease	74% 46%	McGovern et al, 2008 (25) McGovern et al, 2008 (25)
		• High triglyceride levels		62%	McGovern et al, 2008 (25)

Disorder	Clinical manifestations and complications	Patient symptom	Patient impact	Frequency†	Source
Hepatic and spleen	• Hepatomegaly • Liver fibrosis • Portal hypertension • Liver dysfunction • Splenomegaly	Enlarged abdomen	Possible: • Low self-esteem • Bullying for children • Disturbed sleep	-	-
		Abdominal pain/ discomfort	• Disturbed sleep • Nausea	91%	Sanofi data on file (22)
		Eating difficulty due to early satiety	• Inability to eat a normal sized meal	55%	Sanofi data on file (22)
		Diarrhoea	• Anxiety • Reduced social life/inability to go out with friends • Difficulty maintaining weight	55%	Sanofi data on file (22)
		Problems bending forward	• Inability to carry out everyday activities	55%	Sanofi data on file (22)
Haematologic	• Thrombocytopenia with bleeding tendencies	Excessive bleeding or bruising	• Frequent hospitalisation • Patients may require blood transfusion, or experience menorrhagia and uterine bleeding that requires hysterectomy	69%	Pokrzywinski et al, 2021 (9) McGovern et al, 2017 (2)
Skeletal	• Reduced bone density and pathologic fractures • Delayed bone maturation	Joint and limb pain	• Difficulty walking • Inability to move around outside home • Impact on activities of daily living such as work	39%	Sanofi data on file (22) McGovern et al, 2008 (25)

Disorder	Clinical manifestations and complications	Patient symptom	Patient impact	Frequency†	Source
		Prone to bone fractures	• Discouraged from participating in sports • Pain associated with fracture	27%	Sanofi data on file (22) Wasserstein et al, 2013 (10)
Delayed development	• Growth restriction in childhood	Delayed growth and puberty	• Difficulty with pregnancy • Low self-esteem due to appearing different to friends of a similar age • Bullying due to difference in appearance	~50%	Sanofi data on file (22) Cox et al, 2018 (5) McGovern et al, 2008 (25)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol
† Proportion of patients with ASMD type B and A/B reporting symptom

B.1.3.1.1 *Epidemiology*

ASMD is a very rare disease, with approximately 40–50 prevalent patients currently estimated in the UK (3, 4). Of the patients in the UK with ASMD, the majority have type B and type A/B, with currently only 2–3 patients with type A (3). Additionally, due to the increased severity and early mortality in patients with neurological impairment (including type A and A/B), the majority of patients under the care of specialist centres in the UK have ASMD type B (3).

Published global studies have estimated that ASMD has an incidence of approximately 0.1 to 0.9 per 100,000 live births (Table 5) (26-31). Approximately 85% of patients with ASMD have type B or type A/B (5, 32, 33).

Table 5: ASMD epidemiology published studies

Source	Country	Year	Population	ASMD incidence estimate
Pinto R et al, 2004 (29)	Portugal	1982–2001	ASMD type B	0.1 per 100,000
Burton BK et al, 2017 (27)	US	2015	ASMD type A/B	0.9 per 100,000[†]
Poorthuis BJ et al, 1999 (30)	Netherlands	1970–1996	ASMD type A ASMD type A or B ASMD type A and B	0.4 per 100,000 0.13 per 100,000 0.53 per 100,000
Meikle PJ et al, 1999 (28)	Australia	1980–1996	ASMD type A/B	0.4 per 100,000
Poupětová, H et al, 2010 (31)	Czech Republic	1975–2008	ASMD type A/B	0.33 per 100,000
Al-Jasmi FA et al, 2013 (26)	UAE	1995–2010	ASMD type B	0.25 per 100,000

Abbreviations: ASMD, acid sphingomyelinase deficiency
[†] Calculated based on 2 infants affected by ASMD type A/B out of 219,793 infants

As ASMD is an inherited, recessive disease, the epidemiology can vary substantially between populations and countries (26-31). The prevalence of ASMD is substantially lower in the UK than might be expected based on published worldwide estimates. A similar trend towards lower disease prevalence estimates in the UK compared with published estimates is observed with other LSDs (e.g. Pompe and Gaucher disease) (34). Reasons for this may include the sparsity of populations in the UK for whom certain mutations are more prevalent (such as Ashkenazi Jewish population, for whom three mutations account for more than 90% of disease-causing variants (17)) , diagnostic programmes used in the studies (including newborn screening (27), which is not currently available in the UK), and the considerable variation in the phenotype of patients with the same genotype (28, 35, 36). Early mortality in patients with more severe presentation may also contribute to the low prevalence observed in the UK (7).

B.1.3.1.2 *Clinical burden*

As discussed in Section B.1.3.1, both ASMD type B and A/B are typically characterised by severe and multi-systemic manifestations including pulmonary impairment, abnormal lipid profile, cardiovascular manifestations, enlarged liver and spleen, haematological impairment, and delayed growth and puberty (2, 5).

The symptoms associated with ASMD result in significant morbidity and mortality. The most burdensome morbidities include lung and liver disease which become more severe over time, with spleen volume as an important marker of disease severity (37).

Enlarged spleen and liver

Patients with ASMD type B and A/B often present with an enlarged spleen and liver, which are associated with abdominal pain/discomfort, eating difficulty and diarrhoea, as well as worsening clinical outcomes (6, 7, 25, 38). An enlarged liver and spleen results in patients often feeling bloated and requiring many small meals throughout the day, with one caregiver stating,
“[redacted] *(39)*

Significant enlargement of the spleen is often observed in patients with ASMD type B and A/B (>90%), with spleen volumes reaching more than 20 multiples of normal (MN) (14). An enlarged spleen is a result of an underlying tissue pathology and can be considered indicative of disease severity and closely linked to the underlying metabolic and haematological pathologies. It also leads to an increased risk of splenic rupture, bleeding and ultimately death, with bleeding complications being the primary cause of death in 9.6% of patients with ASMD (14). Spleen size is typically measured in patients with ASMD as a marker of overall disease severity (2, 40). Patients are aware of the risk of spleen rupture, with one patient stating
“[redacted]” (41) and another adolescent saying that [redacted] *(39)* Children are unable to participate in playground activities which pose a risk to spleen rupture, which contributes to social exclusion and poor mental health.

Patients with an enlarged liver are at risk of liver dysfunction, cirrhosis, and liver failure. Increased liver size is strongly associated with abnormally high levels of liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]) (25), which are linked to cirrhosis. Liver failure is the cause of premature death in up to 28% of patients with ASMD (6).

Pulmonary impairment

Pulmonary impairment, mainly interstitial lung disease[a] (ILD), is common in patients with ASMD and often leads to symptoms such as breathlessness, fatigue and recurrent respiratory infections including pneumonia (25). One patient described their experience, "[redacted]*."(39).* The clinical presentation of ILD can be asymptomatic, with pathological findings such as ground-glass opacity appearance on CT scans (43). Low forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}) are common in patients with pulmonary impairment. DL_{CO} is a predictor of mortality, both in the general population and in those with chronic lung diseases (44). Respiratory disease primarily manifests as ILD, and is a leading cause of death in patients with ASMD type B and A/B, accounting for 28% of deaths in patients with symptom onset ≤18 years of age, and 44% in patients with symptom onset >18 years of age (6). Of patients who die from respiratory disease, the majority die from ILD (83%) (6).

Lipids and cardiovascular manifestations

Dyslipidaemia, particularly a pattern of low HDL and high LDL cholesterol levels, is a consistent feature of ASMD (20, 45). In a cross-sectional study including 59 patients with ASMD, 74% of patients had a low HDL cholesterol level (as compared with age- and gender-matched controls), 46% had a high LDL cholesterol level, 41% had a high total cholesterol level, and 62% had a high triglyceride level (25). The mean cholesterol/HDL cholesterol level was 2.3 times the upper limit of normal (25). The presence of high cholesterol increases the risk of coronary artery disease, which may ultimately lead to myocardial infarction (25). Cardiac disease has been reported as the cause of death among 7.2% of patients with ASMD type B and A/B (6).

Haematological impairment

Haematologic abnormalities in patients with ASMD include thrombocytopenia, anaemia, or leukopenia, which are generally reported as mild to moderate in severity, but typically worsen over time (18, 25, 32). Some patients experience excessive bruising and bleeding from even small cuts, with one patient stating, "[redacted] (41). At school, children would require additional support and monitoring due to excessive bruising or bleeding. In a long-term follow-up study, coagulopathy was reported in 12.5% of patients with ASMD type B and type A/B (15).

Some patients also suffer from recurrent nosebleeds, which require frequent A&E visits and cauterisations (25), "[redacted]

[a] Interstitial lung disease refers to a large group of lung diseases that are characterised by inflammation and scarring of the lungs (42)

[redacted]. ” (39).

Haematological impairment can also include issues relating to female menstruation and fertility, with heavy or prolonged menstrual bleeding (menorrhagia) and excess uterine bleeding necessitating a hysterectomy (25).

Skeletal system and growth

Children with ASMD experience poor growth and development, which can result in delayed bone age, indicative of delayed puberty (25). In a study including 23 children and adolescents aged between 3 and 18 years with ASMD type B, height and weight was below the 25th percentile for 56% and 42% of patients, respectively (46).

Short stature and low weight were significantly correlated with delayed bone age, with skeletal maturation delayed by an average of 2.5 years (46). [redacted] *(40)*

Patients with ASMD also have decreased bone mineral density which can result in skeletal fracture (25% of paediatric and 53% of adult patients), and results in joint or limb pain (39% of all patients), and back pain (58% of adult patients and 60% paediatric patients) (10).

Patients experiencing bone pain may also receive morphine treatment. However, this comes with side effects such as feeling ‘spaced-out’ and GI problems, with one patient who was receiving morphine for pain management explaining the effect on their social life “[redacted] ” (39).

Mental health

Both children and adults living with ASMD commonly experience an impact on their mental health including depression, anxiety and psychosis due to the symptoms and limitations imposed on them by ASMD (personal communication; [redacted] (40). The emotional well-being of people living with ASMD is significantly affected by their condition, as discussed in Section B.1.3.1.3.

“[redacted] ” (39).

“[redacted] ” (39).

[redacted]."(39).

[redacted](39).

B.1.3.1.3 *Impact on quality of life*

Patient quality of life burden

The clinical manifestations of ASMD (as described in Section B.1.3.1) have a severe impact on patients' QoL. They can affect a patient's ability to care for themselves, attend work/school, perform common daily activities, and take part in social activities. They can also have a profound impact on a patient's self-esteem, and can lead to anxiety and depression (as discussed in Section B.1.3.1.2). Receiving a diagnosis of a life-limiting condition impacts the overall quality of life of patients, beyond the direct impact of the clinical manifestations of ASMD.

Among the variety of symptoms associated with ASMD, patients experience the most burden from respiratory problems, enlarged organs, and fatigue (22). In the recently published Pokrzywinski et al, 2021 study (9), patients living with ASMD type B and A/B in the UK and US reported that ASMD negatively impacts their physical, self-esteem, emotional, personal care, and social function and relationships QoL domains (Table 6) (9). A UK clinical expert has further emphasised the effect ASMD has on patients: [redacted]" (37).

A patient reports [redacted] (39).

Table 6: ASMD type B and A/B symptom experience

Domain	Patients (N=29)	Impact
Physical, n (%)	23 (79)	• Difficulty performing common daily activities • Unable to exercise • Unable to participate in desired recreational activities, sports, and hobbies • Physical exhaustion • Physical limitations (e.g., GI manifestations, restricted mobility) resulting in difficulty to participate fully in school

Domain	Patients (N=29)	Impact
Self-esteem, n (%)	18 (62)	• Effect on self-worth and self-perception • Effect on body image (e.g., delayed growth, enlarged or distended abdomen) • Feelings of being different from peers • Inability to take part in age-appropriate activities • Practical (less desirable) clothing options
Emotional, n (%)	16 (55)	• Feelings of anxiety, depression, sadness, frustration, concern, and fear • Feeling that they disappointed others due to limited ability to fulfil obligations or maintain commitments • Feelings of irritation towards ASMD symptoms • Feeling self-conscious about appearance • Feeling self-conscious about having to answer questions about their condition • Emotions stemming from being bullied by peers
Personal care, n (%)	13 (45)	• Personal hygiene and grooming • Self-dressing • Maintaining a healthy diet (i.e., limited ability to eat sufficiently or as desired)
Social function and relationships, n (%)	16 (55)	• Limited social activities • Frequent cancellation of plans and other arrangements due to exhaustion, limited mobility, and frequent diarrhoea • Bullying • Difficulty interacting with peers and making friends • Inability to date or engage in romantic relationships

Abbreviations: ASMD, acid sphingomyelinase deficiency; GI, gastrointestinal
Source: Adapted from Pokrzywinski et al, 2021 (9)

Enlargement of the liver and spleen are common in patients with ASMD and result in a visible stomach protrusion, which can result in self-esteem issues due to looking different from others, as well as social exclusion due to the inability to partake in activities with a risk of abdominal trauma (such as football, cycling, and rugby) (9, 12, 40). One interviewed patient highlighted the feeling of being different from others, especially for children: [redacted] (22). For children this would limit participation in normal playground activities leading to feelings of social exclusion and poor mental health. Patients with an enlarged spleen or liver also have difficulty sleeping due to their distended abdomen (22). The life-threatening danger associated with some activities (i.e. abdominal trauma for patients with splenomegaly) also limit patients' physical activity (9, 12, 25).

Respiratory symptoms, such as shortness of breath, difficulty breathing, chest pain, and recurrent respiratory infections, limit patients' ability to carry out daily activities, ranging from walking uphill and going upstairs to playing sports and riding a bicycle (9, 22). In patient interviews, one patient explained the effect of respiratory symptoms: "…every time I have to go cycling to school, and when I come to school, I'm like [panting] like I just have to…stand there for a minute and do nothing just to find my normal breathing again…There was one day I had to go babysitting and I have to…get up a hill and not down and it was like it was a really big—I couldn't breathe anymore and I was like going down the hill and I was like not having like short breaths because it was really painful" (9). Another patient emphasised the progression of their respiratory symptoms: "I've noticed within the last two years my breathing has gotten a lot worse to where I can just walk minimal, like from here to the lobby, and I'm already out of breath…I am being told now by my pulmonologist that I have to be on oxygen if I'm doing any amount of walking…I have a little portable concentrator that I carry with me that—just like getting through the airport, from off the plane to where the shuttle picked us up to come here, I was completely out of breath, I mean I literally had my oxygen on and still had to take my time and get through it" (9). The progression of respiratory symptoms may lead to the eventual dependence on supplemental oxygen which is known to have a substantial impact on the everyday lives of patients and their relatives (14, 47), including their social lives and education/employment. Many patients are reluctant to initiate or remain on supplemental oxygen due to the psychological aspects of the therapy; the introduction of, and reliance on, a noisy machine, sleep disturbance and discomfort (48). [redacted] (49). Treatments for respiratory symptoms, in particular supplemental oxygen, can inhibit patient's mobility, inside and outside the home and impact quality of life.

Fatigue is generally perceived by patients to be one of the most impactful symptoms of ASMD, with a severe impact on their ability to carry out even normal daily activities (39). One adolescent patient reported "*Sometimes I get like exhausted. I get really tired by the end of the day. It's hard for me to—to do some things like—like taking my socks off or just basic things, like that. I get over tired and then my mom has to help me do things like take off my socks and um put me into bed and stuff like that, just little—very basic things that I need help wit*h" (9). Due to fatigue, many patients cannot lead normal lives, with one patient stating, [redacted] (41). Fatigue can in turn lead to social isolation and loneliness from missing out on socialising, with patients struggling to maintain relationships with friends as they are unable to engage in activities outside their home due to trouble walking, navigating their way home, or climbing upstairs (22). Patients also miss activities and events due to needing to preserve energy for basic tasks. One parent explained the debilitating effect fatigue has on their child, "[redacted]" (39)

Patients also struggle to attend work which negatively affects their lives, with one patient stating "[redacted] (39). The difficulty to attend school would also result in negative outcomes for the patient's future, with reduced school absence negatively linked to attainment (50), and potential loss of lifetime income for patients (51).

GI symptoms can often result in changes to eating habits, vomiting, constipation, and diarrhoea, which affect patients' ability to work or their social lives, as they feel unable to eat out with friends or stay out for long periods of time. The impact of GI symptoms has also been reported: "*it's not something I can really control, and I know even throughout school my teachers are why do you always have to go to the bathroom… It's kind of embarrassing. When I was little I used to think who's going to want to date me, how's that going to be on a date whenever I have to rush to use the restroom or something*" (9).

Patients with childhood onset of ASMD often suffer from low self-esteem and poor emotional well-being (9, 12). Adolescents and children with ASMD may feel that they lose time being children and teenagers as a result of the disease. They have difficulty making friends as they are treated differently and can be subjected to bullying for their short stature and protruding abdomen. They often find it difficult to engage in normal activities for their age, such as participating in social events, or going on a date, due to underlying symptoms such as enlarged liver or spleen, respiratory symptoms, and fatigue (12). An enlarged spleen, common in children with ASMD, can prevent them from participating in play time at school, with children required to restrict activities and wear a spleen guard to reduce the risk of rupture, further excluding them from their friends. An adult with ASMD type B reported: "[redacted]*" (52).* Enlarged organs also cause difficulty with the development and balance for children, with one caregiver quoting: *"*[redacted] (52). Children with ASMD have difficulty maintaining school attendance due to their symptoms and frequency of medical appointments which leads to low level of academic achievements and impacts future employment (9, 13). One caregiver described how their child was sent home from school due to their symptoms: "*She has been sent home a couple of times [because of the pain]…once she needed the toilet….She said she had pain in the stomach"* (9). A patient with ASMD also explained the effect of medical appointments on their school attendance, "[redacted]*"* (39).

Adults living with ASMD experience a significant impact of the disease on their emotional stability, personality, and relationships. Patients with ASMD type B have indicated a worsening psychosocial impact related to intimacy, isolation, ego integrity and despair, anxiety, and feelings of missed opportunities in life (12). The frequency and invasive nature of medical examinations, including liver biopsies, spinal taps, and organ measurements during childhood has also been reported to have a considerable psychological impact on a patient later in life (12). ASMD can have a major impact on life choices, including career choices (type of career, or the need for flexible work due to their condition), living situation, or location (living close to family or medical centres) (22).

Living with ASMD has a severe emotional impact on patients. They often experience anxiety, depression, frustration, concern and fear, with one patient stating, “[redacted] (39). As there is currently no disease-modifying treatment available, they feel that severe complications are inevitable, with an uncertainty of how their disease may progress (13). Patients also struggle with planning for the future due to the uncertainty of their disease progression, with one patient stating: [redacted] (13). The clinical symptoms of ASMD, such as an enlarged spleen, or respiratory impairment, impact a patient’s ability to live independently. They are often unable to tie their shoes due to a distended abdomen and are unable to carry out daily activities themselves due to shortness of breath. Fatigue is also a common symptom in patients with ASMD, which further reduces their ability to perform tasks themselves, with one patient stating “[redacted] (41).

Caregiver quality of life burden

Caregivers of patients with ASMD also face a substantial QoL burden. As there is no treatment available for patients with ASMD, caregivers face the worry of their loved one deteriorating, with the knowledge that they will not improve, or live a more normal life. They also face the grief of losing their loved one prematurely, especially for those caring for children. They have difficulties maintaining their emotional and mental health, as well as maintaining social activity and relationships. In addition, they face an extreme financial burden due to time spent caregiving and the inability to work, with one parent stating “[redacted] (39). Due to caregiving commitments both parents would not be able to work which contributes to the financial burden and feelings of low self-worth.

In an observational, qualitative study including seven caregivers of people with ASMD in the US (n=4) or UK (n=3), caregivers reported that caring for someone with ASMD impacted them emotionally (i.e. stress, frustration and depression), financially (i.e. having more expenses, having to cut down work hours, missing work days), and physically (i.e. inability to sleep and feeling tired). Requirements related to care taking responsibilities (i.e. having to frequently attend medical visits, changing daily routines and overseeing overall wellbeing of loved one) were also a common theme for caregiver burden.

Caregivers' personal lives are affected by not having a social life or being able to go to places, with negative impacts on their relationships (11).

As with the burden of ASMD on patients, the burden of ASMD for caregivers differs depending on the age of the person with ASMD, and the severity of their condition.

Parents of children with ASMD experience heightened emotional stress due to the prospect of their child dying at a young age. Parents may have to explain to their child that their condition will not improve, and are often unprepared for the grief they experience when their child dies (53). They have to deal with the worry of the disease progressing and the condition of their child worsening, with one parent explaining, "[redacted]*" (39)*. Caregivers also report frustration with the paucity of medical and psychological knowledge and inadequate resources for treatment, with one parent stating: "[redacted]*"* (13). Caregivers may also have a reduced ability to work or socialise due to the child's care requirements, for example when their child is taken out of school due to bullying and/or medical needs (9). ASMD also affects caregivers and parents emotional well-being, with one caregiver stating "[redacted] *(39).*

Adults with ASMD continue to have substantial care requirements, with one patient highlighting their inability to live independently, "[redacted] (41). Caregivers of adults with ASMD express feelings of dealing with issues alone, along with financial difficulties due to a reduced availability or inability to function at work (9). ASMD can also affect the relationship between a caregiver and their spouse who has ASMD, with one caregiver stating [redacted]*"* (11).

B.1.3.2 *Life expectancy*

In the absence of disease-modifying treatment, patients with ASMD continue to deteriorate, with worsening clinical manifestations resulting in increased risk of early mortality. According to clinical experts, there are no patients older than 60 years with ASMD in the UK, with most patients dying due to organ failure in, or before their 50s (37). For patients with ASMD type A/B, neurodegenerative disease is an additional driver of mortality (6). Early onset of disease is also associated with an increased risk of early mortality (8). The causes of death are most commonly respiratory or liver failure (5-8), with spleen volume also associated with increased risk of mortality.

Overall survival, estimated by applying standardised mortality ratios (SMRs) derived from ASMD patients with and without severe splenomegaly, from the SPHINGO-100 observational study, have demonstrated an increased risk of death for patients with severe splenomegaly (>15 MN) (25, 54). The age adjusted general population mortality[b] is increased by a factor of 43.1 for patients with severe splenomegaly (>15 MN), and 4.3 for patients without severe splenomegaly (<15 MN) (54).

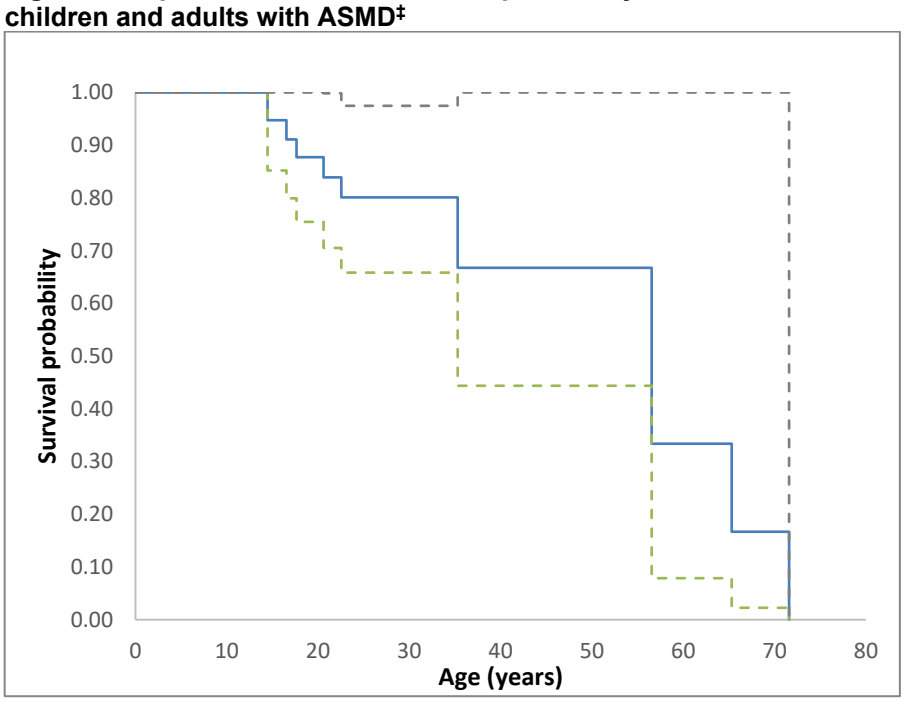
Due to the variability of clinical manifestations and their severity, life expectancy can vary significantly between patients. Four studies have reported worldwide mortality outcomes in adult and paediatric patients with ASMD, including mortality outcomes by disease subtype (5, 6, 8), and the drivers of mortality (6-8). Age at death varied significantly, ranging from 2 to 72 years depending on the subtype, age range of patients, and length of follow up (5-8). An initial analysis of the median survival of patients with ASMD type B and A/B in the US suggests that the impact of ASMD on mortality is likely underestimated (55).

A Kaplan-Meier survival probability curve in children and adults with ASMD enrolled in a prospective natural history study (SPHINGO-100) is presented in Figure 1. The SPHINGO-100 study included 59 patients aged 7 to 64 years with ASMD type B or A/B followed between May 2001 and June 2002 in the US, Brazil, Italy, France, and Germany. Nine deaths were reported (15%), eight of which were caused by ASMD associated morbidities (8). Six of these deaths were in patients aged <50 years, of which three were in patients aged <20 years. Early onset of disease was associated with increased mortality. Six of the patients who died had onset of symptoms by or at 2 years of age. Total splenectomy or severe splenomegaly were associated with an increased risk of early mortality by 10 times compared with patients with moderate splenomegaly or intact spleens (OR: 10.29, 95% CI; 1.7, 62.7). As the SPHINGO-100 study included only patients over 6 years of age, and due to the high mortality in paediatric populations, the survival of ASMD type B and A/B may be underestimated in this study. In addition, due

[b] The SMR is the ratio of the observed number of deaths in a study population divided by the number of deaths that would be expected, based on the age- and sex-specific mortality rates in a general population. The US life tables were used to estimate the SMR as the majority of patients in the SPHINGO-100 study were from North America. The estimated SMR was then applied to the mortality rates of the general population of the UK as a multiplier to calculate the adjusted survival probabilities.

to the small number of events observed, there is large uncertainty around the survival estimates.

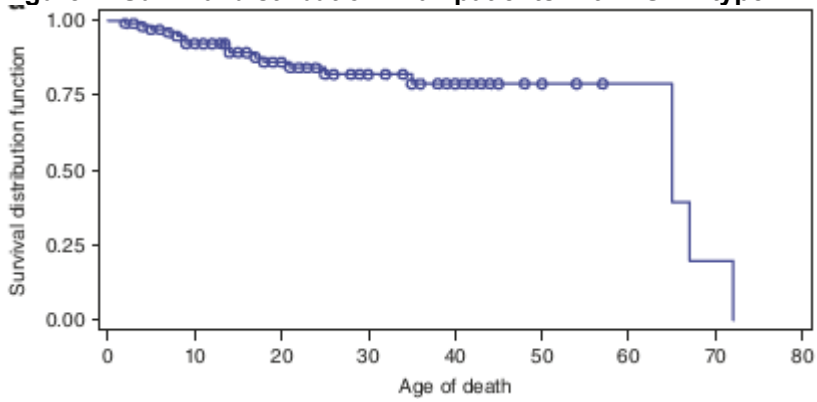
Figure 1: Kaplan-Meier overall survival probability with 95% confidence interval† in children and adults with ASMD‡



Source: Sanofi data on file (54)
Solid line indicates the best estimate; dashed lines indicate the 95% confidence interval
†Patients who died, dropped out, or not reached the time yet were not counted as at risk
‡Patients younger than 7 years of age were not included and so there are no patients at risk at 0 and 5 years

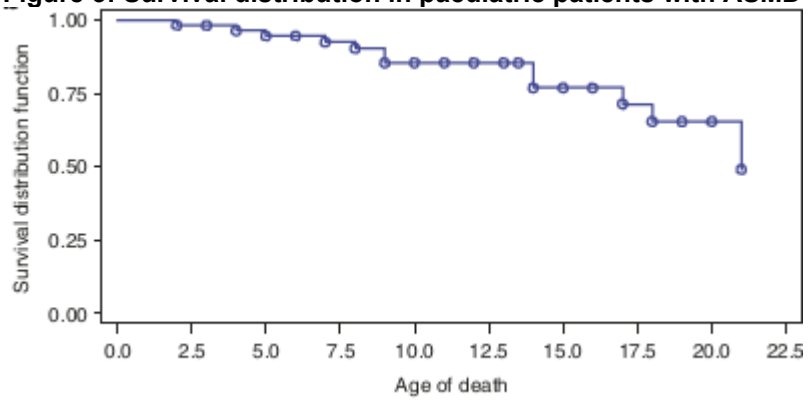
In a retrospective study including 103 US patients with ASMD type B who were enrolled in natural history studies between 1992–2012, the mortality rate was estimated at 17.5% and, although the duration of follow-up was not reported. Age at time of death ranged from 2 to 72 years, illustrating the high variability in disease course characteristic of this disease (7). Common causes of death included; pneumonia or respiratory failure (n=5), liver failure (n=3) and complications of bone marrow transplant (n=3) (7). The median age at death was 17 years (2 to 72 years) among the 18 patients who died and the median age at last follow-up was 19 years (2 to 57 years) among the 85 patients who were alive at the end of the study (7). The survival distribution for the whole population included in the study is shown in Figure 2, with the survival distribution for paediatric patients shown in Figure 3 (7).

Figure 2: Survival distribution in all patients with ASMD type B



Source: McGovern et al, 2013 (7)

Figure 3: Survival distribution in paediatric patients with ASMD type B



Source: McGovern et al, 2013 (7)

A second retrospective study (SPHINGO-302) of 100 patients diagnosed with ASMD in the US, Canada, and Brazil between 2006 and 2008 reported mortality rates by disease subtype (5). Mortality rates were low in patients with ASMD type A/B (0%; n=0/6) or ASMD type B subtypes (2.5%; n=2/81) (5). The primary causes of death for the two type B patients were renal failure secondary to hepatic failure in a female adult (42.8 years of age at time of death), and respiratory failure in a child (2 years of age at time of death) (5).

Respiratory disease and liver disease have been reported as the leading causes of death in patients with ASMD type B and A/B (6) in the case series, which included 85 individuals with ASMD type B and type A/B who were either newly reported by treating physicians (n=27) or identified in the PubMed database between 1966 and 2015 (n=58). Patients who had either died (n=78) or undergone liver transplantation (n=7) were included. For patients with ASMD type B, respiratory disease (30.9%), liver disease (29.1%), and bleeding (12.7%) were the most frequent causes of death, whereas in patients with ASMD type A/B, respiratory disease (23.1%), neurodegenerative disease (23.1%), and liver disease (19.2%) were dominant causes, with transplant complications accounting for 11.5% of deaths (6). Among deceased patients, the median age at death was 17 years in ASMD overall, 23.5 years in ASMD type B and 8.5 years in ASMD type A/B (6).

There are currently no studies reporting life expectancy for patients with ASMD type B and type A/B in England.

B.1.3.3 *Clinical guidelines and pathway of care*

There are currently no specific NICE or NHS England guidelines for the diagnosis and management of ASMD. Three publications reporting international guidelines for the treatment pathway of ASMD are currently available, including:

- Wang et al, 2011: International consensus recommendation covering diagnostic and treatment/management guidelines for presymptomatic LSD patients (56)
- McGovern et al, 2017: International consensus recommendation covering diagnostic and treatment/management guidelines for ASMD (17)
- Wasserstein et al, 2019: International recommendations for monitoring and symptom management (14)

Clinical expert guidance has been sought to elucidate the clinical pathway in England (as described in Section B.1.3.3.1 and B.1.3.4). In the UK, patients are diagnosed and managed for ASMD within highly specialised treatment centres under the NHS England lysosomal storage disorders service. Treatment options for ASMD are limited but include approaches to treat liver disease, splenomegaly, pulmonary involvement, valvular insufficiency, bleeding, and dyslipidaemia (as discussed in Section B.1.3.3.2).(14) Specialist nurses, physical therapists, speech therapists, occupational therapists and disease counsellors are all involved in the supportive care of patients.

The specialist care centres in England are (57):

- Adult centres
    - University College London Hospitals NHS Foundation Trust
    - Royal Free NHS Trust
    - Cambridge University Hospitals NHS Foundation Trust
    - Salford Royal NHS Foundation Trust
    - University Hospitals Birmingham NHS Foundation Trust
- Paediatric centres
    - Great Ormond Street Hospital for Children NHS Trust
    - Central Manchester University Hospitals NHS Foundation Trust
    - Birmingham Children’s Hospital NHS Foundation Trust

B.1.3.3.1 *Diagnosis*

Diagnosis of ASMD is confirmed by biochemical enzyme assays followed by molecular genetic testing to accurately identify patients (17, 58). Due to the similarities in phenotype between ASMD and the more common LSD, Gaucher disease, determination of glucocerebrosidase activity is recommended to distinguish ASMD from Gaucher disease (17). There is currently no clear diagnostic test available to distinguish between type A, type B or type A/B. The subtypes of ASMD are therefore diagnosed based on the clinical presentation.

In the UK, patients with ASMD are generally diagnosed in childhood, with most patients being diagnosed by 20 years of age (37), and are commonly referred to specialist centres by a variety of specialists (depending on their symptoms) including general paediatric clinics, but also by the haematology, hepatology, neurology, respiratory and cardiology clinics (59). Although population-based screening programmes for the early identification of patients with ASMD have been suggested to help to identify patients and prevent delays in treatment, none have been undertaken in the UK (60).

B.1.3.3.2 *Management*

ASMD is a chronic, progressive, debilitating and life-limiting disease for which no treatment currently exists that modifies its natural course (2). Only symptomatic care and palliative/supportive measures are currently available (2, 14) to treat clinical manifestations, including liver disease, splenomegaly, pulmonary involvement, valvular insufficiency, bleeding, and dyslipidaemia are available (Table 7) (14).

Table 7: Approaches to treating ASMD and underlying conditions

Condition	Treatment options
Liver disease	• Maintaining adequate nutrition and controlling fluid retention • Avoiding alcohol use and hepatoxic medications • Vaccinations against viral hepatitis A and B • Non-selective beta blockers for prevention of haemorrhage in patients with oesophageal varices • Ammonia reduction for hepatic encephalopathy • Antibiotics as appropriate for spontaneous bacterial peritonitis • Assessment of candidacy for liver transplant when needed[†]
Splenomegaly	• Although performed historically, splenectomy is often contraindicated due to potential exacerbation of liver disease • Partial splenectomy or partial splenic arterial embolism are potential options for massive splenomegaly, pressure symptoms, and severe unsustainable hypersplenism • Emergency surgery may be necessary because of splenic trauma, necrosis, or rupture. In such cases, surgery should be followed with use of antibiotic prophylaxes and vaccinations

Condition	Treatment options
Pulmonary involvement	• Avoid smoking • Manage all pulmonary infections aggressively • Supplemental oxygen or NPPV should be used for underlying conditions such as hypoxemia and hypoventilation • Treat symptoms with use of bronchodilators • Administer vaccinations for influenza, pneumococcal pneumonia, and haemophilus influenza type B, as appropriate • Lung lavage has been attempted but has not shown to be effective in alleviating symptoms and the procedure may cause complications • Lung transplant, allogeneic bone marrow transplant and hematopoietic stem cell transplantation have been investigated however experience is limited and efficacy is low (61-64).
Valvular insufficiency	• Treat with medications according to standard guidelines • Perform surgery to repair or replace defective heart valves‡ • Stenting and/or CABG for CVD as indicated‡
Bleeding	• Common interventions are nasal packing and cauterisation for nosebleeds. • Transfusion may be required but is infrequently needed
Dyslipidaemia	• Manage dietary requirements • Statins (for use post-puberty) may be prescribed with monitoring of liver function
Other interventions and lifestyle modifications	• Dietary and lifestyle modifications to minimise bone loss • Exercise to prevent osteopenia • Calorie intake for adequate growth • Physical therapy • Educational support • Physical therapy for pain management

† Patients are often too unwell due to other symptoms such as spleen or lung disease to have the possibility to receive a liver transplant (37)
‡ Surgical intervention should be evaluated based on potential risks of bleeding issues or other contraindications
Abbreviations: CABG, coronary artery bypass grafting; CVD, cardiovascular disease; NPPV, non-invasive positive pressure ventilation
Source: Wasserstein et al, 2019 (14)

Although treatment options for ASMD are limited, a retrospective review of 100 patients with ASMD in the US, Brazil and Canada, reported the use of pain medication, antibiotics, respiratory drugs and surgical procedures (Table 8) (5). Antibiotics were the most frequent intervention for patients with ASMD type B (received by 54% of patients) and surgery (including tonsillectomy, ear tube insertion, adenoidectomy, liver biopsy, cholecystectomy, splenectomy, and gastrostomy tube insertion) was the most common intervention for patients with ASMD type A/B (performed in 83% of patients). Interviews of 11 patients recruited through the National Niemann-Pick Disease Foundation (NNPDF) in the US and Niemann-Pick UK in the UK, have highlighted that current treatments include statins to lower their cholesterol, bisphosphonates and calcium to help strengthen their bones, opioid for pain, migraine medication and vitamin supplements for overall health (22). [redacted] Personal communication with a UK clinical expert also highlighted that patients with ASMD require supplemental oxygen (5% of patients), with the majority of patients also receiving statins (personal communication; [redacted]

Table 8: Treatments received by patients with ASMD type B and type A/B

Treatment/therapy used	ASMD Type B	ASMD Type A/B
Any treatment/therapy, n (%)	56 (69%)	4 (67%)
Pain medication, n (%)	35 (43%)	3 (50%)
Antibiotics, n (%)	44 (54%)	3 (50%)
Respiratory drugs, n (%)	20 (25%)	0 (0%)
Surgical procedure, n (%)	42 (52%)	5 (83%)
Tonsillectomy	12 (15%)	0 (0%)
Ear tube insertion	8 (10%)	1 (17%)
Adenoidectomy	8 (10%)	0 (0%)
Liver biopsy	5 (6%)	1 (17%)
Cholecystectomy	5 (6%)	1 (17%)
Splenectomy	5 (6%)	1 (17%)
Gastrostomy tube insertion	1 (1%)	0 (0%)

Abbreviations: ASMD, acid sphingomyelinase deficiency
Source: Cox et al, 2018 (5)

Due to the wide range of symptoms and potential treatments, a wide range of specialists are involved in the management of patients with ASMD, including endocrinology, haematology, cardiology, ophthalmology, and radiology departments (personal communication; [redacted]). Adults and paediatric patients in the UK are assessed every

6 months. However, for adult patients, reviews can be less frequent, and may reflect their regular pattern of care for ASMD (59).

Despite the availability of treatments and surgeries to manage the symptoms of ASMD type B and A/B, patients continue to deteriorate, with a severe impact on their QoL and survival due to a lack of a disease-specific treatment. Clinical experts have highlighted the lack of treatment available for ASMD, resulting in HCPs only being able to manage a patient's symptoms as opposed to the disease itself (3). There is therefore a need for additional treatment options which reverses the accumulation of sphingomyelin, thereby improving symptoms and patients' QoL and survival.

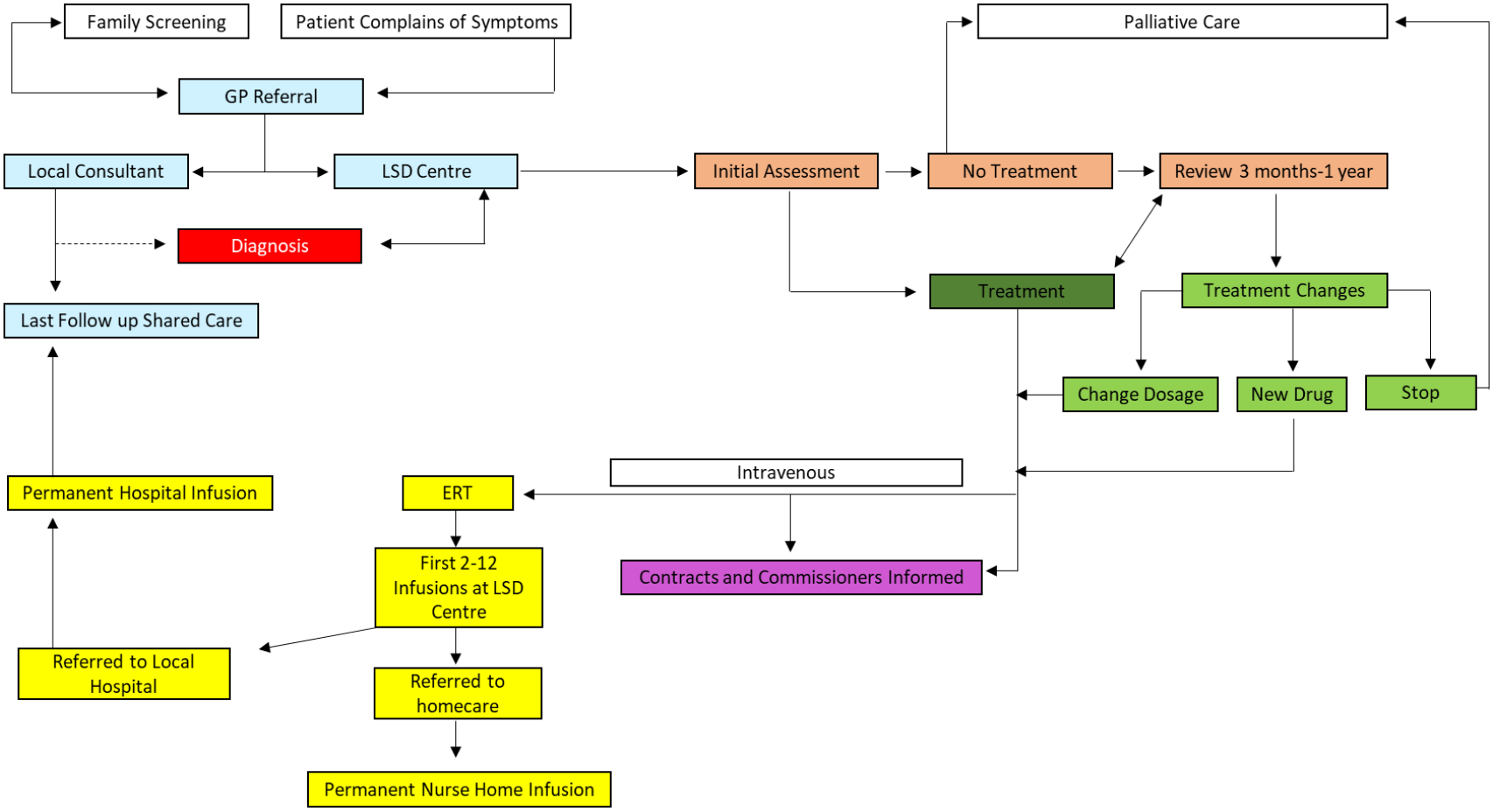
B.1.3.4 *Olipudase alfa place in therapy*

Olipudase alfa (recombinant human acid sphingomyelinase) is an enzyme replacement therapy designed to replace the ASM enzyme, which is lacking in people with ASMD. Olipudase alfa specifically targets the underlying pathology of ASMD, reversing the accumulation of sphingomyelin. As the first and only disease-modifying treatment for ASMD, olipudase alfa represents a major step-change in the management of this condition. The clinical results from the ASCEND and ASCEND-Peds trial demonstrate that olipudase alfa is associated with significant improvements in multisystemic clinical manifestations of ASMD (including respiratory function, spleen volume and liver volume) in both adults and children, with increased growth and musculoskeletal development in children (66, 67). The olipudase alfa clinical data are presented in full in Section B.2.

Olipudase alfa is indicated as an enzyme replacement therapy for the treatment of patients with non-CNS manifestations of ASMD in paediatric and adult patients with type B or type A/B. Treatment with olipudase alfa is expected to come under the NHS England lysosomal storage disorders highly specialised service which sets out commissioning criteria for all currently reimbursed enzyme replacement therapies for LSDs. The current pathway of care for LSDs in England (for which olipudase alfa is expected to be incorporated) is illustrated in Figure 4.

Olipudase alfa is intended to fit into the current pathway of care available for LSDs and will be initially administered from all UK LSD centres (before patients transition to homecare). Specialised centres currently administer ERTs for other LSDs, such as Gaucher disease. As current specialised centres would be utilised for the administration of olipudase alfa, no major changes to structure, staffing, or training are expected with the introduction of olipudase alfa.

Figure 4: Current pathway of care for ERT in LSDs



Source: Adapted based on NHS England (68)

Abbreviations: ERT, enzyme replacement therapy; GP, general practitioner; LSD, lysosomal storage disease

B.1.3.5 *Issues relating to current clinical practice*

Lack of ASM leads to the build-up of sphingomyelin in cells, causing widespread multi-organ damage (2). Both ASMD type B and ASMD type A/B are typically characterised by severe and progressive multi-systemic manifestations which negatively impact patients' and caregivers QoL (2, 9, 12, 13), and result in significant morbidity and mortality (2, 5-7, 25).

There is currently no disease-specific treatment available for patients in the UK with ASMD. The current clinical practice for children and adults with ASMD includes monitoring patients, providing symptomatic relief and supportive care. Despite current BSC, patients continue to deteriorate, with significant morbidity, mortality, and detrimental impact on QoL remaining. Therefore, there is a significant and urgent unmet need for a disease-modifying intervention that reverses the disease, thereby improving patient and caregiver QoL, and improving clinical outcomes of patients with ASMD.

B.1.4 *Equality considerations*

Although the use of olipudase alfa is unlikely to cause major equality issues, there is significant inequity in terms of patients' socioeconomic outlook. The inability to work and attend school has a negative impact on future earning potential for patients in school, and current income for those who work. This is often worsened by the need to travel to numerous medical appointments. The introduction of olipudase alfa would enable patients to more fully attend school and work alleviating this inequity. Caregivers may have difficulty maintaining full-time work due to caregiving commitments and therefore face financial burdens which are likely to cause socioeconomic inequity. The impact of the time needed to receive treatment would be minimised by the ability to receive ERT at home following the escalation phase.

B.2. Clinical effectiveness

Improvement in ASMD clinical outcomes was seen across all olipudase alfa trials.

The efficacy and safety of olipudase alfa has been evaluated for the treatment of ASMD in a phase II/III placebo-controlled RCT (ASCEND [DFI12712]) and a phase I/II single-arm study (ASCEND-Peds [DFI13803]). Additional supporting studies include the ongoing extension trial LTS13632, and the completed phase I single-arm trial DFI13412

The results of the ASCEND study show that olipudase alfa treatment significantly reduced spleen volume and significantly improved lung function (as measured by DL_{CO}) in adult patients with ASMD, compared with placebo at 52 weeks. Spleen volume and DL_{CO} are clinically meaningful disease markers that contribute to reduced QoL and increased clinical burden in ASMD (44).

Primary efficacy outcomes

- Treatment with olipudase alfa significantly improved diffusing capacity for carbon monoxide (DL_{CO}) compared with placebo at Week 52 (19.01% increase, p=0.0004). DL_{CO} improvement was consistent across all sensitivity analyses
- Treatment with olipudase alfa significantly reduced spleen volume compared with placebo at Week 52 (39.93% decrease, p <0.0001). Spleen volume reductions were consistent across all sensitivity analyses

Additional key efficacy outcomes

- Treatment with olipudase alfa significantly reduced liver volume compared with placebo at Week 52 (26.60% decrease, p<0.0001)
- Treatment with olipudase alfa resulted in a significant increase in platelet count compared with placebo Week 52 (14.33% increase, p=0.0185)
- Treatment with olipudase alfa resulted in a significant reduction in percentage change in ALT from baseline to Week 52 compared with placebo (0.98% vs 36.55% decrease, p=0.0060)
- Treatment with olipudase alfa resulted in a significant improvement in exercise capacity from baseline to Week 52 compared with placebo, as measured by O_2 uptake (mL/min) (-411.033 vs 137.611, p=0.0149), percent predicted O_2 uptake (%) (-15.137 vs 0.918, p=0.0429), and calculated maximal O_2 uptake (mL/min/kg) (-6.699 vs -0.129, p=0.0374)

Safety outcomes

- Olipudase alfa was generally well-tolerated, with no treatment emergent adverse events (TEAEs) leading to treatment discontinuation, and no deaths

The results of the ASCEND-Peds study show that olipudase alfa treatment reduced spleen and liver volume and significantly improved DL_{CO} in paediatric patients with ASMD, compared with baseline at 52 weeks

Secondary efficacy outcomes

- Treatment with olipudase alfa improved DL_{CO} compared with baseline (32.94% increase, p=0.0053)
- Treatment with olipudase alfa reduced spleen volume compared with baseline (49.21% decrease, p<0.0001)
- Treatment with olipudase alfa reduced liver volume compared with baseline (40.56% decrease, p<0.0001)
- Treatment with olipudase alfa resulted in improved liver function compared with baseline, with decreases in mean ALT, AST, and total bilirubin (no statistical analysis conducted)
- Treatment with olipudase alfa resulted in improved height Z-scores compared with baseline (mean improvement of 0.56, p<0.0001)
- Treatment with olipudase alfa significantly improved HRQoL compared with baseline for 4 of the 6 subsets of the PedsQL Generic Core Scale (6.8–14.6, p<0.05), and 4 of the 4 subsets of the PedsQL Multidimensional Fatigue Scale (10.6–16.2, p<0.001)

Safety outcomes

- Olipudase alfa was generally well-tolerated, with no TEAEs leading to treatment discontinuation, and no deaths having occurred

As of the latest data cut (01 March 2021), with data available for up to 6.5 years for adult patients and 4 years for paediatric patients, all patients continue to demonstrate improvement following treatment with olipudase alfa (data from the ongoing LTS13632 study)

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify publications reporting the clinical efficacy and safety of the enzyme replacement therapy, olipudase alfa, in the treatment of ASMD type B or A/B. A description of the methodology is provided in Table 9, and a PRISMA study attrition diagram is shown in Figure 5. Full details of the process and methods used to identify and select clinical evidence relevant to the technology being appraised are reported in Appendix D.

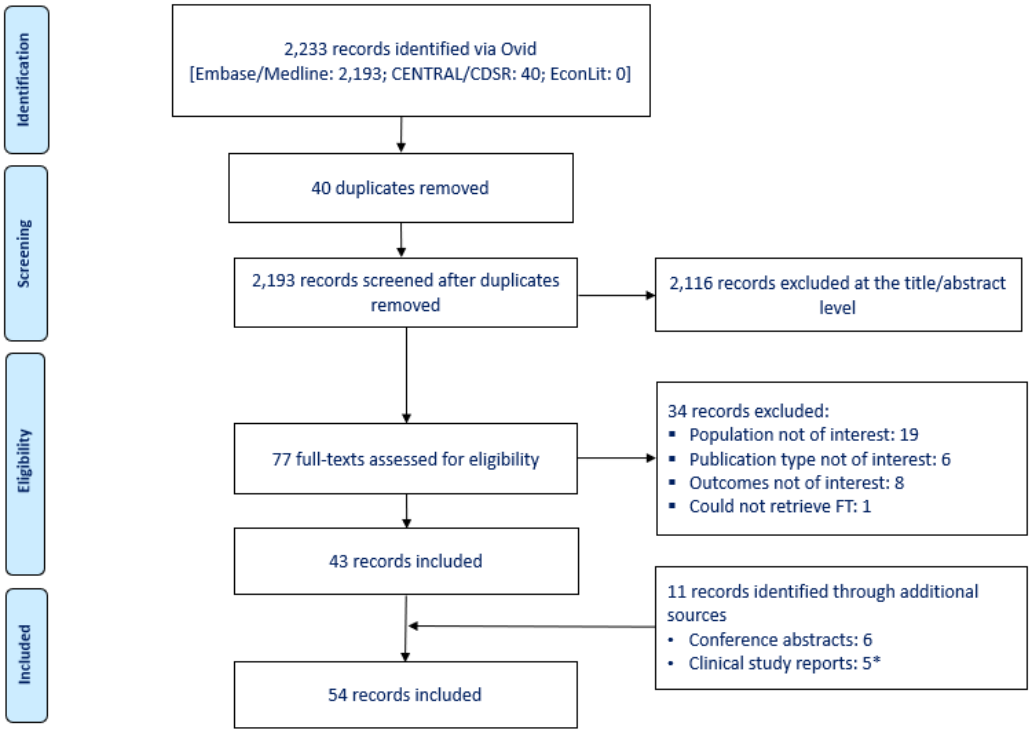
Table 9: Methodology of clinical SLR

Domain	Methodology	Section
Objectives/questions addressed by the review	The SLR aimed to answer the following research questions: • What is the clinical efficacy/effectiveness and safety of treatment for ASMD? • What is the cost-effectiveness of treatment for ASMD? • What is the economic burden associated with ASMD? • What is the humanistic burden associated with ASMD? • What is the natural history, including prevalence, complications and mortality rates, for patients with ASMD? • What is the current treatment pathway and standard of care for ASMD?	Appendix D
Searches	• Exhaustive literature searches were conducted in Embase, MEDLINE, MEDLINE In-Process, and the Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials) databases via Ovid SP, to identify English-language articles on humans • No limits placed on publication date or geographic location • Unpublished or “grey” literature sources were searched to supplement the published literature	Appendix D
Study selection	• All identified titles and abstracts were independently assessed for inclusion by two researchers according to the PICOS inclusion and exclusion criteria, with any discrepancies resolved by a third, senior researcher • Full texts of the studies were screened for all SLR research questions of interest during both levels of review, and tagged according to SLR topic during full-text screening	Appendix D
Data extraction	• Extraction of data from the included studies was performed by a single investigator trained in critical assessment of evidence, with validation by a second investigator • Data were captured in a DET designed in Microsoft Excel	Sanofi data on file

Domain	Methodology	Section
Critical appraisal	The approach to quality assessment of evidence from randomised controlled trials (RCTs), non-randomised studies and economic models was based on the Cochrane risk-of-bias tool (69) (mapped to the NICE tool (70)), Cochrane Risk of Bias in Non-randomized Studies- of Interventions (ROBINS-I) (71) and Drummond's checklist (72), respectively.	Appendix D
Evidence synthesis	An assessment for possible evidence synthesis was planned. If more than one study is available and the methodology is comparable, a meta-analysis was considered	Appendix D

Abbreviations: ASMD, acid sphingomyelinase deficiency; CRD, Centre for Reviews and Dissemination; DET, data extraction table; NICE, National Institute for Heath and Care Excellence; PICOS, population, interventions/comparators, outcomes, and study design; RCT, randomised clinical trial

Figure 5: PRISMA diagram



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CSR, clinical study report; FT, full text; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
*Includes four CSRs with interim (n=2) and updated (n=2) results for the ASCEND (DFI12712) and LTS13632 trials, respectively, and one CSR for the ASCEND-Peds (DFI13803) trial

B.2.2 *List of relevant clinical effectiveness evidence*

The systematic review of clinical evidence identified one placebo-controlled randomised trial (ASCEND) (73), one phase I/II open-label single-arm trial (ASCEND-Peds) (74), one phase I open-label single-arm trial (DFI13412) (75), and one long-term study (LTS13631) (76) of olipudase alfa in the population of interest to this submission (Table 10). As the trial LTS13632 is currently still ongoing, evidence has been provided as an ongoing study in Section B.2.11. The phase I open-label single-arm trial DFI13412 is an earlier trial, and not considered a pivotal study. However, as data from the study were used to support the economic modelling, additional supporting evidence is provided in Appendix M. An overview of the olipudase alfa trials is presented in Table 11 and Table 12.

Table 10: List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Additional references	Is study excluded from further discussion? If yes state rationale
DFI12712 (ASCEND): NCT02004691	Adults aged ≥18 years with ASMD type B and A/B (n=18 placebo, n=18 olipudase alfa)	Olipudase alfa (IV)	Placebo	CSR (73)	Wasserstein et al, 2022 (77) Villarubia et al, 2022 (78)	No
DFI13803 (ASCEND-Peds) NCT02292654	Patients aged <18 years with ASMD type B and A/B (n=20)	Olipudase alfa (IV)	None	CSR (74)	Diaz 2021 (79)	No
DFI13412	Adults aged ≥18 years with ASMD type B and A/B (n=5)	Olipudase alfa (IV)	None	CSR (75)	Wasserstein 2015 (80)	As this was not considered a pivotal study, further details have been provided as supporting information (Appendix M)
LTS13632 NCT02004704	Paediatric and adult patients with ASMD type B and A/B previously enrolled in DFI13412 or ASCEND-Peds (n=25 as per 01 March 2021 data-cut)	Olipudase alfa (IV)	None	CSR (76)	Thurberg et al, 2020 (81) Wasserstein 2018 (82) Lachmann et al, 2022 (83) Diaz et al, 2022 (84)	This study is currently ongoing, further details provided in Section B.2.11

Abbreviations: ASMD, acid sphingomyelinase deficiency; CSR, clinical study report; IV, intravenous

Table 11: Clinical effectiveness evidence ASCEND

<table>
<tr><th>Study</th><th colspan="5">ASCEND (DFI12712)</th></tr>
<tr><td>Study design</td><td colspan="5">Phase II/III, multicentre, randomised, double-blinded, placebo-controlled, repeat dose clinical trial</td></tr>
<tr><td>Population</td><td colspan="5">Adults aged ≥18 years with ASMD</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Olipudase alfa (3.0 mg/kg target dose)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo (0.9% sodium chloride)</td></tr>
<tr><td rowspan="2">Indicate if study supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale if trial not used in model</td><td colspan="5">Not applicable.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">Efficacy outcomes (presented in Section B.2.6):
• Change in spleen volume
• Change in lung function
• Change in liver function and volume
• Change in fatigue and exercise tolerance
• Health-related quality of life
Safety outcomes (presented in Section B.2.10):
• Change in biomarkers (including high sensitivity C reactive protein; ceramide, cardiac troponin, ferritin chitotriosidase, CCL18 levels, lysosphingomyelin, oxysterols, and lipid profile)
• Change in physical observations (including observations or measurements from examination of the eyes, nose and throat; heart, lungs, bone marrow, extremities and joints)
• Change in neurological observations (including observations or measurements from examination of coordination; cranial nerves; extrapyramidal features; fundoscopy; gait; motor skills; peripheral nervous system; reflexes; sensory nervous system; strength and mental status)
• Mortality
• Adverse effects of treatment</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Change in platelet counts
• Change from baseline in fatigue, pain, and dyspnoea severity
• Change in splenomegaly-related score
• Pulmonary imaging by HRCT and chest X-ray
• Bone disease assessments
• Haematology parameters</td></tr>
</table>

Study	ASCEND (DFI12712)
	• Post-hoc treadmill ergometry • Physician's global assessment of change • NMR of HDL • Echo-Doppler imaging • Patient global impression of symptom severity • Patient global impression of change scale

Abbreviations: ASMD, acid sphingomyelinase deficiency; CCL18, chemokine ligand 18; HDL, high density lipoprotein; HRCT, high resolution computed tomography; kg, kilogram; mg, milligram; NMR, nuclear magnetic resonance

Table 12: Clinical effectiveness evidence ASCEND-Peds

<table>
<tr><th>Study</th><th colspan="5">ASCEND-Peds (DFI13803)</th></tr>
<tr><td>Study design</td><td colspan="5">Phase I/II, multicentre, open-label, ascending dose study</td></tr>
<tr><td>Population</td><td colspan="5">Patients aged <18 with ASMD</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Olipudase alfa (3.0 mg/kg target dose)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Not applicable</td></tr>
<tr><td rowspan="2">Indicate if study supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale if trial not used in model</td><td colspan="5">Not applicable.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">Efficacy outcomes (presented in Section B.2.6):
• Change in spleen volume
• Change in lung function
• Change in liver function and volume
• Change in weight, height and onset of puberty in children and young people
• Change in fatigue and exercise tolerance
• Health-related quality of life
Safety outcomes (presented in Section B.2.10):
• Change in physical observations (including observations or measurements from examination of the eyes, nose and throat; heart, lungs, bone marrow, extremities and joints and height)
• Change in neurological observations (including observations or measurements from examination of coordination; cranial nerves; extrapyramidal features; fundoscopy; gait; motor skills; peripheral nervous system; reflexes; sensory nervous system; strength and mental status)
• Change in biomarkers (including high sensitivity C reactive protein; ceramide, cardiac troponin, ferritin chitotriosidase, CCL18 levels, lysosphingomyelin, oxysterols, and lipid profile)
• Mortality
• Adverse effects of treatment</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Platelet count and haemoglobin
• Pulmonary imaging by HRCT
• Chest X-ray
• Bone age by hand X-ray</td></tr>
</table>

Study	ASCEND-Peds (DFI13803)
	• Cycle ergometry • Physician's global assessment of change • Bone biomarkers • Cognitive and adaptive function testing • Efficacy analyses by manufacturing process

Abbreviations: ASMD, acid sphingomyelinase deficiency; CCL18, chemokine ligand 18; HRCT, high resolution computed tomography; kg, kilogram; mg, milligram.

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 *Description of clinical assessments*

An overview of the key efficacy outcome measures used in the olipudase alfa ASCEND and ASCEND-Peds trial is provided below.

Percentage change in % predicted DL_{CO}

Patients with ASMD often present with pulmonary impairment, as measured by DL_{CO}. Reduction in % predicted DL_{CO} is a clinically meaningful endpoint in ASMD as it significantly increases the risk of mortality and reduces patients' QoL. Furthermore, changes in DL_{CO} can objectively show the effect of olipudase alfa treatment on lung function. A targeted literature review conducted in 2020, including publications from the last 5–10 years, supported the use of DL_{CO} as a clinically meaningful endpoint in ASMD trials (44). The use of DL_{CO} as a relevant endpoint was also considered appropriate by clinical expert advisors consulted during a 2022 advisory board (37).

DL_{CO} was calculated by comparing the amount of CO exhaled following a known amount of inhaled CO. As anaemia is common in patients with ASMD and can lower DL_{CO}, all calculations of DL_{CO} were adjusted for haemoglobin concentration and ambient barometric pressure (85). Change in % predicted DL_{CO} was assessed at baseline, Week 26, and Week 52.

A patient was considered a responder if his/her absolute change from baseline value on % predicted DL_{CO} was ≥15%. The clinically meaningful change was selected on the basis of the literature and international guidelines. A decrease of >15% DL_{CO} in absolute values is associated with increased risk of mortality, the Connective Tissue Disease-associated interstitial lung disease-OMERACT CTD-ILD working group have published a consensus guideline that a relative 15% change constitutes a clinical meaningful change (86).

Percentage change in spleen volume (in MN)

The endpoint of percentage change in spleen volume (in MN), was considered appropriate as splenomegaly is a significant, consistently present manifestation of ASMD. A targeted literature review conducted in 2020, which included publications from all years for ASMD, supported the use of spleen volume as a clinically meaningful endpoint in ASMD trials (44). The degree of splenomegaly has been recognised as clinically relevant by disease area experts and shown to be positively correlated with liver volume and triglyceride levels, and negatively correlated with white blood cell count, haemoglobin, high density lipoprotein, percent predicted FVC, and height Z score (18). .. An enlarged spleen is indicative of underlying metabolic and haematological pathologies, with an increased risk of splenic rupture, bleeding and ultimately death. Splenomegaly is central to the underlying pathophysiology and usually the first presenting clinical sign in ASMD, as well as in Gaucher disease, a similar LSD (87), wherein a reduction in spleen volume is also recognised as a clinically meaningful endpoint (88, 89).

Spleen volume was assessed by abdominal MRI and expressed as percentage change in spleen volume (MN) from baseline. Conversion from the unit of cubic millimetres to MN was performed by the following algorithm:

Spleen volume (MN) = Spleen volume (cm^3) / [2*weight (kg)]

A patient was considered a responder if they had a ≥30% reduction in spleen volume (MN) from baseline. The clinically meaningful change was selected on the basis of literature. In Gaucher disease, therapeutic goals for splenomegaly include a 30–50% reduction in spleen volume within 1 year of enzyme replacement therapy (90).

Percentage change in liver volume (in MN)

Th endpoint of percentage change in liver volume (in MN), was considered appropriate as hepatomegaly is a common manifestation of ASMD. Patients with an enlarged liver are at risk of liver dysfunction, cirrhosis, liver failure, and ultimately an increased risk of death (6). Liver related issues are the major cause of death in patients with ASMD type A/B (37).

Liver volume was assessed by abdominal MRI and expressed as percentage change in liver volume (MN) from baseline. Conversion from the unit of cubic millimetres to MN was performed by the following algorithm:

Liver volume (MN) = Liver volume (cm^3) / [25*weight (kg)]

Fatigue/exercise tolerance

Fatigue and exercise tolerance was considered an appropriate endpoint as the majority of patients with ASMD, report a significantly reduced QoL due to these two factors (9). Fatigue can result in patients not being able to perform common daily activities and can affect their school/work performance. A lack of exercise tolerance can also affect their social lives and may lead to feelings of social exclusion. Furthermore, exercise tolerance and level of fatigue may also be a reflection on a patient's cardiac function.

Fatigue

In the ASCEND trial, fatigue was measured using the self-administered BFI Item 3 questionnaire, administered via eDiary. Results of the BFI questionnaire are presented as change from baseline in fatigue severity as measured by item 3 of the BFI scale at Week 52.

In the ASCEND-Peds trial, fatigue was measured using the patient self-reported PedsQL Multidimensional Fatigue Scale at screening, Week 26, and Week 52. The PedsQL Multidimensional Fatigue Scale consisted of 18 questions, six regarding general fatigue, six regarding sleep/rest fatigue and six regarding cognitive fatigue. It also included a child self-report for patients aged 5–18 years of age and a report for parents of patients 2–18 years of age. Scale scores and total scale scores were calculated based on the 0-100 scale score and presented by age group cohort at each scheduled time point as their computed value and change from baseline.

Exercise tolerance

In the ASCEND trial, exercise capacity was determined using a treadmill ergometer. Maximum oxygen (O_2) uptake (absolute and % predicted), maximum carbon dioxide (CO_2) output, and tidal volume were monitored. Maximum heart rate (absolute and % predicted), maximum respiratory exchange ratio, maximum respiratory rate (breaths/min), and maximum O_2 saturation, maximum workload (absolute and % predicted) and working time were also recorded.

As post-hoc analyses, the following cardiopulmonary exercise test (CPET) parameters were derived using collected values from treadmill ergometry eCRF:

- Calculated maximum workload is expressed as metabolic equivalents (METs) at peak exercise to normalize the value to each patient's baseline Calculated VO_2 max (mL/min/kg)
- Calculated predicted maximal voluntary ventilation (L)
- Calculated ventilatory reserve at maximal exercise (L/min)
- Calculated maximum tidal volume (mL)
- Calculated percent predicted O_2 uptake (%)
- Calculated Percent Predicted Heart Rate (%)
- Calculated predicted maximum O_2 uptake (mL/min)

In the ASCEND-Peds trial, exercise capacity was determined by cycle ergometry within one week after infusion. Continuous measurements of O_2 uptake, CO_2 output, and tidal volume were recorded. Heart rate, respiratory rate, and digital O_2 saturation were also to be continuously monitored. Steady state levels for each workload were calculated for O_2 uptake, CO_2 output, tidal volume, ventilation, and respiratory exchange ratio. Maximum workload achieved was recorded and expressed as percent predicted. In addition, percent predicted maximum were calculated for O_2 uptake and HR. Note that cycle ergometry assessments had to occur at the same time for each assessment (ie, ±2 hours of the screening assessment). Cycle ergometry assessments included maximum workload (watts), percent predicted maximum workload (%), working time (min), maximum HR (breaths/min), maximum percent predicted HR (%), maximum O_2 saturation (%), maximum respiratory rate (breaths/min), maximum ventilation (L/min), maximum O_2 uptake (mL/min), maximum percent predicted O_2 uptake (%), maximum CO_2 output (mL/min), and maximum respiratory exchange ratio. Assessments were summarised at each time point along with change from baseline by age group cohorts and overall.

HRQoL endpoints

In the ASCEND trial changes in HRQoL after 52 weeks administration of olipudase alfa or placebo were assessed with the following HRQoL questionnaires:

- The EQ-5D is a standardised measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal. The EuroQoL 5 dimension, 5 level (EQ-5D-5L) health status measure consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. Index-based values (ie, utilities) are a major feature of the EQ-5D-5L instrument, facilitating the calculation of quality-adjusted life years that are used to inform economic evaluations of health care interventions

- The SF-36 is a 36-item, multidimensional, generic health-related quality of life measure that has been validated for adults in numerous healthy and ill populations internationally (14). The SF-36 consists of 8 scales, including physical functioning, role physical, bodily pain, mental health, role emotional, social functioning, vitality, and general health and includes two summary measures of physical health and mental health derived from scale aggregates

- The BPI-SF self-administered questionnaire designed to measure a patient's perceived level of pain. The BPI-SF measures the patient's intensity of pain (sensory dimension), the interference of pain in the patient's life (reactive dimension), and asks the patient about pain relief, pain quality, and the patient's perception of the cause of pain. The BPI-SF consists of 15 items that use a numeric rating scale to assess pain severity and pain interference in the past 24 hours and the past week. Item 3 of the BPI-SF was also separately administered via eDiary

- The splenomegaly-related score (SRS) rates 5 items: abdominal pain, abdominal discomfort, early satiety, abdominal body image, and ability to bend down. The 5 items were selected from the Myelofibrosis Symptom Assessment Form (MF-SAF). Using a numerical rating scale of 0 (absent) to 10 (worst imaginable), these questions assess within the last 24 hours the impact of splenomegaly-related items that are common in patients with ASMD. The scores were collected via an eDiary over 7 days. Daily scores were averaged over 7 consecutive assessments prior to the baseline or quarterly visit. If there were days with missing scores, then the mean of the available daily scores were used for those respondents who had data for 4 or more of the 7 days

- The FACIT-dyspnoea short form is a 2-part questionnaire: 10 questions in each part. In Part 1, patients are asked to rate how short of breath they felt during the past 7 days doing activities, such as dressing, walking, and common household chores; in Part 2, patients rate how functionally limiting the dyspnoea experienced was while doing the activities presented in Part 1. This instrument was administered via eDiary

- The NPB-HAQ is a disease-specific questionnaire that covers various aspects of fatigue, pain, respiratory, abdominal complaints, and quality of life as well as questions specific to ASMD symptoms and physical activity. The questionnaire administered at baseline consisted of items to gather information on patient background, diagnostic history, family history, medical/surgical history, resource utilisation, current symptomatology, and functional status. The questionnaire administered during subsequent visits assessed interval history and resource utilisation, as well as current symptomatology and functional status

- Health-related productivity questionnaire is a self-administered questionnaire that was developed to measure how treatment of disease impacts an individual's ability to participate in the workforce and complete daily household duties

In the ASCEND-Peds trial the following HRQoL questionnaires were completed at screening, Week 25, and Week 52 by patients and parents:

- The PedsQL scale is a brief, standardised, generic assessment instrument that systematically assessed patients' and parents' perceptions of health-related quality of life in paediatric patients with chronic health conditions (6). The PedsQL consists of a 23-item core measure including a child self-report for patients aged 5 to 18 years and a report for parents of patients from birth to 18 years of age

- The PedsQL Multidimensional Fatigue Scale consisted of 18-questions, 6 regarding general fatigue, 6 regarding sleep/rest fatigue and 6 regarding cognitive fatigue. It also included a child self-report for patients aged 5 to 18 years and a report for parents of patients aged 2 to 18 years

- The PedsQL Pediatric Pain Questionnaire consisted of 3 questions and includes a child self-report (ages 5 to 18) and a proxy report for parents of patients aged 5 to 18 years, with visual analogue scales (VAS) from 0 (not hurting/no discomfort/no pain) to 100 (hurting a whole lot/very uncomfortable/severe pain)

Height, weight, and onset of puberty in children (ASCEND-Peds)

Children with ASMD experience poor growth and development, which can result in delayed puberty, and increased risk of bone fracture (10). Patients' height and weight was included as part of the physical examination. The weight, and height (standing height was used for patients >2 years of age and supine height was used for patients ≤2 years of age) was collected at Screening and within 24 hours prior to every infusion visit from Day 1/Week 0 to Week 64 (or withdrawal if withdrawn prematurely). Change from baseline, in addition to observed values, were calculated and summarised for all scheduled visits by age group cohorts and overall.

Patient puberty stage was evaluated according to Tanner staging. Tanner stage for genitals (male, stage I–V), breasts (females, stage I–V), and pubic hair (both genders, stage I–V) were documented at screening, Week 12, Week 26, Week 38, and Week 52.

B.2.3.2 *Comparative summary of study methodology*

The methodology of the relevant studies is summarised in Table 13.

Table 13: Comparative summary of methodology of relevant studies

Trial number (acronym)	ASCEND-Peds (DFI13803)	ASCEND (DFI12712)
Settings and locations	Six investigational sites in six countries (Brazil, France, Germany, Italy, the UK, and the US)	23 sites across 17 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, France, Germany, Italy, Japan, the Netherlands, Portugal, Spain, Tunisia, Turkey, the UK, and the US)
Trial design	Phase I/II, multicentre, open-label, repeated-dose study. Patients were enrolled into three age cohorts and received an IV infusion Q2W of up to a target dose of 3.0 mg/kg (or their highest tolerated dose) following an intra-patient dose escalation of ≥16 weeks. The first 12 patients received olipudase alfa and were enrolled in a staggered fashion into the three age cohorts as follows: Adolescent cohort (12 to <18 years, ≥3 patients), Child cohort (6 to <12 years, ≥3 patients), and Infant/Early child cohort (<6 years, ≥2 patients). To open enrolment in a younger age cohort, the Sponsor and a Data Monitoring Committee reviewed the safety data from the first 3 patients who completed the dose escalation phase in the previous age cohort.	Phase II/III, multicentre, repeat-dose, clinical trial Divided into two consecutive major periods: 1) A 1:1 randomised placebo-controlled, double-blind PAP from Day −60 to Week 52, followed by 2) An ETP, which was double-blind as patients in the placebo group crossed over to active treatment
Eligibility criteria for participants	Male or female paediatric patients aged from birth to <18 years with documented ASMD who have a spleen volume ≥5 MN measured by MRI and a height Z-score ≤−1. Patients with acute or rapidly progressive neurological abnormalities, or who are homozygous for the *SMPD1* mutations p.Arg498Leu, p.Leu304Pro, or p.Phe333SerfsTer52 or any combination of these three mutations were excluded. A mean platelet count <60 x 103/μL, ALT or AST >250 IU/L, total bilirubin >1.5 mg/dL, or an international normalized ratio >1.5 at screening were also exclusion criteria.	Males or females, aged ≥18 years, with documented deficiency of ASM as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes; a clinical diagnosis consistent with ASMD Type B and the following additional criteria: • DL_{CO} ≤70% of the predicted normal value • Spleen volume ≥6 MN measured by MRI • SRS ≥5
Sample size	N=20 planned and treated (adolescent cohort: n=4; child cohort: n=9, and infant/early child cohort: n=7) N=20 evaluated for efficacy/pharmacodynamics, safety, and pharmacokinetics	N=36 planned, randomised, and treated N=36 evaluated for efficacy and safety

Trial number (acronym)	ASCEND-Peds (DFI13803)	ASCEND (DFI12712)
Planned analysis	All the safety analyses were performed using the safety population. Patient data were summarised and displayed by age group cohorts and overall. Safety data were reported up to and including the time of treatment withdrawal, and follow-up for AEs, where applicable. The baseline value was the last available value before the first infusion of olipudase alfa, except for white blood cell count, platelet count, haemoglobin and possibly ECG parameters. For all safety data, the observation period was divided into two segments: • The pretreatment period, defined as the time between when the patient gave informed consent and the start of the first infusion (excluded) The on-treatment period defined as the time from the start of the first infusion (included) till the end of the study	The primary efficacy endpoints were analysed after 52 weeks in the mITT population using the mixed model for repeated measures. The secondary efficacy endpoints were analysed in the mITT population using the mixed model for repeated measures and 2-sided hypothesis tests.
Trial drugs	• Olipudase alfa Formulation: Olipudase alfa is a sterile, non-pyrogenic white to off-white lyophilised cake supplied in single use, 20 cc Type 1 glass vials. Each vial contained 20 mg of extractable olipudase alfa. The lyophilized powder was reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL olipudase alfa, which was further diluted in 0.9% sodium chloride solution to a specific volume based on the dose to be administered. Route(s) of administration: Intravenous infusion Dose regimen: Once every 2 weeks ±3 days (Q2W regimen). Target maintenance dose of 3.0 mg/kg or highest tolerable dose, preceded by an intra-patient dose escalation phase starting at 0.01 mg/kg.	• Placebo (0.9% sodium chloride) • Olipudase alfa Formulation: Olipudase alfa is a sterile, non-pyrogenic white to off-white lyophilised cake supplied in single use, 20 cc Type 1 glass vials[†]. Each vial contained 20 mg of extractable olipudase alfa. The lyophilized powder was reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL olipudase alfa, which was further diluted in 0.9% sodium chloride solution to a specific volume based on the dose to be administered. Route(s) of administration: Intravenous infusion Dose regimen: Once every 2 weeks ±3 days (Q2W regimen). Target maintenance dose of 3.0 mg/kg or highest tolerable dose, preceded by an intra-patient dose escalation phase starting at 0.01 mg/kg.

Trial number (acronym)	ASCEND-Peds (DFI13803)	ASCEND (DFI12712)
Permitted and disallowed concomitant medication	Prohibited medications included those that may decrease olipudase alfa activity (e.g. fluoxetine, chlorpromazine, tricyclic antidepressants). Cationic amphiphilic antihistamines, such as loratadine, desloratadine, astemizole, ebastine, terfenadine, and clemastine, may decrease olipudase alfa activity. Therefore, the need for their use in oral or intravenous administration was to be carefully considered. There was no restriction on topical antihistamines.	Prohibited medications included those that may decrease olipudase alfa activity (e.g., fluoxetine, chlorpromazine, tricyclic antidepressants). Cationic amphiphilic antihistamines, such as loratadine, desloratadine, astemizole, ebastine, terfenadine, and clemastine, may decrease olipudase alfa activity. Therefore, the need for their use in oral or intravenous administration was to be carefully considered. There was no restriction on topical antihistamines.
Method of randomisation and blinding	Not applicable	Randomisation was performed centrally by the Interactive (Voice or Web) Response System, which generated the patient randomisation list. The patient number allocated was a specific 9-digit number consisting of the following: 3-digit country code (ISO), 3-digit site number, and 3-digit sequential number at the site with leading zeroes, beginning with 001. During both the PAP and the first part of the ETP, patients, Investigators, and the Sponsor study team were blinded to the identity of study treatment. Patients and investigators did not have access to the randomisation (treatment codes) until after the database lock for PAP and dose escalation in ETP was complete. All patients regardless of treatment underwent dose escalation in the same manner to maintain the double-blind. Investigators and sponsors were also blinding to the PK data.
Primary outcomes (including scoring methods and timings of assessments)	• AEs/TEAEs, including IARs, physical examinations, neurological examinations, clinical laboratory evaluations, vital sign measurements, ECGs, safety biomarkers, doppler echocardiography, liver ultrasound doppler, and immune response assessments.	• Percentage change in spleen volume (in MN) from baseline to Week 52 (combined with change in SRS from baseline to Week 52 in the US only, and referred to as the “combination spleen endpoint”) • Percentage change in % predicted DL_{CO} adjusted for haemoglobin and ambient barometric pressure, (referred to as “% predicted DL_{CO}”) from baseline to Week 52
Other outcomes	Secondary outcome	Secondary outcome

Trial number (acronym)	ASCEND-Peds (DFI13803)	ASCEND (DFI12712)
	• Pharmacokinetic variables Exploratory outcomes • Spleen and liver volume by abdominal magnetic resonance imaging • Pulmonary function testing • Pulmonary imaging by high resolution computed tomography • Chest X-ray • Height Z-score • Bone age by hand x-ray • Cycle ergometry • Physician's global assessment of change • Efficacy biomarkers • Lipid profile • Bone biomarkers • Health outcome questionnaires • Cognitive and adaptive function	• Percentage change in liver volume (in MN) from baseline to Week 52 • Percentage change in platelet counts from baseline to Week 52 • Week 52 change from baseline in fatigue severity as measured by Item 3 of the BFI scale • Week 52 change from baseline in pain severity as measured by Item 3 of the BPI-SF scale • Week 52 change from baseline in dyspnoea severity as measured by the FACIT dyspnoea tool • Change in SRS from baseline to Week 52 (except US, where it is part of the primary "combination spleen endpoint") Safety outcome • Assessment of AEs, including SAEs, infusion-associated reactions (e.g., CRS, acute phase reactions) and AESIs
Other outcomes used in the economic model/specified in the scope	Not applicable	Not applicable

Trial number (acronym)	ASCEND-Peds (DFI13803)	ASCEND (DFI12712)
Pre-planned subgroups	There were no subgroup analyses.	There were no pre-planned subgroup analyses. Subgroup analyses (based on DL_{CO} and spleen volume) were added in 2019 at the request of the FDA.

† Also known as "neutral", type 1is a borosilicate glass with good chemical resistance

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; ASM, acid sphingomyelinase; ASMD, ASM deficiency; AST, aspartate aminotransferase; BFI, Brief Fatigue Inventory; BPI-SF, Brief Pain Inventory – Short Form; CRS, cytokine release syndrome; DL_{CO}, diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; ETP, extension treatment period; FACIT, Functional Assessment of Chronic Illness Therapy; FDA, Food and Drug Administration; IAR, infusion-associated reaction; mITT, modified intention-to-treat population; MN, multiples of normal; MRI, magnetic resonance imaging; NPD, Niemann-Pick disease; PAP, primary analysis period; PFT, pulmonary function test; Q2W, once every 2 weeks; SAE, serious AE; SRS, splenomegaly related score; TEAE, treatment-emergent AE.

B.2.3.3 *Patient disposition*

B.2.3.3.1 *ASCEND*

Patients were enrolled at 23 sites across Europe, North America, and South America. In total, 62 patients were screened, and 36 patients were randomised to placebo (n=18) and olipudase alfa (n=18) groups. As of the cut-off date, 4 of the 36 randomised patients (2 patients receiving placebo and 2 patients receiving olipudase alfa) discontinued the study. One patient in the placebo group did not complete the PAP due to poor compliance. [redacted]. Please see Section 1.2 of Appendix D for further details.

B.2.3.3.2 *ASCEND-Peds*

Patients were enrolled at six sites across Europe, North America, and South America. A total of 23 patients were screened and 20 patients were enrolled and received olipudase alfa, including four patients in the adolescent cohort, nine in the child cohort, and seven in the infant/early child cohort. All 20 (100%) patients completed the study and enrolled into the LTS13631 study, which is ongoing.

B.2.3.4 *Patient demographics and baseline characteristics*

B.2.3.4.1 *ASCEND*

Demographic characteristics of patients in the mITT population are summarised in Table 14. Generally, demographics and baseline characteristics were well balanced between both groups, apart from gender where there were more females (61%) than males (39%). There was an unbalanced distribution of gender between the groups (50% females and 50% males in the olipudase alfa group, and 72% females and 28% males in the placebo group). The mean age at randomisation was 34.81 years. The treatment arms were generally well matched at baseline, and disease characteristics between the two arms were similar (Table 15).

Table 14: Summary of demographic and baseline characteristics in ASCEND – mITT population

Baseline demographics	Placebo (N=18)	Olipudase alfa (N=18)	Overall (N=36)
Age, years, mean (SD)	33.5 (17.1)	36.2 (12.7)	34.8 (14.9)
Weight, mean (kg)[a]	61.6 (13.4)	67.4 (14.1)	64.5 (13.7)
Sex, n (%)			
Male	5 (28)	9 (50)	14 (39)
Female	13 (72)	9 (50)	22 (61)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	1 (6)	1 (6)	2 (6)
Black	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	16 (89)	16 (89)	32 (89)
Not Reported	0	0	0
Unknown	0	0	0
Other	1 (6)	1 (6)	2 (6)
Ethnicity, n (%)			
Hispanic or Latino	6 (33)	5 (28)	11 (31)
Not Hispanic or Latino	12 (67)	12 (67)	24 (67)
Not reported	0	1 (6)	1 (3)
Unknown	0	0	0

[a] Sanofi data on file

Baseline demographics	Placebo (N=18)	Olipudase alfa (N=18)	Overall (N=36)
Ancestry, n (%)			
Arab	[redacted]	[redacted]	[redacted]
Jewish	[redacted]	[redacted]	[redacted]
Turkish	[redacted]	[redacted]	[redacted]
South American Native Indian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Ancestry – Jewish, n (%)			
Number of patients with value	[redacted]	[redacted]	[redacted]
Ashkenazi Jewish	[redacted]	[redacted]	[redacted]
Sephardic Jewish	[redacted]	[redacted]	[redacted]
Jewish - unspecified	[redacted]	[redacted]	[redacted]
HIV antibody testing			
Non-Reactive	[redacted]	[redacted]	[redacted]
Hepatitis B surface antigen test			
Negative	[redacted]	[redacted]	[redacted]
Hepatitis C antibody test			
Negative	[redacted]	[redacted]	[redacted]
Country, n (%)			
Argentina	[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]	[redacted]
Brazil	[redacted]	[redacted]	[redacted]
Chile	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
Turkey	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]

Abbreviations: n, number; SD, standard deviation
Note: Percentages are calculated using the number of patients who have available data in each treatment group as the denominator.
Source: Sanofi data on file

Table 15: Baseline disease characteristics in ASCEND – mITT population

Characteristic	Placebo (N=18)	Olipudase alfa (N=18)	Overall (N=36)
Age at ASMD diagnosis, years, mean (SD)	14.6 (16.1)	21.4 (20.3)	18.0 (18.4)
Number of years since ASMD diagnosis, years, mean (SD)	18.9 (13.7)	14.8 (13.4)	16.8 (13.5)
ASM activity (peripheral leukocytes), nmol/h/mg, mean (SD)	0.121 (0.086)	0.118 (0.073)	0.119 (0.079)
ASM activity (dried blood spot), nmol/hr/mL, mean (SD)	[redacted]	[redacted]	[redacted]
Spleen status, n (%)			
Partial splenectomy	0	0	0
Fully splenectomy	0	0	0
Intact spleen	18 (100%)	18 (100%)	36 (100%)
Spleen volume, n (%)			
Severe splenomegaly (>15 MN)	3 (16.7)	5 (27.8%)	8 (22.2)
% Predicted DL_{CO} adjusted for haemoglobin and ambient barometric pressure, n (%)			
Severely reduced (<40%)	4 (22.2)	3 (16.7)	7 (19.4)
CHIT1 genotype classification, n (%)			
Normal / 2 functional alleles	[redacted]	[redacted]	[redacted]
Heterozygous mutation /1 functional allele	[redacted]	[redacted]	[redacted]
Homozygous mutation / 2 non-functional alleles	[redacted]	[redacted]	[redacted]
SMPD1 genotype, n (%)			
Homozygous for Arg610del	1 (5.6%)	4 (22.2%)	5 (13.9%)
Heterozygous for Arg610del	5 (27.8%)	5 (27.8%)	10 (27.8%)
Other mutations	12 (66.7%)	9 (50.0%)	21 (58.3%)

Abbreviations: ASM, acid sphingomyelinase; ASMD, acid sphingomyelinase deficiency; CHIT1, chitotriosidase-1; DL_{CO}, diffusing capacity for carbon monoxide; h, Planck's constant; hr, hour; mg, milligram; mL, millilitre; MN, multiples of normal; n, number; nmol, nanomole; SD, standard deviation; SMPD1, sphingomyelin phosphodiesterase 1

B.2.3.4.2 *ASCEND-Peds*

Demographic characteristics of patients are summarised in Table 16. Patient ages ranged from 1.5 to 17.5 years, with both sexes represented in each age cohort and equally represented in the overall group (total of 10 males and 10 females). Testing for HIV antibodies was conducted for all patients, with all patients reported as non-reactive. However, local regulations in Italy did not allow these data to be collected, hence results were only collected in the database for 16 patients. Body weight at baseline ranged from 9.9 kg to 51.5 kg, with a mean weight of 40.60 kg in the adolescent cohort, 22.8 kg in the child cohort, and 14.3 kg in the infant/early child cohort.

A summary of baseline disease characteristics is presented in Table 17. Median age at diagnosis was 2 years, with symptoms appearing at approximately 1 year of age (median). At disease onset, 18 patients (90.0%) had hepatomegaly and/or splenomegaly and seven patients (35.0%) had respiratory disease. Twelve patients (60.0%) had severe splenomegaly (>15 MN) at baseline, and one patient (11.1%) had a severely reduced percent predicted DL_{CO} value (<40.0%) among those who could perform the test (n=9).

Table 16: Summary of demographic and baseline characteristics ASCEND-Peds – safety population

Baseline demographics	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Age, years, mean (SD)	14.8 (2.2)	8.7 (1.7)	3.8 (1.4)	8.2 (4.4)
Weight, mean (kg)	40.6 (9.7)	22.8 (3.9)	14.3 (3.1)	23.4 (10.8)
Sex, n (%)				
Male	3 (75)	4 (44)	3 (43)	10 (50)
Female	1 (25)	5 (56)	4 (57)	10 (50)
Race, n (%)				
American Indian or Alaska Native	0	0	0	0
Black	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Northeast Asian	0	0	0	0
Southeast Asian	1 (25)	1 (11)	0	2 (10)
White	3 (75)	7 (78)	7 (100)	17 (85)
Other	0	1 (11)	0	1 (5)
Unknown	0	0	0	0
Not reported	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	0	0	1 (14)	1 (5)
Not Hispanic or Latino	4 (100)	9 (100)	6 (86)	19 (95)
Not reported	0	0	0	0
Unknown	0	0	0	0
Ancestry, n (%)				
Arab	[redacted]	[redacted]	[redacted]	[redacted]
Jewish	[redacted]	[redacted]	[redacted]	[redacted]
Turkish	[redacted]	[redacted]	[redacted]	[redacted]
South American Native Indian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Ancestry – Jewish, n (%)				
Ashkenazi Jewish	[redacted]	[redacted]	[redacted]	[redacted]
Sephardic Jewish	[redacted]	[redacted]	[redacted]	[redacted]
Jewish - unspecified	[redacted]	[redacted]	[redacted]	[redacted]

Baseline demographics	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
HIV antibody testing				
Non-Reactive	2 (100)	7 (100)	7 (100)	16 (100)
Hepatitis B surface antigen test				
Negative	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis C antibody test				
Negative	[redacted]	[redacted]	[redacted]	[redacted]
Country, n (%)				
Brazil	[redacted]	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HIV, human immunodeficiency virus; n, number; SD, standard deviation
Note: Percentages are calculated using the number of patients who have available data in each treatment group as the denominator.

Table 17: Baseline disease characteristics in ASCEND-Peds – safety population

Characteristic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Age at symptom onset, years, mean (SD)	1.4 (0.6)	1.6 (1.3)	1.2 (0.9)	1.4 (1.1)
Age at diagnosis, years, mean (SD)	2.1 (0.7)	3.4 (3.4)	1.6 (1.2)	2.5 (2.5)
ASM activity (peripheral leukocytes), nmol/h/mg, mean (SD)	0.210 (0.092)	0.129 (0.061)	0.095 (0.067)	0.135 (0.078)
Spleen status, n (%)				
Fully intact	4 (100%)	9 (100%)	7 (100%)	20 (100%)
Spleen volume, n (%)				
Severe splenomegaly (>15 MN)	1 (25.0%)	5 (55.6%)	6 (85.7%)	12 (60.0%)
% Predicted DL_{CO} adjusted for haemoglobin, n (%)				
Severely reduced (<40%)	1 (33.3%)	0	0	1 (11.1%)
Symptoms present at disease onset, n (%)				
None	[redacted]	[redacted]	[redacted]	[redacted]
Splenomegaly	[redacted]	[redacted]	[redacted]	[redacted]
Hepatomegaly	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory disease	[redacted]	[redacted]	[redacted]	[redacted]
Excessive bleeding/bruising	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Failure to thrive	[redacted]	[redacted]	[redacted]	[redacted]
Short stature	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Family history, n (%)				
Sibling(s)	[redacted]	[redacted]	[redacted]	[redacted]
Parent(s)	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
UGT1A1 genotype classification, n (%)				
No Gilbert Syndrome	[redacted]	[redacted]	[redacted]	[redacted]
CHIT1 genotype classification, n (%)				
Normal / 2 functional alleles	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Heterozygous mutation /1 functional allele	[redacted]	[redacted]	[redacted]	[redacted]
Homozygous mutation / 2 non-functional alleles	[redacted]	[redacted]	[redacted]	[redacted]
SMPD1 genotype, n (%)				
Heterozygous for Arg610del	1 (25.0%)	3 (33.3%)	2 (28.6%)	6 (30.0%)
Other mutations	3 (75.0%)	6 (66.7%)	5 (71.4%)	14 (70.0%)
CRIM testing, n (%)				
Positive	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASMD, acid sphingomyelinase deficiency; CHIT1, chitotriosidase-1; CRIM, cross-reactive immunological material; DL_{CO}, diffusing capacity for carbon monoxide; MN, multiples of normal; n, number; SD, standard deviation; SMPD, sphingomyelin phosphodiesterase; UGT1A1, UDP Glucuronosyltransferase Family 1 Member A1

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The statistical analysis for ASCEND and ASCEND-Peds are provided in Section B.2.4.1 and B.2.4.2, respectively.

B.2.4.1 *ASCEND*

B.2.4.1.1 *Populations analysed*

Definitions of the populations analysed in ASCEND are listed below:

- **Randomised population:** included any patient who had been allocated to a randomised treatment group regardless of study drug administration.
- **mITT population:** included randomised patients who received at least 1 infusion (partial or total). The mITT population was used for all efficacy data analysis and patients were analysed according to treatment group to which they were randomised.
- **Safety population**: included randomised patients who received at least 1 infusion (partial or total). The safety population was used for all safety data analysis and patients were analysed according to the actual treatment received during the PAP, irrespective of the treatment to which the patients were randomised.
- **Per protocol population**: subset of the mITT population who had no critical or major protocol deviations that were expected to interfere with assessments of the primary efficacy endpoints.
- **mITT-C population:** subset of mITT population which excludes patients who had exposure to Process B (non-commercial scale material) of olipudase alfa in the active treatment group.
- **PK population:** consisted of mITT patients who had evaluable drug concentration data.
- **PD population:** consisted of mITT patients who had at least 1 evaluable PD marker data available post-baseline.

B.2.4.1.2 *Statistical information*

A summary of the statistical methods used in ASCEND is presented in Table 18.

Table 18: Summary of statistical analyses in ASCEND

Trial number (acronym)	ASCEND
Hypothesis objective	To evaluate the efficacy of olipudase alfa administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD
Statistical analysis of primary efficacy endpoint	• **Primary efficacy analysis:** o The primary endpoint, % change in DL_{CO}, was analysed using MMRM. The MMRM included baseline DL_{CO}, baseline age, treatment arm, study visit, and study visit by treatment arm interaction as covariates; have an unstructured variance-covariance matrix; and be fit using restricted maximum likelihood estimation. The first (co)variance structure yielding convergence was used as the primary analysis. Comparisons between treatment arms were made using least-square mean contrasts at the 52 week visit with denominator degrees of freedom estimated using the Kenward-Roger approximation. o The percentage change in spleen volume (MN) and the change in the SRS (for US, SRS is part of primary endpoints) were analysed using an analogous MMRM model: a) For Europe and the ROW outside of US: the percentage change in spleen volume (expressed in MN) from baseline to Week 52 b) For US: the combination spleen endpoint which consists of two components: the percentage change in spleen volume (expressed in MN) from baseline to Week 52 and change in splenomegaly-related score from baseline to Week 52 • **Sensitivity analyses** Sensitivity analyses for the primary efficacy endpoints to support robustness of results included the following: o MMRM analysis using the per-protocol population to demonstrate whether the results vary depending on the population analysed. o MMRM analysis excluding observations made after the initiation of rescue therapy. As a sensitivity analysis, the observations collected after the initiation of rescue therapy were included in the MMRM; the treatment arm for rescued patients remained as randomised treatment. o The MMRM planned for the primary efficacy analysis assumed MAR. To assess the robustness of the primary results to that assumption a pattern mixture model will be used. o The MMRM planned for the primary efficacy analysis assumes multivariate normality. To assess the robustness of conclusions under this assumption, nonparametric testing method will be used: A WMW will be used to compare the primary efficacy endpoints; missing Week 52 data will be imputed using LOCF, excluding patients who initiate rescue therapy. • **Subgroup analyses:**

Trial number (acronym)	ASCEND
	○ Spleen volume by baseline spleen volume severity (severe vs not severe). Severity is defined as baseline spleen volume >15 MN. ○ % predicted DL_{CO} by baseline % predicted DL_{CO} severity (severe vs not severe). Severity is defined as baseline % predicted DL_{CO} <40%. ○ Baseline ALT or AST abnormality (ALT or AST 21 ULN vs ALT and AST <1 ULN). ○ Baseline total bilirubin abnormality (total bilirubin 21.5 ULN vs total bilirubin <1.5 ULN). ○ Presence vs absence of portal hypertension at baseline (detected signs of portal vein hyperpressure is “likely severe portal hypertension” or “likely portal hypertension” for presence of portal hypertension vs detected signs of portal vein hyperpressure is “unlikely portal hypertension” for absence of portal hypertension). • **Responder analyses:** ○ Change in % predicted DL_{CO} at Week 52. Patients with ≥15% change in % predicted DL_{CO} from baseline were considered responders. ○ Change in spleen volume at Week 52. Patients with ≥30% reduction in spleen volume from baseline were considered responders.
Statistical analysis of secondary efficacy endpoints	• The MMRM model, as used in the primary analysis of spleen volume under primary efficacy endpoints, was used to compare treatment groups for secondary efficacy endpoints including liver volume, platelet counts, BFI – Item 3, FACIT-Dyspnoea symptom score.
Statistical analysis of safety endpoints	• The analysis of the safety variables was descriptive, and no systematic testing was performed.
Sample size, power calculation	The sample size calculations were based on the 2 primary efficacy endpoints using the following assumptions: • DL_{CO}: ○ A 20% common standard deviation ○ A 25% mean difference from baseline to Week 52 between olipudase alfa and placebo in percentage change in DL_{CO} (in % predicted) ○ An expected exclusion rate from the primary analysis due to non-availability of results at Week 52 is 11% Based on the above assumptions, 36 patients randomised 1:1 to placebo and olipudase alfa were required to achieve a 93% power, using a t-test at a 2-sided 5% significance level, for the study • Spleen volume: ○ An 11.8% common standard deviation based on data from previous ASMD and Gaucher disease Type 1 studies ○ A 30% mean difference from baseline to Week 52 between olipudase alfa and placebo in percentage change in spleen volume (MN) ○ An expected exclusion rate from the primary analysis due to non-availability of results at Week 52 is 11%

Trial number (acronym)	ASCEND
	Based on the above assumptions, 36 patients randomised 1:1 to placebo and olipudase alfa were required to achieve a 99% power, using a t-test at a 2-sided 5% significance level, for the study. • Splenomegaly-related score (US): o A common standard deviation of 9.4 o A mean difference of 8.0 from baseline to Week 52 between olipudase alfa and placebo in the SRS score o An expected exclusion rate from the primary analysis due to non-availability of results at Week 52 is 11% Based on the above assumptions, 36 patients randomised 1:1 to placebo and olipudase alfa were required to achieve an 82% power, using a t-test to detect a statistical trend, defined as 2-sided p-value ≤0.15, for the study.
Data management	Management of clinical trial data was performed according to the following rules and procedures. Data entry, verification and validation were carried out using a standard validated electronic data capture computer software (Medidata RAVE® 2017.2.3). Data entry was performed directly from the Investigator site from the data source documents and signed electronically by the authorized site personnel. Moreover, any modification in the database was tracked using an audit trail.

Abbreviations: ALT, alanine transaminase; ASMD, acid sphingomyelinase deficiency; AST, aspartate transaminase; BFI, brief fatigue inventory; DL_{CO}, diffusing capacity for carbon monoxide; FACIT-Dyspnoea; Functional Assessment of Chronic Illness Therapy-Dyspnoea; LOCF, last observation carried forward; MAR, missing at random; MMRM, mixed model for repeated measures; MN, multiple of normal; ROW, rest of the world; SRS, splenomegaly-related score; ULN, upper limit of normal; US, United States; WMW, Wilcoxon-Mann-Whitney

B.2.4.2 *ASCEND-Peds*

B.2.4.2.1 *Populations analysed*

Definitions of the populations analysed in ASCEND-Peds are listed below:

- **mITT population:** includes all subjects who were exposed to the study treatment olipudase alfa. The mITT population was used as the primary population for the efficacy analysis.
- **Safety population:** includes all subjects who were exposed to the study treatment olipudase alfa. The safety population was used for all safety data analysis.
- **PK population:** includes all subjects who received at least 1 infusion of olipudase alfa and had evaluable PK data available post-baseline.
- **PD population:** includes all subjects who were treated and had at least 1 evaluable PD measurement available post-baseline.

B.2.4.2.2 *Statistical information*

A summary of the statistical methods used in ASCEND-Peds is presented in Table 19.

Table 19: Summary of statistical analyses in ASCEND-Peds

Trial number (acronym)	ASCEND-Peds
Hypothesis objective	To evaluate the efficacy of olipudase alfa administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD
Statistical analysis of safety endpoints	The analysis of the safety variables was descriptive, and no systematic testing was performed
Statistical analysis of exploratory efficacy endpoint	• **Exploratory efficacy analysis:** o All exploratory efficacy analyses were performed using the mITT population. o For each exploratory efficacy assessment, observed measures and changes from baseline, as appropriate, were listed and summarised, including the p-value from analysis of covariance with baseline as covariate and 95% CIs as appropriate, separately by time point, age group cohorts and overall. o Change in baseline was analysed with ANCOVA model with baseline as the covariate and WMW test p-values for the change from baseline and percent change from baseline for exploratory endpoints. • **Sensitivity analysis** Sensitivity analysis to assess the effect of age group cohorts was utilised for the mITT population with the following model for spleen/liver volume, FVC (L), FEV1 (L), TLC (L) and DL_{CO} (mL/min): Percent change from baseline at Week 26 or 52 = Age group cohorts + Baseline value
Sample size, power calculation	A sample size power calculation was not performed for this study. The sample size was based upon empirical considerations.
Data management	Management of clinical study data was performed according to the following rules and procedures. At regular intervals during the clinical study, the centre was contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical study protocol requirements and any emergent problems. Should a correction have been made, the corrected information was entered in the e-CRF overwriting the initial information. An audit trail allowed identification of the modification. Data were available within the system to the Sponsor as soon as they were entered in the e-CRF. The computerised handling of the data by the Sponsor generated additional requests in the discrepancy resolution form to which the Investigator was obliged to respond by confirming or modifying the data questioned. The requests with their responses were managed through the e-CRF.

Abbreviations: ASMD, acid sphingomyelinase deficiency; ANCOVA, analysis of covariance; CI, confidence interval; DL_{CO}, diffusing capacity for carbon monoxide; eCRF, electronic case report form; FEV, forced expiratory volume; FVC, forced vital capacity; mITT, modified intent-to-treat; ml, millilitre; TLC, total lung capacity; WMW, Wilcoxon-Mann-Whitney

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

The quality assessment for the ASCEND trial and ASCEND-Peds trials is presented in Table 20 and Table 21, respectively.

Table 20: Critical appraisal of ASCEND

Study name	**ASCEND**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomisation was performed using an IXRS, which generated the patient randomisation list.
Was the concealment of treatment allocation adequate?	Yes	Treatment assignment and randomisation were performed using an IXRS. Patients were randomly and centrally assigned in a 1:1 ratio across sites using blocks of 4 into 1 of the 2 groups, placebo (0.9% sodium chloride solution) or 3.0 mg/kg olipudase alfa target dose.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics were well balanced between both groups, including age at ASMD diagnosis, spleen volume, and % predicted DL_{CO}. However, there were more females, and less males, in the placebo treatment arm compared with the olipudase alfa treatment arm.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	All patients, Investigators, and the Sponsor were blinded to the identity of the study treatment. All patients, Investigators, and the Sponsor were blinded to the identity of the study treatment. During the double-blind period, olipudase alfa was packaged with kit codes and sent to an unblinded pharmacist at the investigational site for preparation. The appropriate quantity of vials was assigned via IXRS based on patient weight, current dose level, and randomisation group. Treatment group allocation continued to be blinded for all patients until the end of dose escalation portion in the ETP
Were there any unexpected imbalances in drop-outs between groups?	No	Discontinuation rates were equal across the two treatment groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The primary and key secondary outcomes listed in the methodology section are consistent with those reported in the results section.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Analyses for efficacy endpoints were conducted in the mITT, comprising all patients randomised to receive at least 1 infusion of treatment. For the primary analysis, missing data were not imputed and were assumed as missing at random

Abbreviations: ASMD, acid sphingomyelinase deficiency; DL_{CO}, diffusing capacity for carbon monoxide; IXRS, Interactive Voice Response System/Interactive Web Response System; mITT, modified intention-to-treat

Table 21: Critical appraisal of ASCEND-Peds

Study name	**ASCEND-Peds**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	The cohort was representative of the relevant targeted population. Clear inclusion/exclusion criteria were described in the publication and protocol
Was the exposure accurately measured to minimise bias?	Yes	Details of interventions the cohort was fully described
Was the outcome accurately measured to minimise bias?	Yes	Measurements for primary and secondary outcomes were clearly described. Safety was determined on the assessment of AEs/TEAEs, AESI, physical examinations, neurological examinations, clinical laboratory evaluations. Vital sign measurement, ECG, doppler echocardiography and liver ultrasound Doppler, safety biomarkers, and immune response assessments. Secondary outcomes were PK measurements and timings, and exploratory efficacy.
Have the authors identified all important confounding factors?	Yes	The inclusion criteria were carefully considered by investigators with regards to confounding factors. Adjustment of results for confounders was performed, such as the adjustment of DL_{CO} for haemoglobin.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	See above
Was the follow-up of patients complete?	Yes	All patients were alive at the end of the 64-week treatment period. After the 64-week treatment phase, patients were eligible to enrol in the long-term study LTS13632.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	When appropriate, p-values and 95% CIs from analysis of covariance with baseline as covariance were provided for change from baseline values.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; ECG, electrocardiogram; N/A, not applicable; PK, pharmacokinetic; TEAE, treatment emergent adverse event

B.2.6 *Clinical effectiveness results of the relevant studies*

B.2.6.1 *ASCEND*

B.2.6.1.1 *Primary efficacy endpoints*

Percentage change in DL_{CO} (% predicted) from baseline to Week 52

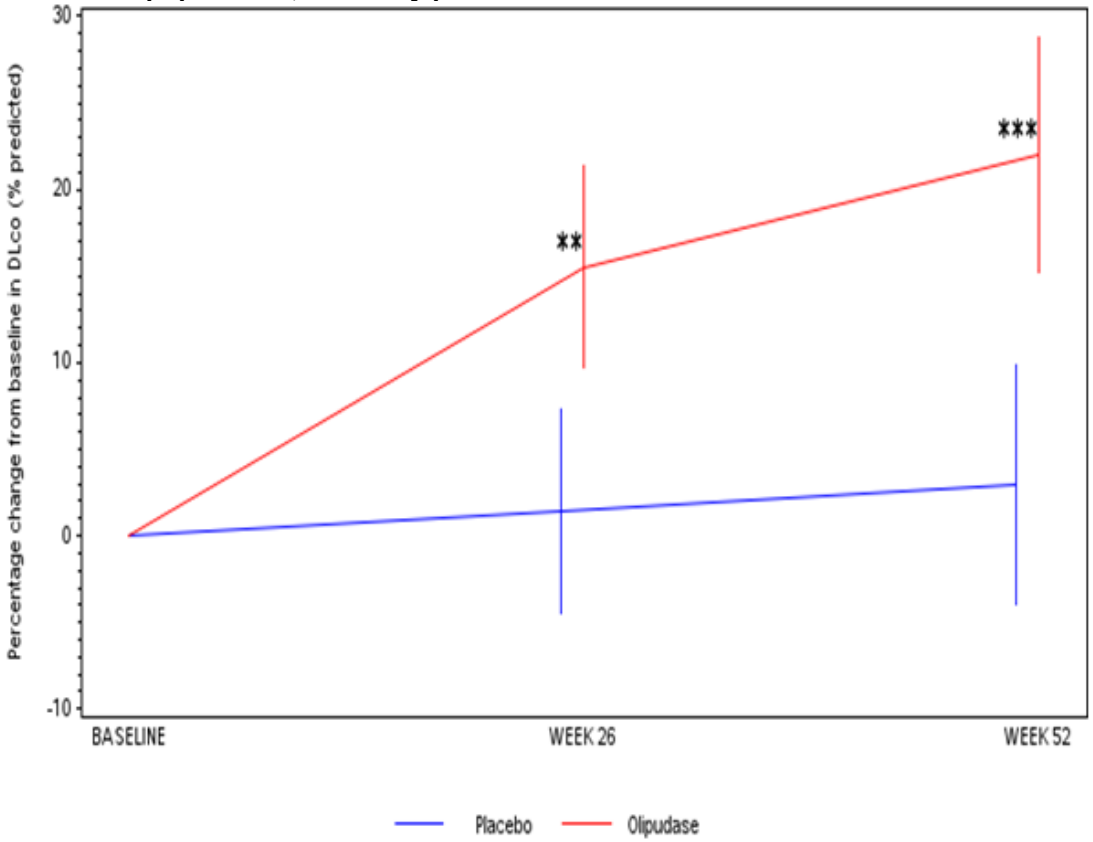
As anaemia is common in patients with ASMD and can lower DL_{CO}, all calculations of DL_{CO} were adjusted for haemoglobin concentration and ambient barometric pressure (85). The mean % predicted DL_{CO} at baseline was similar in both groups (48.45% in placebo and 49.44% in olipudase alfa) and reflected an overall moderate impairment of diffusion capacity (Table 22 and Figure 6). In the mITT population, treatment with olipudase alfa resulted in significantly greater percentage improvement in % predicted DL_{CO} at Week 52, with a 19.01% (95% CI; 9.32, 28.70) increase compared with placebo (p=0.0004) (Table 22 and Figure 6). In the ETP, in the olipudase alfa/olipudase alfa group, the mean % predicted DL_{CO} increased by 28.5±6.2% at year 2 (n=10). In the placebo/olipudase alfa group, the mean % predicted DL_{CO} increased by 28.0±6.2% at year 2 (n=10) (78).

Table 22: Percentage change in DL_{CO} (% predicted) from baseline to 52 weeks in ASCEND PAP - mITT population, using a mixed model for repeated measures

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Baseline	Mean (SD)	48.45 (10.77)	49.44 (10.99)	-
Week 26	Number of patients with value	17	17	-
	LS Mean	1.37	15.51	14.14
	SE	2.88	2.85	4.06
	95% CI†	(-4.51, 7.26)	(9.71, 21.32)	(5.85, 22.44)
	P-value for the within treatment comparison†	0.64	<.0001	-
	P-value for the difference between groups†	-	-	0.0015
	Mean (SD)	1.49 (9.42)	15.85 (14.40)	-
Week 52	Number of patients with value	17	17	-
	LS Mean	2.96	21.97	19.01
	SE	3.38	3.34	4.76
	95% CI†	(-3.9, 9.85)	(15.18, 28.76)	(9.32, 28.70)
	P-value for the within treatment comparison†	0.39	<.0001	-
	P-value for the difference between groups†	-	-	0.0004
	Mean (SD)	3.08 (11.24)	22.06 (17.01)	-
	P-value for the difference between groups‡	-	-	0.0001

Abbreviations: SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares.
† The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline derived % Predicted DL_{CO} adj. for Hb and Pressure, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
‡ The p-value is based on a Wilcoxon-Mann-Whitney test and the missing data at Week 52 were imputed using LOCF by considering the last available post-baseline data. Mean (SD) reported at each visit are based on the available data in each treatment group.
Analysis based on 15 March 2021 data cut off

Figure 6: Percentage change in DL_{CO} (% predicted) from baseline to 52 weeks in ASCEND PAP - mITT population†, summary plot of the LS means from the MMRM



Abbreviations: CI, confidence interval; DL_{CO}, lung diffusion of carbon monoxide; LS, least square; MMRM, mixed-effect model repeated measure
† The vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on a mixed model for repeated measures approach with baseline % Predicted DL_{CO} adj. for Hb and Pressure, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
* indicates nominal p-value <0.05, ** indicates nominal p-value <0.01, *** indicates nominal p-value

Sensitivity analyses

Pre-specified sensitivity analyses of the percentage change in DL_{CO} were conducted in the ASCEND trial (Section B.2.4.1.2). The results of all analyses were consistent with the primary analysis.

Responder analysis

Responder analysis was performed in the ASCEND trial to determine the proportion of patients with a clinically meaningful improvement (Section B.2.4.1.2). A greater number of responders, defined as % predicted DL_{CO} ≥15% at Week 52, were observed with olipudase alfa treatment compared with placebo (27.8% vs 0% respectively).

Percentage change in spleen volume (in MN) from baseline to Week 52

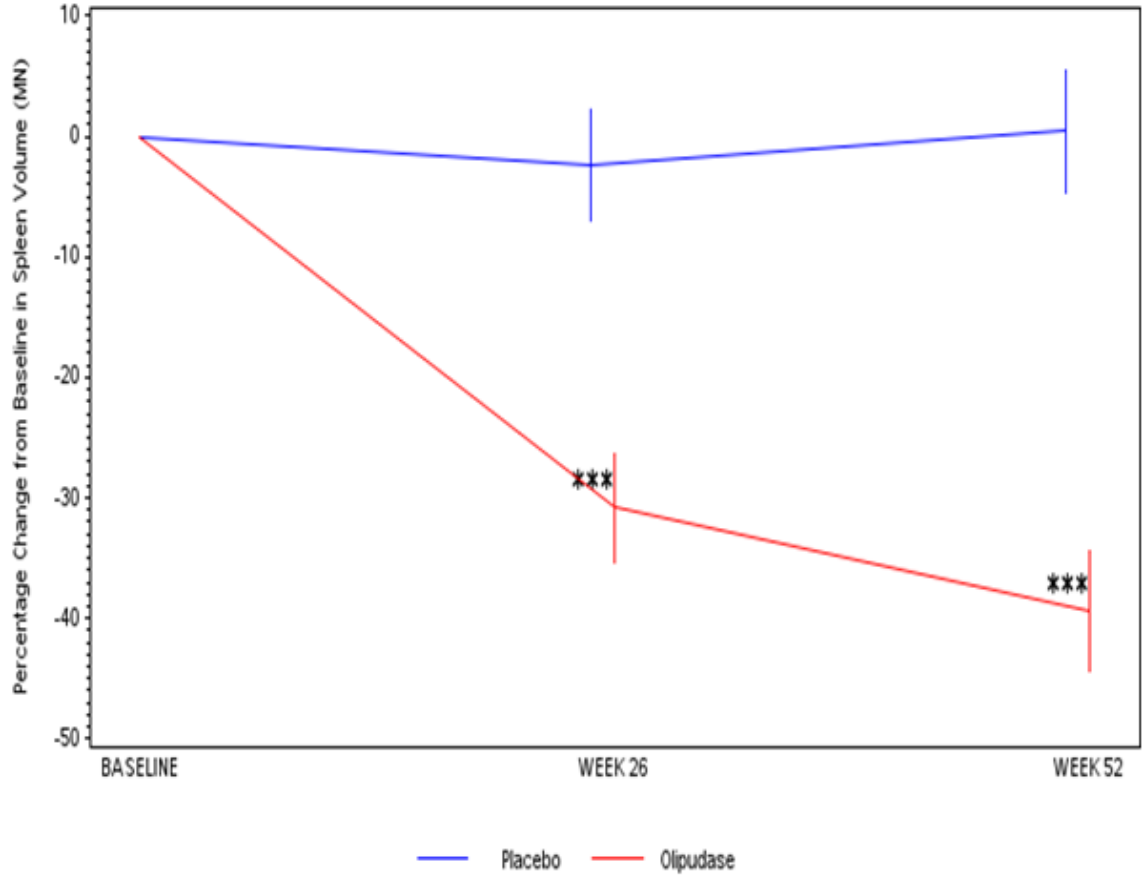
The mean spleen volume at baseline was similar in the olipudase alfa and placebo groups at baseline (11.70 MN and 11.21 MN, respectively), indicating moderate splenomegaly (Table 23 and Figure 7). In the ETP, in the olipudase alfa/olipudase alfa group, spleen volume decreased by 47.0±2.7% at year 2 (n=14). In the placebo/olipudase alfa group, spleen volume decreased by 36.0±3.0% at year 2 (n=11) (78).

Table 23: Percentage change in spleen volume (MN) from baseline to 52 weeks in ASCEND PAP - mITT population, using a mixed model for repeated measure

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Baseline	Mean (SD)	11.214 (3.8407)	11.696 (4.9239)	-
Week 26	LS Mean	-2.37	-30.84	-28.48
	SE	2.24	2.173	3.13
	95% CI†	(-6.93, 2.20)	(-35.27, -26.41)	(-34.86, -22.10)
	P-value for the within treatment comparison†	0.30	<.0001	-
	P-value for the difference between groups†	-	-	<.0001
	Mean (SD)	-2.43 (9.82)	-30.79 (8.40)	-
Week 52	LS Mean	0.48	-39.45	-39.93
	SE	2.50	2.43	3.50
	95% CI†	(-4.62,5.58)	(-44.40, -34.50)	(-47.05, -32.80)
	P-value for the within treatment comparison†	0.85	<.0001	-
	P-value for the difference between groups†	-	-	<.0001
	Mean (SD)	0.42 (11.99)	-39.39 (8.12)	-
	P-value for the difference between groups‡	-	-	<.0001

Abbreviations: SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares.
† The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline Spleen Volume (MN), baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
‡ The p-value is based on a Wilcoxon-Mann-Whitney test and the missing data at Week 52 were imputed using LOCF by considering the last available post-baseline data.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Analysis based on 15 March 2021 data cut off

Figure 7: Percentage change in spleen volume (MN) from baseline to 52 weeks in ASCEND PAP - mITT population†, summary plot of the LS means from the MMRM



Abbreviations: CI, confidence interval; LS, least square; MMRM, mixed-effect model repeated measure; MN, multiples of normal
† The vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on an MMRM approach with baseline spleen volume (MN), baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
*** p<0.001

Sensitivity analyses

Pre-specified sensitivity analyses of the percentage change in spleen volume were conducted in the ASCEND trial (Section B.2.4.2.2). The results of all analyses were consistent with the primary analysis.

Responder analysis

Post-hoc responder analysis was performed in the ASCEND trial to determine the proportion of patients with a clinically meaningful improvement (Section B.2.4.1.2). In Gaucher disease, therapeutic goals for splenomegaly include a 30–50% reduction in spleen volume within 1 year of enzyme replacement therapy (90). Therefore, a patient was considered a responder if they had a ≥30% reduction in spleen volume (MN) at Week 52. Treatment with olipudase alfa resulted in a statistically greater number of responders, compared with placebo (94.4% vs 0%, respectively, p=0.002).

B.2.6.1.2 *Secondary efficacy endpoints*

Percentage change in liver volume

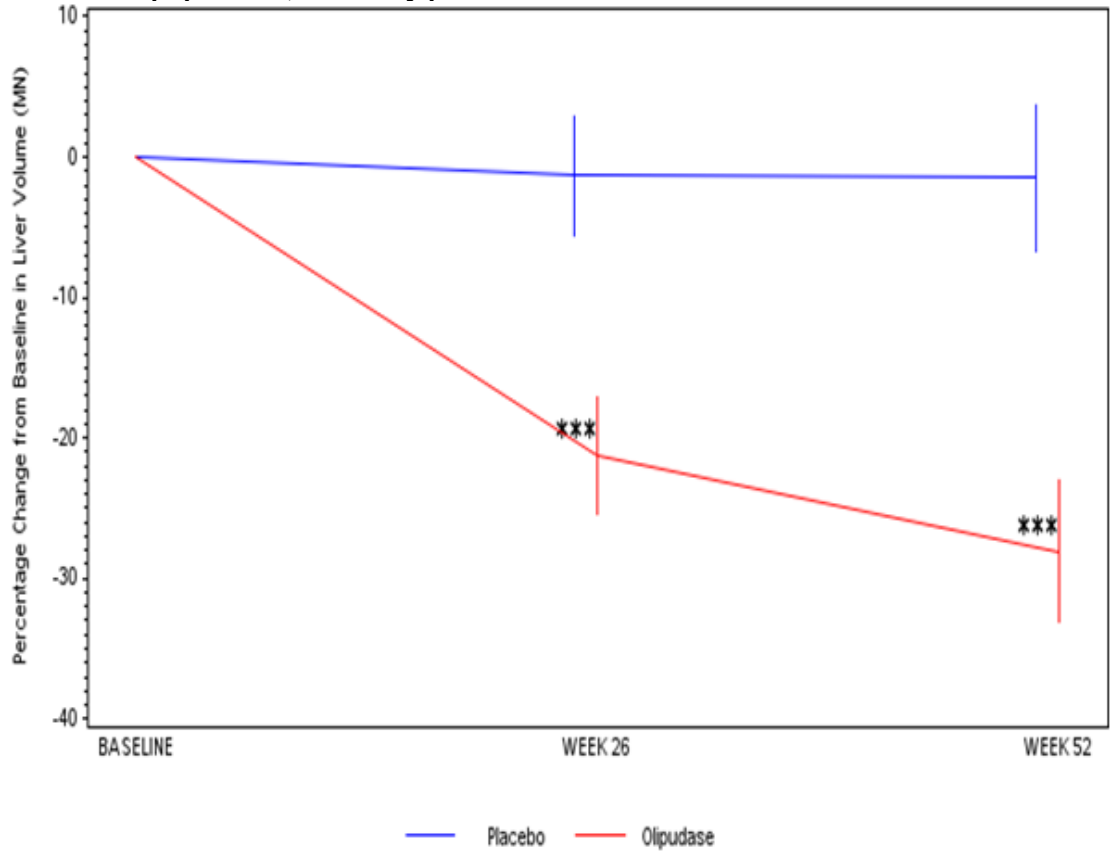
The mean liver volume (calculated in MN) at baseline was similar in olipudase alfa and placebo trial arms (1.44 MN and 1.62 MN, respectively), indicating moderate hepatomegaly (Table 24 and Figure 8). In the mITT population, treatment with olipudase alfa resulted in a significant reduction in percentage change in liver volume MN from baseline to Week 52 compared with placebo (-26.60% [95% CI; -33.91, -19.28], p<0.0001) (Table 24 and Figure 8). In the ETP, in the olipudase alfa/olipudase alfa group, liver volume decreased by 33.4±2.2% at year 2 (n=14). In the placebo/olipudase alfa group, liver volume decreased by 30.5±2.5% at year 2 (n=11) (78).

Table 24: Percentage change in liver volume (MN) from baseline to 52 weeks in ASCEND PAP - mITT population using a mixed model for repeated measures

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Baseline	Mean (SD)	1.616 (0.50)	1.444 (0.32)	-
Week 26	LS Mean	-1.30	-21.28	-19.98
	SE	2.08	2.02	2.93
	95% CI†	(-5.53,2.93)	(-25.40, -17.16)	(-25.96, -14.01)
	P-value for the within treatment comparison†	0.54	<.0001	-
	P-value for the difference between groups†	-	-	<.0001
	Mean (SD)	-1.53 (6.43)	-21.00 (10.33)	-
Week 52	LS Mean	-1.47	-28.06	-26.60
	SE	2.54	2.49	3.59
	95% CI†	(-6.66,3.72)	(-33.14, -22.99)	(-33.91, -19.28)
	P-value for the within treatment comparison†	0.5677	<.0001	-
	P-value for the difference between groups†	-	-	<.0001
	Mean (SD)	-1.697 (4.7865)	-27.375 (13.6991)	-

Abbreviations: SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares.
† The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline Liver Volume (MN), baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance. Mean (SD) reported at each visit are based on the available data in each treatment group.
Analysis based on 15 March 2021 data cut off

Figure 8: Percentage change in liver volume (MN) from baseline to 52 weeks in ASCEND PAP - mITT population, summary plot of the LS means from the MMRM†



† The vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on a mixed model for repeated measures approach with baseline Liver Volume (MN), baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.
* indicates nominal p-value <0.05, ** indicates nominal p-value <0.01, *** indicates nominal p-value <0.001.
Analysis based on 15 March 2021 data cut off

Percentage change in platelet counts

The mean platelet count at baseline was similar in the olipudase alfa and placebo group (107.18 X 10^9/L and 115.58 X 10^9/L, respectively) reflecting mild thrombocytopenia (Table 25 and Figure 9).

In the mITT population, treatment with olipudase alfa resulted in a significant increase in percentage change in platelet count from baseline to Week 52 compared with placebo (14.33% [95% CI; 2.56, 26.10], p=0.019) (Table 25 and Figure 9). In the ETP, in the olipudase alfa/olipudase alfa group, platelet count increased by 24.9±6.9% at year 2 (n=13). In the placebo/olipudase alfa group, platelet count increased by 21.7±6.4% at year 2 (n=15) (78).

Table 25: Percentage change in pre-infusion platelet counts from baseline to 52 weeks in ASCEND PAP - mITT population, using a mixed model for repeated measures

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Baseline	Mean (SD)	115.58 (36.27)	107.18 (26.93)	-
Week 14	LS Mean	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]
	95% CI[a]	[redacted]	[redacted]	[redacted]
	P-value for the within treatment comparison[a]	[redacted]	[redacted]	[redacted]
	P-value for the difference between groups [a]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
Week 26	LS Mean	-5.69	10.81	16.50
	SE	3.44	3.15	4.68
	95% CI[a]	(-12.71,1.33)	(4.38,17.23)	(6.96,26.04)
	P-value for the within treatment comparison[a]	0.1082	0.0018	-
	P-value for the difference between groups[a]	-	-	0.0013
	Mean (SD)	-5.93 (10.11)	11.12 (15.73)	-
Week 38	LS Mean	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]
	95% CI[a]	[redacted]	[redacted]	[redacted]
	P-value for the within treatment comparison[a]	[redacted]	[redacted]	[redacted]
	P-value for the difference between groups a	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
Week 52	LS Mean	2.49	16.82	14.33
	SE	4.192	3.96	5.78
	95% CI[a]	(-6.04,11.02)	(8.76,24.89)	(2.56,26.10)
	P-value for the within treatment comparison[a]	0.56	0.0002	-
	P-value for the difference between groups[a]	-	-	0.019

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
	Mean (SD)	1.93 (16.30)	17.14 (17.96)	-

Abbreviations: SD, standard deviation; SE, standard error; CI, confidence interval; LS, least squares.
a The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline Platelets, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. The variance-covariance structure used in the model is unstructured covariance.
Note: Mean (SD) reported at each visit are based on the available data in each treatment group.
Note: The baseline value is the average of all available values before the start of the first infusion of study treatment.
Note: In the mixed model for repeated measures, the data collected at pre-infusion timepoint for Week 14, Week 26 and Week 38 were used; For Week 52, the average value of the earliest assessments from haematology & differential panel and the latest assessments from the hemogram panel that were collected at pre-infusion timepoint was used.
Analysis based on 15 March 2021 data cut off

Figure 9: [redacted]

[redacted]

B.2.6.1.3 *Additional key efficacy endpoints*

Additional key efficacy endpoints in ASCEND included % change from baseline in liver function tests, pulmonary function tests, fasting lipid profile, change in efficacy

biomarkers, and exercise tolerance measured by post-hoc treadmill ergometry (Table 26). Overall treatment with olipudase alfa resulted in:

- A significant improvement in liver function at Week 52 (ALT: LS mean difference of -33.60%; p=0.006, AST: LS mean difference of -31.60%; p=0.0003)
- Significantly improved patients' lipid profile at Week 52, with significant % change in non-HDL cholesterol, HDL cholesterol, and triglycerides
- Significant improvement in pulmonary function at Week 52, as measured by % change in FVC (LS mean difference of 5.28; p=0.026)
- Improvement (reduction) in efficacy biomarkers at Week 52 (ACE, CCL18, and chitotriosidase)
- Significant improvement in exercise capacity at Week 52, as measured by O_2 uptake at peak exercise

Additional details are provided in Appendix N.6.

Table 26: Summary of additional key efficacy endpoints ASCEND PAP mITT population

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Liver function tests					
% Change in ALT (IU/L)	Baseline	Mean (SD)	44.67 (30.79)	40.78 (28.32)	-
	Week 26	LS Mean (SE)	-2.53 (8.46)	-30.71 (8.09)	-28.18 (11.72)
		95% CI†	(-19.90, 14.85)	-(47.37, -14.05)	(-52.29, -4.08)
		P-value for the difference between groups†	-	-	0.0237
	Week 52	LS Mean (SE)	-0.98 (8.68)	-36.55 (8.32)	-35.58 (12.03)
		95% CI†	(-18.69, 16.74)	-53.55, -19.56)	(-60.15, -11.00)
		P-value for the difference between groups†	-	-	0.006
% Change in AST (IU/L)	Baseline	Mean (SD)	42.28 (30.23)	43.44 (34.38)	-
	Week 26	LS Mean (SE)	1.372 (4.57)	-28.12 (4.35)	-29.49 (6.31)
		95% CI†	(-7.98, 10.72)	(-37.02, -19.21)	(-42.41, -16.57)
		P-value for the difference between groups†	-	-	<0.0001
	Week 52	LS Mean (SE)	2.00 (5.88)	-31.60 (5.71)	-33.60 (8.20)
		95% CI†	(-10.01, 14.00)	(-43.27, -19.93)	(-50.35, -16.85)
		P-value for the difference between groups†	-	-	0.0003
Lipid profile					
% Change in non-HDL cholesterol (mg/dL)	Baseline	Mean (SD)	5.12 (1.75)	4.43 (0.94)	-
		LS Mean (SE)	-1.59 (4.41)	-22.54 (4.00)	-20.95 (5.83)
		95% CI†	(-10.06, 6.88)	(-30.72, -14.35)	(-32.85, -9.05)

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
	Week 26 (change from baseline)	P-value for the difference between groups†	-	-	0.001
	Week 52	LS Mean (SE)	-2.0 (4.46)	-28.35 (4.25)	-26.15 (6.23)
		95% CI†	(-11.32, 6.91)	(-37.04, -19.65)	(-38.86, -13.43)
		P-value for the difference between groups†	-	-	0.0002
% Change in HDL cholesterol (mg/dL)	Baseline	Mean (SD)	0.53 (0.25)	0.62 (0.22)	-
	Week 26	LS Mean (SE)	0.54 (6.66)	34.66 (6.48)	34.12 (9.34)
		95% CI†	(-13.00, 14.08)	21.48, 47.84)	15.12, 53.12
		P-value for the difference between groups†	-	-	0.0009
	Week 52	LS Mean (SE)	5.83 (7.02)	39.34 (6.72)	33.52 (9.77)
		95% CI†	(-8.44, 20.09)	(25.66, 53.02)	(13.65, 53.39)
		P-value for the difference between groups†	-	-	0.0016
% Change in LDL cholesterol (mg/dL)	Baseline	Mean (SD)	4.01 (1.69)	3.56 (0.74)	-
	Week 26	LS Mean (SE)	-1.49 (5.06)	-19.05 (4.71)	-17.57 (6.95)
		95% CI†	(-11.85, 8.88)	(-28.71, -9.39)	(-31.80, -3.33)
		P-value for the difference between groups†	-	-	0.0174
	Week 52	LS Mean (SE)	0.11 (5.65)	-25.74 (5.09)	-25.85 (7.67)
		95% CI†	(-11.43, 11.65)	(-36.16, -15.32)	(-41.49, -10.22)

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
		P-value for the difference between groups†	-	-	0.0021
% Change in triglycerides (mg/dL)	Baseline	Mean (SD)	2.50 (1.01)	1.91 (0.74)	-
	Week 26	LS Mean (SE)	-0.91 (5.23)	-33.22 (5.08)	-32.30 (7.47)
		95% CI†	(-11.58, 9.75)	(-43.57, -22.86)	(-47.51, -18.00)
		P-value for the difference between groups†	-	-	0.0001
	Week 52	LS Mean (SE)	-1.39 (5.64)	-34.34 (5.40)	-32.95 (7.96)
		95% CI†	(-12.85, 10.07)	(-45.33, -23.36)	(-49.12, -16.79)
		P-value for the difference between groups†	-	-	0.0002
Pulmonary function tests					
% Change in FVC (% predicted)	Baseline	Mean (SD)	83.14 (11.75)	81.62 (17.99)	-
	Week 26	LS Mean (SE)	-0.75 (1.40)	3.81 (1.59)	4.56 (2.13)
		95% CI†	(-3.63, 2.13)	(0.54, 7.07)	(0.19, 8.92)
		P-value for the difference between groups†	-	-	0.04
	Week 52	LS Mean (SE)	1.48 (1.54)	6.76 (1.64)	5.28 (2.25)
		95% CI†	(-1.66, 4.62)	(3.41, 10.011)	(0.68, 9.88)
		P-value for the difference between groups†	-	-	0.026
% Change in FEV1 (% predicted)	Baseline	Mean (SD)	78.61 (8.63)	75.25 (21.50)	-
	Week 26	LS Mean (SE)	-2.09 (1.54)	3.79 (1.71)	5.88 (2.31)
		95% CI†	(-5.25, 1.08)	(0.30, 7.28)	(1.16, 10.59)

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
		P-value for the difference between groups†	-	-	0.0164
	Week 52	LS Mean (SE)	0.47 (1.39)	4.38 (1.48)	3.91 (2.03)
		95% CI†	(-2.37, 3.31)	(1.35, 7.42)	(-0.25, 8.08)
		P-value for the difference between groups†	-	-	0.0644
% Change in TLC (% predicted)	Baseline	Mean (SD)	77.85 (12.30)	79.89 (16.48)	-
	Week 26	LS Mean (SE)	1.57 (2.25)	4.28 (2.26)	2.71 (3.19)
		95% CI†	(-3.05, 6.20)	(-0.35, 8.91)	(-3.84, 9.26)
		P-value for the difference between groups†	-	-	0.40
	Week 52	LS Mean (SE)	0.95 (3.03)	9.98 (2.96)	8.03 (4.26)
		95% CI†	(-5.34, 7.25)	(2.88, 15.09)	(-0.74, 16.80)
		P-value for the difference between groups†	-	-	0.0710
Efficacy biomarkers					
Angiotensin Converting Enzyme (uKat/L)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
CCL18 (ug/L)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Chitotriosidase (umol/L/h)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Treadmill ergometry (exercise capacity)					
O_2 uptake (mL/min)	Week 52	LS mean change from baseline	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Calculate percent predicted O_2 uptake (%)		LS mean change from baseline	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups	[redacted]	[redacted]	[redacted]
Calculated maximal O_2 uptake (mL/min/kg)		LS mean change from baseline	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups	[redacted]	[redacted]	[redacted]

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; FEV1, volume of air expired during the first second of FVC; FVC, forced vital capacity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; O_2, oxygen; SD, standard deviation; SE, standard error; TLC, total lung capacity
† The 95% CI and p-values are based on a mixed model repeated measures approach with baseline test, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

B.2.6.1.4 *Health-related quality of life (HRQoL)*

The HRQoL of patients within the ASCEND trial was assessed via several commonly used instruments, including EQ-5D-5L and SF-36. Results of the EQ-5D-5L and SF-36 QoL questionnaires are presented in Table 27 and Table 28, respectively. Results of additional QoL questionnaires are presented in Appendix N.7. There were no statistically significant differences between treatment groups from baseline to Week 52 between olipudase alfa and placebo for the following QoL questionnaires:

- Brief pain inventory – short form
- Brief fatigue inventory
- EQ-5D-5L
- SF-36
- NPB-HAQ
- FACIT-dyspnoea functional limitation scores
- Health-related productivity questionnaire

As discussed in Section B.1.3.1.2 and 0, symptoms of ASMD negatively impact the QoL of patients. Patients consider spleen and liver volume, respiratory impairment, and fatigue as the most impactful symptoms to their daily lives. Clinical outcomes of the ASCEND trial provide strong evidence of a significant improvement in symptoms with olipudase alfa compared with placebo. The improvement with olipudase alfa treatment would be expected to be reflected in HRQoL of patients. However, it appears that the instruments used may be insensitive to the ASMD population (further discussion in Section B.2.12.2). Although there were no statistically significant differences in HRQoL following olipudase alfa treatment, as measured via HRQoL instruments, interviews from patients that had previously participated in the ASCEND trial highlight the positive impact olipudase alfa treatment has had on their HRQoL. Olipudase alfa was reported to improve patients' symptoms and mental health, with one patient stating, [redacted] (41). Aspects not captured in the HRQoL data that patients have expressed improvement within post-trial interviews also include their improved ability to attend work/school, with one patient reporting, "[redacted] (41). Patients have also expressed improvements in their performance at school, with one patient stating, "[redacted]" (41). Additionally, treatment with olipudase alfa was reported to improve patients' fatigue, and ability to do "normal" things, with one patient stating, [redacted]*" (41).* Another patient described their improved QoL due to a reduction in fatigue, "[redacted]

[redacted] (41). Patients also expressed an improvement in their image of themselves, and being included with their peers, with one patient stating, [redacted] (41).

Table 27: Analysis of the change in the VAS scale score on 'your health today' in EQ-5D-5L questionnaire from baseline to 52 weeks in ASCEND PAP- mITT population, using a MMRM

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]
	P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
	95% CI†	[redacted]	[redacted]	[redacted]
	P-value for the difference between groups†	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error
† The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline VAS scale score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates

Table 28: Analysis of the change in 8 scales measured by SF36 and 2 summary measures of physical health and mental health from baseline to 52 weeks in ASCEND PAP - mITT population, using a MMRM

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Bodily pain scale: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
General health scare: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Mental health scale: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26 (change from baseline)	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Physical function scale: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Role emotional scale: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Role physical scale: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
Social function scale: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Vitality scale: norm-based score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Mental component summary	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Physical component summary	Baseline	Mean (SD)	[redacted]	[redacted]	
	Week 26	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
	Week 52	LS Mean (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error
† The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline scale score or summary score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates

B.2.6.1.5 *Efficacy conclusions for ASCEND*

Primary efficacy endpoint

- Treatment with olipudase alfa resulted in a significant improvement in diffusing capacity of the lung, as measured by percent predicted DL_{CO}, compared with placebo at Week 52 (LS mean difference of 19.01%, p=0.0004).
- Treatment with olipudase alfa resulted in a statistically significant reduction in spleen volume at Week 52 compared with placebo (LS mean difference of -39.93%; p<0.0001).

Key secondary efficacy endpoints

- Treatment with olipudase alfa resulted in a significant reduction in liver volume at Week 52 compared with placebo (LS mean difference of -26.60%; p<0.0001).
- Treatment with olipudase alfa resulted in a significant increase in platelet count at Week 52 compared with placebo (LS mean difference of 14.33%; p=0.0185).

Additional key efficacy endpoints

- Treatment with olipudase alfa resulted in a significant improvement in in liver function at Week 53 (AST: LS mean difference of -33.60%; p=0.0003).
- Treatment with olipudase alfa significantly improved patients' lipid profile, with a significant reduction in non-HDL cholesterol (LS mean difference of -26.15%; p=0.0002), LDL cholesterol (LS mean difference of -25.85%; p=0.0021), and triglycerides (LS mean difference of -32.95%; p=0.0002) compared with placebo at Week 52.
- Treatment with olipudase alfa improved pulmonary function at Week 52 compared with placebo in the following pulmonary function tests;, FEV1 and TLC.
- Treatment with olipudase alfa resulted in an improvement (reduction) in exploratory disease biomarkers related to macrophage proliferation (ACE, CCL18, and chitotriosidase).
- Evidence of an impact of olipudase alfa treatment on HRQoL was inconclusive, highlighting that administering generic QoL instruments such as EQ-5D-5L and SF-36 in a clinical trial may not be appropriate for ASMD (further discussion in Section B.2.12.2).

B.2.6.2 *ASCEND-Peds*

B.2.6.2.1 *Primary endpoints*

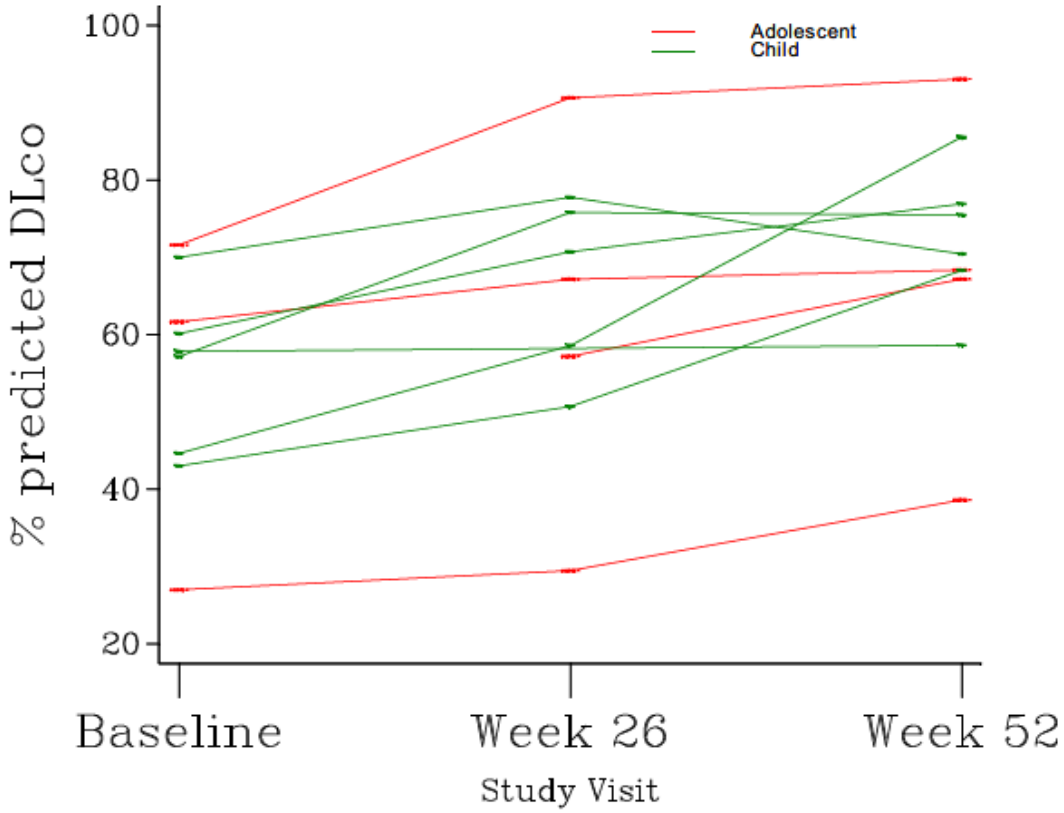
The primary objective of ASCEND-Peds was to evaluate the safety and tolerability of olipudase alfa in paediatric patients. Efficacy was assessed as a secondary endpoint, as summarised in Section B.2.6.2.2.

B.2.6.2.2 *Exploratory efficacy endpoints*

Percentage change in DL_{CO} (% predicted) from baseline to Week 52

As anaemia is common in patients with ASMD and can lower DL_{CO}, all calculations of DL_{CO} were adjusted for haemoglobin concentration and ambient barometric pressure (85). The effect of treatment with olipudase alfa on percent predicted DL_{CO} adjusted for haemoglobin is displayed by patient in Figure 10, and percent change from baseline summarised in Table 29. After 1 year of treatment (52 weeks), percent predicted DL_{CO} adjusted for haemoglobin increased by a mean of 32.94% (relative change from baseline) in 9 patients who were able to perform the test at baseline (individual patient changes varied from 0.7% to 91.7%) which was statistically significantly different from baseline (p=0.0053).

Figure 10: Percentage change in DL_{CO}. (% predicted) in ASCEND-Peds overall mITT population, by-patient plot over time



Including one patient whose DL_{CO} was performed at the Week 64 visit but within the Week 52 analysis window as described in the SAP.

Table 29: Summary of percentage change in DL_{CO} (% predicted) in ASCEND-Peds mITT population

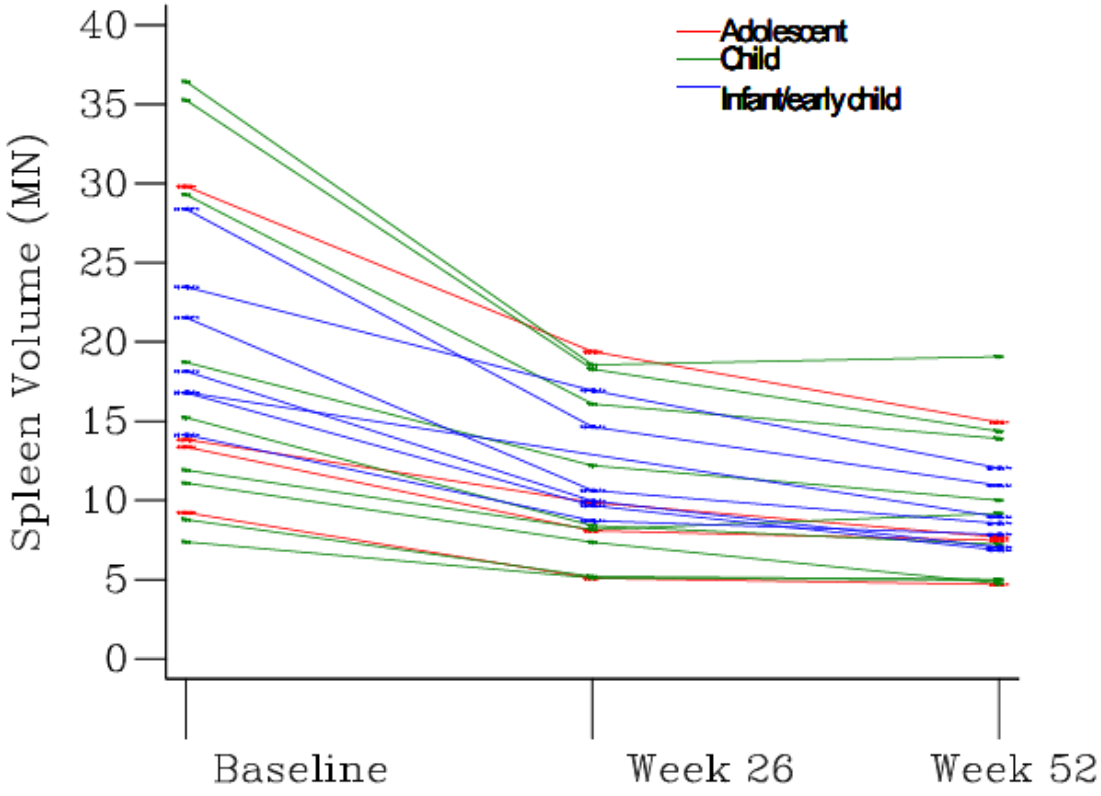
Visit		Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Baseline	Observed	Mean (SD)	53.43 (23.43)	55.48 (10.13)	-	54.79 (14.23)
Week 26	% Change from Baseline	Mean (SD)	14.90 (10.12)	22.08 (9.41)	-	19.39 (9.68)
		LS Mean (SE)†	14.90 (6.19)	22.08 (4.23)	-	19.39 (3.67)
		95% CI†	(-63.70, 93.50)	(8.61, 35.55)	-	(10.41, 28.36)
		P-value†	0.2505	0.0137	-	0.0019
Week 52	% Change from Baseline	Mean (SD)	28.01 (16.22)	35.41 (35.08)	-	32.94 (29.13)
		LS Mean (SE)†	28.01 (9.89)	35.41 (8.19)	-	32.94 (8.27)
		95% CI†	(-97.66, 153.67)	(12.66, 58.15)	-	(13.37, 52.50)
		P-value†	0.2161	0.0124	-	0.0053

Abbreviations: CI, confidence interval; DL_{CO}, diffusing capacity for carbon monoxide; SD, standard deviation; SE, standard error
† Based on regression of change from baseline (or percent change from baseline) with baseline value as the covariate.
Pulmonary function tests were performed per protocol in patients at least 5 years old on Study Day 1, and the completion of the test depended on the patient age and cooperation. Including one patient whose DL_{CO} was performed at the Week 64 visit but within the Week 52 analysis window as described in the SAP.

Percentage change in spleen and liver volume (in MN) from baseline to Week 52

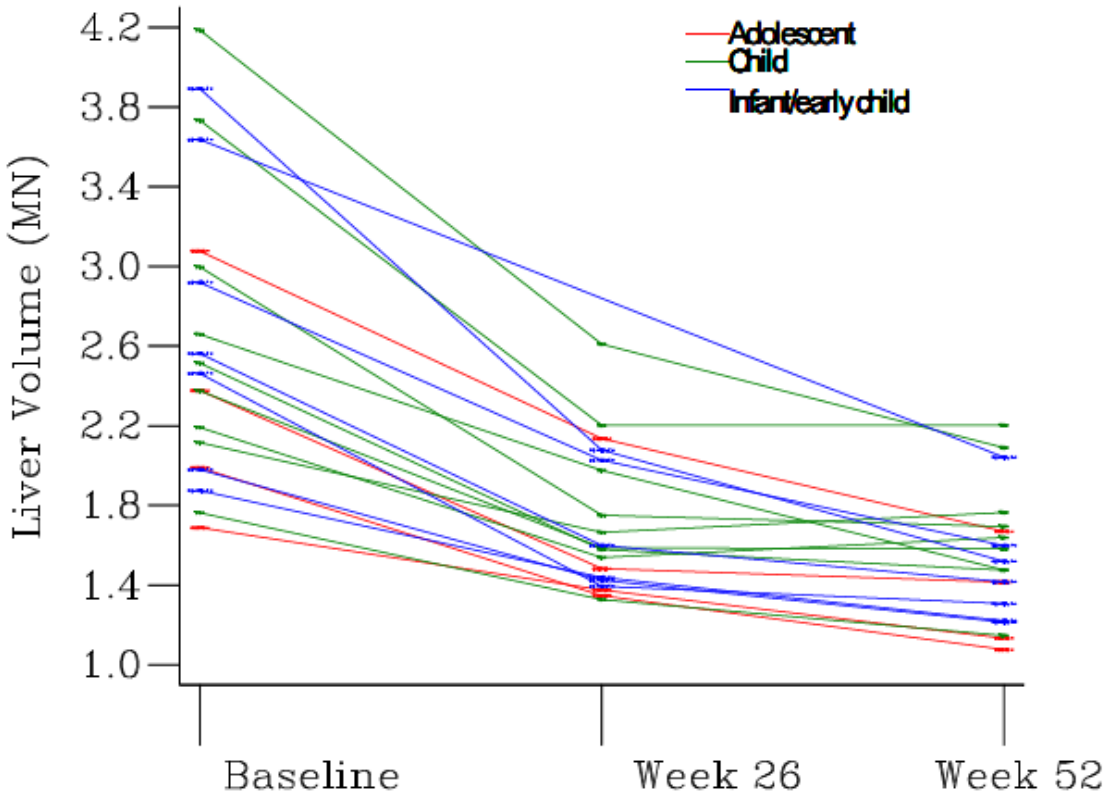
The effect of treatment with olipudase alfa on spleen and liver volume are presented in Figure 11 and Figure 12, respectively. An effect of olipudase alfa was observed in all patients from the first post-dose assessment at Week 26 on both spleen and liver volume.

Figure 11: Spleen volume (multiples of normal) in ASCEND-Peds mITT population, by-patient plot over time



Abbreviations: mITT, intention-to-treat population; MN, multiples of normal

Figure 12: Liver volume (multiples of normal) in ASCEND-Peds mITT population, by-patient plot over time



Abbreviations: mITT, intention-to-treat population; MN, multiples of normal

After 52 weeks of treatment, in the overall group (ie, all age cohorts combined), spleen volume decreased by 49.21% in mean MN (individual patient decreases ranged from 22.91% to 61.46%; Table 30) and liver volume decreased by 40.56% in mean MN (individual patient decreases ranged from 16.57% to 60.99%; Table 31). Both improvements were statistically significantly different from baseline ($p<0.0001$).

Table 30: Summary of Spleen Volume (MN) over time in ASCEND-Peds mITT Population

Visit		Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Baseline	Observed	Mean (SD)	16.56 (9.08)	19.34 (11.40)	19.90 (4.88)	18.98 (8.77)
Week 26	% Change from Baseline	Mean (SD)	-37.01 (6.866)	-39.86 (7.28)	-42.15 (8.25)	-39.98 (7.34)
		LS Mean (SE)†	-37.01 (3.900)	-39.86 (1.53)	-42.15 (3.73)	-39.98 (1.54)
		95% CI†	(-53.79, -20.23)	(-43.47, -36.24)	(-52.49, -31.80)	(-43.23, -36.73)
		P-value†	0.01	<0.0001	0.0003	<0.0001
Week 52	% Change from Baseline	Mean (SD)	-46.94 (3.04)	-46.04 (11.77)	-54.59 (7.56)	-49.21 (9.713
		LS Mean (SE) †	-46.94 (1.65)	-46.04 (3.61)	-54.59 (2.77)	-49.21 (1.99)
		95% CI†	(-54.01, -39.86)	(-54.56, -37.51)	(-61.71, -47.47)	(-53.39, -45.04)
		P-value†	0.001	<.0001	<.0001	<.0001

Abbreviations: CI, confidence interval; MN, multiples of normal; SD, standard deviation; SE, standard error
† Based on regression of change from baseline (or percent change from baseline) with baseline value as the covariate

Table 31: Summary of Liver Volume (MN) over time in ASCEND-Peds mITT Population

Visit		Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Baseline	Observed	Mean (SD)	2.28 (0.600)	2.73 (0.79)	2.76 (0.78)	2.65 (0.74)
Week 26	% Change from Baseline	Mean (SD)	-29.78 (8.09)	-32.48 (7.46)	-34.93 (9.14)	-32.69 (7.90)
		LS Mean (SE)†	-29.78 (4.27)	-32.48 (1.86)	-34.93 (2.76)	-32.69 (1.36)
		95% CI†	(-48.15, -11.40)	(-36.88, -28.08)	(-42.60, -27.27)	(-35.56, -29.81)
		P-value†	0.02	<0.0001	0.0002	<0.0001
Week 52	% Change from Baseline	Mean (SD)	-41.28 (6.13)	-36.74 (10.47)	-45.06 (8.20)	-40.56 (9.37)

Visit		Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
		LS Mean (SE)†	-41.28 (2.87)	-36.74 (2.71)	-45.06 (2.03)	-40.56 (1.67)
		95% CI†	(-53.64, -28.92)	(-43.14, -30.34)	(-50.28, -39.84)	(-44.07, -37.05)
		P-value†	0.0048	<0.0001	<0.0001	<0.0001

Abbreviations: CI, confidence interval; MN, multiples of normal; SD, standard deviation; SE, standard error
† Based on regression of change from baseline (or percent change from baseline) with baseline value as the covariate

B.2.6.2.3 *Additional key efficacy endpoints*

Additional key efficacy endpoints in ASCEND-Peds included % change from baseline in liver function tests, pulmonary function tests, fasting lipid profile, change in efficacy biomarkers, and exercise capacity as measured by cycle ergometry (Table 26). Overall treatment with olipudase alfa resulted in:

- An improvement (i.e. reduction) of ALT and AST levels at Week 52
- A decrease in mean total cholesterol, LDL-cholesterol, and triglycerides over the course of the study, with an increase in mean HDL-cholesterol
- Improvements in pulmonary function at Week 52, as measured by % change in FVC, % change in FEV_1, and % change in total lung capacity
- Statistically significant height Z-score mean improvement of 0.56 from baseline at Week 52 ($p<0.0001$)
- Reduced efficacy biomarkers at Week 52 (ACE, CCL18, and chitotriosidase)
- A trend toward improvement in cycle ergometry at Week 52

Additional details are provided in Appendix N.3.

Table 32: Summary of additional key efficacy endpoints in ASCEND-Peds mITT population

Test		Visit	Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Liver function tests							
ALT (IU/L)	Observed	Baseline	Mean (SD)	52.0 (16.4)	62.9 (38.1)	69.4 (33.0)	63.0 (32.2)
	% Change from Baseline	Week 26	Mean (SD)	-47.8 (21.4)	-55.9 (23.2)	-41.5 (42.0)	-49.3 (30.0)
	% Change from Baseline	Week 52	Mean (SD)	-60.0 (15.9)	-56.3 (27.1)	-63.1 (19.4)	-59.4 (21.9)
AST (IU/L)	Observed	Baseline	Mean (SD)	56.3 (27.3)	80.6 (46.4)	104.4 (66.0)	84.1 (52.2)
	% Change from Baseline	Week 26	Mean (SD)	-40.1 (12.9)	-50.1 (20.2)	-43.0 (11.5)	-45.6 (16.1)
	% Change from Baseline	Week 52	Mean (SD)	-49.2 (9.0)	-52.6 (17.5)	-52.7 (17.1)	-51.9 (15.2)
Lipid profile							
Total cholesterol (mg/dL)	Observed	Baseline	Mean (SD)	5.2 (0.8)	5.8 (2.5)	4.8 (0.9)	5.4 (1.8)
	% Change from Baseline	Week 26 (change from baseline)	Mean (SD)	-22.4 (11.0)	-21.9 (19.1)	-7.9 (21.0)	-17.1 (19.0)
	% Change from Baseline	Week 52	Mean (SD)	-32.7 (8.9)	-27.8 (20.3)	-26.9 (13.0)	-28.5 (15.6)
	Observed	Baseline	Mean (SD)	0.3 (0.1)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)

Test		Visit	Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
HDL cholesterol (mg/dL)	% Change from Baseline	Week 26	Mean (SD)	83.7 (63.4)	71.5 (43.4)	80.1 (21.3)	77 (40.0)
	% Change from Baseline	Week 52	Mean (SD)	118.2 (66.9)	87.5 (52.4)	125.6 (86.723)	107.0 (67.6)
LDL cholesterol (mg/dL)	Observed	Baseline	Mean (SD)	3.9 (0.90)	4.3 (2.2)	3.2 (0.4)	3.9 (1.6)
	% Change from Baseline	Week 26	Mean (SD)	-24.9 (9.8)	-26.1 (25.7)	-9.7 (30.7)	-20.6 (25.1)
	% Change from Baseline	Week 52	Mean (SD)	-38.3 (7.5)	-35.8 (23.0)	-34.0 (16.7)	-35.8 (18.0)
Triglycerides (mg/dL)	Observed	Baseline	Mean (SD)	2.1 (0.6)	2.2 (1.2)	2.4 (1.2)	2.2 (1.1)
	% Change from Baseline	Week 26	Mean (SD)	-46.4 (17.7)	-37.8 (24.8)	-46.1 (18.3)	-42.4 (20.8)
	% Change from Baseline	Week 52	Mean (SD)	-56.3 (6.0)	-47.4 (18.1)	-56.5 (25.0)	-52.3 (19.0)
Pulmonary function tests							
FVC (% predicted)	Observed	Baseline	Mean (SD)	69.5 (16.0)	81.0 (17.0)	80.9 (NC)	77.5 (16.2)
	% Change from Baseline	Week 26	LS Mean (SE)[†]	19.2 (8.7)	8.3 (4.3)	-	11.9 (3.7)
			95% CI[†]	(-18.4,56.9)	(-2.2,18.8)	-	(3.6,20.2)
			P-value[‡]	-	-	-	0.4687

Test		Visit	Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
	% Change from Baseline	Week 52	LS Mean (SE)†	16.9 (2.5)	19.4 (6.0)	-	15.2 (5.1)
			95% CI†	(6.1,27.8)	(4.7,34.1)	-	(4.0,26.4)
			P-value‡	-	-	-	0.0436
FEV1 (% predicted)	Observed	Baseline	Mean (SD)	62.9 (12.1)	83.7 (14.6)	73.7 (NC)	76.5 (16.1)
	% Change from Baseline	Week 26	LS Mean (SE)†	16.3 (6.1)	3.8 (3.5)	-	7.9 (2.7)
			95% CI†	(-9.7,42.3)	(-4.8,12.4)	-	(1.8,14.1)
			P-value‡	-	-	-	0.9189
	% Change from Baseline	Week 52	LS Mean (SE)†	13.7 (5.4)	9.0 (4.6)	-	9.1 (3.7)
			95% CI†	(-9.69,36.9)	(-2.3,20.3)	-	(0.9,17.2)
			P-value‡	-	-	-	0.2
TLC (% predicted)	Observed	Baseline	Mean (SD)	93.7 (18.6)	89.3 (22.3)	46.6 (NC)	86.8 (23.3)
	% Change from Baseline	Week 26	LS Mean (SE)†	1.9 (7.3)	16.7 (9.0)	-	10.1 (6.9)
			95% CI†	(-29.4,33.1)	(-12.0,45.4)	-	(-6.3,26.5)
			P-value‡	-	-	-	0.3
	% Change from Baseline	Week 52	LS Mean (SE)†	14.3 (2.6)	25.5 (11.9)	-	19.9 (7.2)
			95% CI†	(3.1,25.6)	(-25.7,76.7)	-	(2.3,37.5)
			P-value‡	-	-	-	0.7
Height z-score	Observed	Baseline§ (Week 26)	Mean (SD)	-2.3 (1.0)	-2.2 (1.0)	-2.1 (0.8)	-2.2 (0.9)
	Change from baseline	Week 26	Mean (SD)	0.2 (0.2)	0.1 (0.3)	0.5 (0.4)	0.2 (0.4)
			P-value†	0.3	0.5	0.03	0.01

Test		Visit	Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
	Observed	Baseline[§] (Week 52)	Mean (SD)	-2. 3 (1.0)	-2.3 (0.9)	-2.0 (0.7)	-2.2 (0.8)
	Change from baseline	Week 52	Mean (SD)	0.6 (0.3)	0.4 (0.3)	0.7 (0.4)	0.65 (0.4)
			P-value[†]	0.0763	0.0148	0.0023	<.0001
Efficacy biomarkers							
Angiotensin Converting Enzyme (uKat/L)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	% Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	% Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
CCL18 % (ug/L)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	% Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	% Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Test		Visit	Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Chitotriosidase (nmol/hr/mL)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	% Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	% Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Cycle ergometry (exercise capacity)¶							
Maximum workload	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Percent predicted maximum workload	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Working time (min)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Test		Visit	Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Maximum heart rate (breaths/min)	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum percent predicted heart rate (%)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum O2 saturation (%)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum respiratory rate (breaths/min)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum ventilation (L/min)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Test		Visit	Statistic	Adolescent (N=4)	Child (N=9)	Infant/early child (N=7)	Overall (N=20)
Maximum O2 uptake (mL/min)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum percent predicted O2 uptake (%)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum CO2 output (mL/min)	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maximum respiratory exchange ratio	Observed	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from Baseline	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; FEV1, volume of air expired during the first second of FVC; FVC, forced vital capacity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; SD, standard deviation; SE, standard error; TLC, total lung capacity
† Based on regression of change from baseline (or percent change from baseline) with baseline value as the covariate

‡ From ANCOVA model: percent change from baseline = age group cohorts + baseline value. P-value is the age cohort effect
§ Based on patients who had Week X value
¶ N=5 (Adolescent N=3, Child N=2)

B.2.6.2.4 *Health-related quality of life (HRQoL)*

The PedsQL Generic Core Scale, PedsQL Multidimensional Fatigue Scale, and Pediatric Pain Questionnaire was selected as the patient-reported outcome endpoint in the ASCEND-Peds study (Table 33). Olipudase alfa treatment resulted in a significant improvement in Generic Core Scale and Multidimensional Fatigue Scale for the majority of subtests at Week 52 compared with baseline.

PedsQL Generic Core Scale

- Treatment with olipudase alfa resulted [redacted]
- Treatment with olipudase alfa resulted in a [redacted]

PedsQL Multidimensional Fatigue Scale

- Treatment with olipudase alfa resulted [redacted]
- Treatment with olipudase alfa resulted in [redacted]

Pediatric Pain Questionnaire

- The degree of “present pain” was [redacted]
- Child and parent reports were [redacted]
- The degree of “worst pain over the past week” was [redacted]

Table 33: Summary of child self-report of QoL questionnaires for 5 to 18 years old patients, change from baseline in ASCEND-Peds mITT population

Test	Visit	Statistic	5-7 years (N=5)	8-12 years (N=7)	13 – 18 years (N=3)	Overall (N=15)
PedsQL Generic Core Scales						
Physical Functioning Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Emotional Functioning Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Social Functioning Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
School Functioning Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	5-7 years (N=5)	8-12 years (N=7)	13 – 18 years (N=3)	Overall (N=15)
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Psychosocial Health Summary Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Generic Core Total Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
PedsQL Multidimensional Fatigue Scale						
General Fatigue Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Sleep/Rest Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	5-7 years (N=5)	8-12 years (N=7)	13 – 18 years (N=3)	Overall (N=15)
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Multidimensional Fatigue Total Scale Score	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
Paediatric Pain Questionnaire						
Degree of present pain	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	5-7 years (N=5)	8-12 years (N=7)	13 – 18 years (N=3)	Overall (N=15)
Degree of the worst pain	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 26	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; mITT, intention-to-treat; QoL, quality of life; SD, standard deviation; SE, standard error
† Based on regression of change from baseline with baseline value as the covariate

B.2.6.2.5 *Efficacy conclusions for ASCEND-Peds*

Exploratory efficacy endpoints

- Treatment with olipudase alfa resulted in a statistically significant improvement in diffusing capacity of the lung, as measured by percent predicted DL_{CO}, compared with baseline at Week 52 (32.94%; p=0.0053)
- Treatment with olipudase alfa demonstrated a statistically significant reduction in spleen volume and liver volume at Week 52 compared with baseline (-49.21% and 40.56%, respectively; p<0.0001)
- Treatment with olipudase alfa resulted in a significant improvement in Height Z-scores, with a mean overall increase of 0.56 at Week 52 (p<0.0001), and 0.78 at the end of study at Week 64
- While no statistical analysis was conducted, treatment with olipudase resulted in improved liver function, with decreases in mean ALT, AST, and total bilirubin
- Treatment with olipudase alfa resulted in reduced efficacy biomarkers (lipid profile, CCL18, and chitotriosidase)
- Treatment with olipudase alfa resulted in a [redacted]

B.2.6.3 *Study DFI13412*

Study DFI13412 was a phase I, open-label, multicentre, ascending, repeated-dose study. The primary objective of DFI13412 was to determine the safety and tolerability of dose escalation to a dose of 3.0 mg/kg olipudase administered IV once every two weeks for 26 weeks. The primary exploratory efficacy analysis was change from baseline after 26 weeks of olipudase alfa treatment in spleen and liver volume, separately. The methods and results for this trial are summarised in Table 34 (full details in Appendix M).

Table 34: Summary of phase I study DFI13412

Study objective	**Primary objective** To determine the safety and tolerability of dose escalation to a dose of 3.0 mg/kg olipudase alfa administered IV once every 2 weeks for 26 weeks **Secondary objectives** • To assess the pharmacokinetics and pharmacodynamics of olipudase alfa administered IV Q2W for 26 weeks • To explore the efficacy of olipudase alfa administer IV Q2W for 26 weeks
Trial design	Phase I, open-label, multicentre, ascending, repeated-dose study
Patient population	The study included adult patients aged between 18 and 65 years of age with ASMD Baseline characteristics included: • Three male and two female patients • Aged between 23 and 48 years old at baseline • All patients Caucasian

	• One patient of Jewish heritage
Key findings	• No TEAEs were reported to be serious and a majority (97%) of events was assessed as mild in severity • No SAEs were reported • No deaths or TEAEs that resulted in treatment discontinuation • Spleen volume reduced by 29.4% • Liver volume reduced by 21.9%
Conclusions	• Olipudase alfa is well tolerated at a dose of 3.0 mg/kg • All patients within the study experienced a reduction in spleen volume and liver volume from baseline to Week 26

Abbreviations: IV, intravenous; Q2W, once every 2 weeks; SAE, serious adverse event; TEAE, treatment emergent adverse event

B.2.7 *Subgroup analysis*

B.2.7.1 *ASCEND*

There were no planned subgroup analyses for the ASCEND study. Post hoc subgroup analyses were performed for primary endpoints.

The effect of olipudase alfa treatment on the percentage change in DL_{CO} from baseline to 52 weeks was assessed based on baseline characteristics including:

- Baseline DL_{CO} severity
- Baseline ALT or AST abnormality
- Total bilirubin abnormality

The effect of olipudase alfa treatment on the percentage change in spleen volume (MN) from baseline to 52 was assessed based on baseline characteristics including:

- Baseline ALT or AST abnormality
- Total bilirubin abnormality
- Spleen severity
- Presence of portal hypertension

Subgroup analyses results

Results in the subgroups analysed in ASCEND, stratified by baseline characteristics (such as DL_{CO} severity, spleen severity, baseline ALT or AST abnormality, total bilirubin abnormality, and presence of portal hypertension) were consistent with the overall population. There was no differential treatment effect between the subgroups for percentage change in DL_{CO}, or percentage change in spleen volume. More detailed results for subgroup analyses are detailed below.

Percentage change in DL_{CO} by subgroups

By baseline DL_{CO} severity

The first subgroup was based on % predicted DL_{CO} severity (severe versus not severe). Severe was defined as % predicted DL_{CO} <40%, and not severe defined as % predicted DL_{CO} ≥40%.

Treatment with olipudase alfa resulted in [redacted]

13 [redacted]

Figure 13: [redacted]

[redacted]

[redacted]

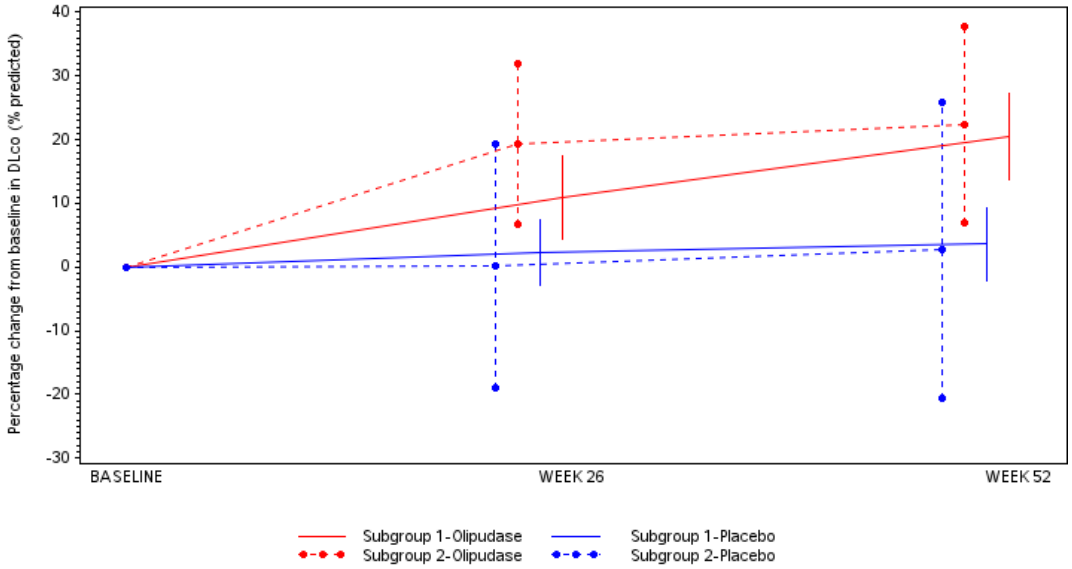
Baseline ALT or AST abnormality

Percentage predicted DL_{CO} was assessed based on baseline ALT or AST abnormality, with two populations, patients with ALT or AST ≥1 ULN [abnormal] (placebo, n=13; olipudase alfa, n=9) and patients with ALT or AST <1 ULN [normal] (placebo, n=5; olipudase alfa, n=9).

Treatment with olipudase alfa resulted [redacted]

14 [redacted].

Figure 14: Percentage change in DL_{CO} (% predicted) from baseline to 52 weeks by subgroups on baseline ALT or AST abnormality in PAP - mITT population, summary plot of the LS means from the MMRM†



† Subgroup 1 includes patients whose baseline ALT or AST ≥1 ULN/ Subgroup 2 includes patients whose baseline ALT and AST <1 ULN. The vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on a mixed model for repeated measures with baseline Derived % Predicted DL_{CO} adjusted for Hb and Pressure, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates
Analysis based on 15 March 2021 data cut off

Total bilirubin abnormality

Percentage predicted DL_{CO} was assessed based on total bilirubin abnormality. Total bilirubin abnormality was defined as ≥1.5 ULN (placebo, n=0; olipudase alfa, n=4, with normal total bilirubin defined as <1.5 ULN (placebo, n=18; olipudase alfa, n=14). For baseline total bilirubin abnormality subgroups, [redacted]

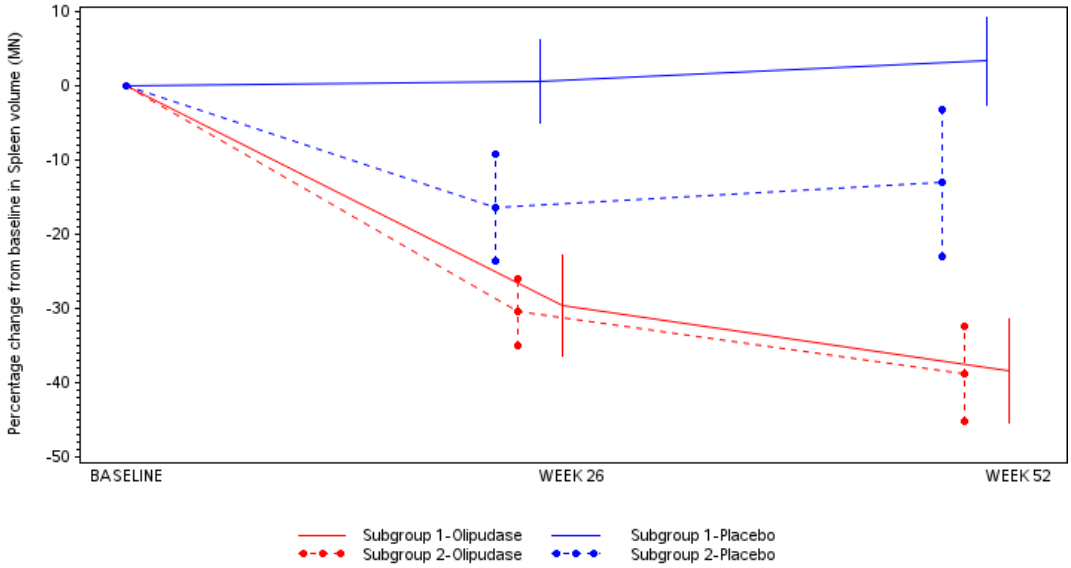
Spleen volume by subgroups

Baseline ALT or AST abnormality

Percentage change in spleen volume was assessed based on baseline ALT or AST abnormality, with two populations, patients with ALT or AST ≥1 ULN (abnormal) (placebo, n=13; olipudase alfa, n=9) and patients with ALT or AST <1ULN (normal) (placebo, n=5; olipudase alfa, n=9).

Treatment with olipudase alfa resulted [redacted] (Figure 15).

Figure 15: Percentage change in spleen volume (MN) from baseline to 52 weeks by subgroups on baseline ALT or AST abnormality in PAP - mITT population, summary plot of the LS means from the MMRM†



† Subgroup 1 includes patients whose baseline ALT or AST ≥1 ULN/ Subgroup 2 includes patients whose baseline ALT and AST <1 ULN. The vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on a mixed model for repeated measures approach with baseline Spleen volume (MN), baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates. Analysis based on 15 March 2021 data cut off

Total bilirubin abnormality

Percentage change in spleen volume was assessed based on total bilirubin abnormality. Total bilirubin abnormality was defined as ≥1.5 ULN (placebo, n=0; olipudase alfa, n=4, with normal total bilirubin defined as <1.5 ULN (placebo, n=18; olipudase alfa, n=14). For baseline total bilirubin abnormality subgroups, [redacted]

By spleen severity

Percentage change in spleen volume was assessed based on baseline spleen severity. Severe was defined as >15MN (placebo, n=3; olipudase alfa, n=5, with not severe defined as ≤15MN (placebo, n=15; olipudase alfa, n=13). Treatment with olipudase alfa resulted in [redacted] (Figure 16).

Figure 16: [redacted]

[redacted]

Presence of portal hypertension

Percentage change in spleen volume was assessed based on the presence of portal hypertension. For the presence of portal hypertension, [redacted].

B.2.7.2 *ASCEND-Peds*

There were no planned subgroup analyses for the ASCEND-peds study.

B.2.8 *Meta-analysis*

Only one RCT evaluating olipudase alfa was identified and therefore no meta-analysis was performed.

B.2.9 *Indirect and mixed treatment comparisons*

Olipudase alfa has been studied in the phase II/III ASCEND trial in which olipudase alfa was compared with placebo. Best supportive care is referenced in the NICE scope as the appropriate comparator. Additionally, as ASMD is a very rare condition, with no current treatment available, and limited available data, performing an indirect comparison for paediatric patients was not considered feasible.

B.2.10 *Adverse reactions*

B.2.10.1 *Studies reported in section 2.2*

Adverse reactions were recorded throughout the olipudase alfa clinical development programme; the identification, study details, methodologies, and results of the olipudase alfa trials are presented in Sections B.2.1–B.2.6. Key safety evidence provided by the phase I–III studies of olipudase alfa are presented below.

B.2.10.1.1 *Adverse reaction overview*

ASCEND

An overview of all TEAEs is presented in Table 35, with a summary of most common TEAEs provided in Table 36.

All patients in both the olipudase alfa and placebo groups experienced at least 1 TEAE (Table 35). The total number of events was lower in the olipudase alfa group compared with the placebo group (242 vs 270, respectively). The number of patients with TEAEs related to the study drug was greater in the olipudase alfa group compared with the placebo group (12 vs 6 [66.7% vs 33%], respectively). The percentage of patients with TEAEs of mild and moderate severity were similar in the olipudase alfa and placebo groups (100 and 72.2% respectively); however, severe TEAEs were observed in 1 (5.6%) patient in the olipudase alfa group and 6 (33.3%) patients in the placebo group. The number of patients with SAEs was similar in the olipudase alfa group (n=3; 16.7%) and the placebo group (n=4; 22.2%), and no SAE was considered drug related. No SAE led to treatment discontinuation.

One patient in the olipudase alfa group (5.6%) experienced a TEAE (alanine aminotransferase increased) that led to a temporary dose reduction. There were no TEAEs that led to treatment discontinuation or study withdrawal. The number of patients who experienced TEAEs that led to temporary study treatment interruption was identical (3 patients, 16.7%) in both treatment groups.

No deaths occurred. The percentage of patients with a protocol defined infusion-associated reaction (IAR) was higher in the olipudase alfa group compared with the placebo group (44.4% and 27.8%, respectively) (Table 35). One patient (5.6%) in the olipudase alfa group experienced a TEAE (one event) that met criteria for dose limiting toxicity 1 (DLT1) compared to 5 patients in the placebo group (4 patients [22.2%] with 6 events that met the DLT2 criteria, and 1 patient [5.6%] with 1 event that met the laboratory criteria for DLT3 but did not exhibit the clinical symptom component).

Headache was most frequently observed TEAE across the two treatment groups, with 64 events in 12 patients (66.7%) in the olipudase alfa group, and 32 events in 8 patients (44.4%) in the placebo group (Table 36). The most common TEAEs were observed in the infections and infestations SOC, including nasopharyngitis and upper respiratory tract infection events, occurring in 83.3% of patients in both treatment groups.

Table 35: Overview of treatment-emergent adverse events in PAP ASCEND - Safety population

Adverse reactions	Placebo (N=18)		Olipudase alfa (N=18)	
	N (%)	Events	N (%)	Events
Any treatment-emergent adverse events (TEAEs)[†]	18 (100%)	270	18 (100%)	242
Any TEAEs potentially related to study drug[‡]	6 (33.3%)	40	12 (66.7%)	77
Treatment-emergent AEs by severity				
Mild	18 (100%)	206	18 (100%)	190
Moderate	13 (72.2%)	51	13 (72.2%)	49
Severe	6 (33.3%)	13	1 (5.6%)	3
Any serious TEAEs	4 (22.2%)	11	3 (16.7%)	5
Any serious TEAEs potentially related to study drug[§]	0	0	0	0
Any TEAEs leading to treatment withdrawn	0	0	0	0
Any TEAEs leading to study withdrawal	0	0	0	0
Any TEAEs leading to dose reduction	0	0	1 (5.6%)	1
Any TEAEs leading to study treatment interruption	3 (16.7%)	9	3 (16.7%)	14
Any TEAEs leading to death	0	0	0	0
Any protocol-defined infusion-associated reactions	5 (27.8%)	22	8 (44.4%)	51
Any algorithm-defined infusion-associated reactions	13 (72.2%)	67	15 (83.3%)	102
Any treatment-emergent pregnancies	0	0	0	0
Any TEAEs considered symptomatic overdose	0	0	0	0
Any TEAEs for dose limiting toxicity criteria met				

Adverse reactions	Placebo (N=18)		Olipudase alfa (N=18)	
	N (%)	Events	N (%)	Events
DLT1: Any increase in AST, ALT, total bilirubin, or alkaline phosphatase (AP) >3x baseline (prior to olipudase alfa therapy) and > the upper limit of normal range >2x ULN	0	0	1 (5.6%)	1
DLT2: Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT above the normal range >2x ULN	4 (22.2.%)	6	0	0
DLT 3: DLT3: Any increase in ALT or AST >3x the upper limit of normal (ULN) combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>ULN)	1 (5.6%)	1	0	0

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; DLT, dose limiting toxicity; n, number; PAP, primary analysis period; SAE, serious adverse event; TEAE, treatment emergent adverse event; ULN, upper limit of normal

† TEAEs = Treatment-emergent adverse events. Includes all adverse events that started during the treatment epoch of the primary analysis period (for details, refer to SAP). If due to incomplete date/time, this determination could not be made unambiguously, the AE is assumed to be treatment-emergent.

‡ Includes TEAEs that were identified by the investigator as related or possibly related to the study treatment in the primary analysis period.

§ Includes serious TEAEs that were identified by the investigator as related or possibly related to the study treatment in the primary analysis period.

MedDRA version 23.1 has been used for coding the adverse events.

N=Number of patients treated within each treatment group, n (%) = number and % of patients with at least one TEAE in each category,

Events=number of TEAEs.

Analysis based on 15 March 2021 data cut off

Table 36: Summary of the most common treatment-emergent adverse events by SOC and PT in ASCEND PAP - Safety population

Primary System Organ Class (SOC) Preferred Term (PT)	Placebo (N=18)		Olipudase alfa (N=18)	
	N (%)	Events	N (%)	Events
Any class†	18 (100%)	270	18 (100%)	242
Infections and infestations	15 (83.3%)	36	15 (83.3%)	45
Nasopharyngitis	6 (33.3%)	8	8 (44.4%)	18
Upper respiratory tract infection	4 (22.2%)	6	6 (33.3%)	8
Nervous system disorders	9 (50.0%)	40	13 (72.2%)	71
Headache	8 (44.4%)	32	12 (66.7%)	64
Musculoskeletal and connective tissue disorders	11 (61.1%)	26	12 (66.7%)	23
Arthralgia	3 (16.7%)	3	4 (22.2%)	10
Respiratory, thoracic, and mediastinal disorders	5 (27.8%)	15	9 (50.0%)	14
Cough	2 (11.1%)	3	5 (27.8%)	5

Abbreviations: PAP, primary analysis period; PT, preferred term; SOC, system organ class
† Includes treatment-emergent adverse events with percentages of events >= 2% and number of patients >= 2 in the olipudase alfa treatment group and in addition, the percentage of patients with the specific treatment-emergent adverse events in the olipudase alfa treatment group is greater than placebo treatment group.
MedDRA version 23.1 has been used for coding the adverse events.
N=Number of patients treated within each treatment group, n (%) = number and % of patients with at least one TEAE in each category, Events=number of TEAEs.
Analysis based on 15 March 2021 data cut off

ASCEND-Peds

An overview of all TEAEs is presented in Table 37. with a summary of most common TEAEs provided in Table 38.

Over the 64-week treatment period, all patients experienced at least one TEAE. In the 20 patients, 798 TEAEs were reported. The highest frequency of TEAEs was observed in the child cohort (457 TEAEs in the 9 child cohort patients, versus 278 TEAEs in the 7 infant/early child cohort patients and 63 TEAEs in the 4 adolescent cohort patients). The reported TEAEs were mostly mild and moderate, with one patient in each age group experiencing at least one severe TEAE, and 15% of patients experiencing a severe TEAE.

Five patients experienced 12 SAEs, among whom three (all in the infant/early child cohort) experienced five treatment-related SAEs as determined by the Investigator. No deaths occurred in this study.

During the study, two patients had three events leading to a temporary “treatment discontinuation” (i.e. the infusion was stopped at that visit and not completed). However, patients were able to tolerate the next infusions, and completed the study. No patients permanently discontinued treatment due to TEAEs. Three patients (one in the child cohort and two in the infant/early child cohort) had 25 events leading to “study treatment interruption”, i.e., the infusion was paused until event resolution, and then completed. Several dose “reductions” (corresponding to the decrease of a dose at the next infusion or the repetition of a dose when the schedule was planning for an increase) occurred during the study.

Seven patients (35.0%) met at least one protocol defined DLT criterion. All DLTs but one happened during the dose escalation phase. The criteria for DLT1 were met by two patients, the criteria for DLT2 were met by five patients, and DLT3 by one patient. No patients in the adolescent cohort met any DLT criteria.

As shown in Table 38, pyrexia was the most common TEAE. Cough was also a very common TEAE. The most common TEAEs, by primary SOC, were observed in the infections and infestation, and gastrointestinal disorders (Table 38).

Table 37: Overview of treatment-emergent adverse events in ASCEND-Peds - Safety population

Adverse reaction	Adolescent (N=4)		Child (N=9)		Infant/Early child (N=7)		Overall (N=20)	
	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events
Any treatment-emergent adverse events (TEAEs)†	4 (100%)	63	9 (100%)	457	7 (100%)	278	20 (100%)	798
Any TEAEs potentially related to study drug‡	2 (50.0%)	5	6 (66.7%)	94	5 (71.4%)	37	13 (65.0%)	136
Treatment-emergent AEs by severity								
Mild	4 (100%)	50	9 (100%)	414	7 (100%)	241	20 (100%)	705
Moderate	3 (75.0%)	12	8 (88.9%)	41	5 (71.4%)	36	16 (80.0%)	89
Severe	1 (25.0%)	1	1 (11.1%)	2	1 (14.3%)	1	3 (15.0%)	4
Any serious TEAEs	0	0	1 (11.1%)	4	4 (57.1%)	8	5 (25.0%)	12
Any serious TEAEs potentially related to study drug§	0	0	0	0	3 (42.9%)	5	3 (15.0%)	5
Any TEAEs leading to treatment discontinuation¶	0	0	0	0	2 (28.6%)	3	2 (10.0%)	3
Any TEAEs leading to study withdrawal	0	0	0	0	0	0	0	0
Any TEAEs leading to dose reduction	0	0	4 (44.4%)	10	3 (42.9%)	10	7 (35.0%)	20
Any TEAEs leading to study treatment interruption††	0	0	1 (11.1%)	22	2 (28.6%)	3	3 (15.0%)	25
Any TEAEs leading to death	0	0	0	0	0	0	0	0
Any protocol-defined infusion-associated reactions‡‡	0	0	6 (66.7%)	68	5 (71.4%)	34	11 (55.0%)	102
Any algorithm-defined infusion-associated reactions	4 (100%)	12	9 (100%)	125	7 (100%)	55	20 (100%)	192

Adverse reaction	Adolescent (N=4)		Child (N=9)		Infant/Early child (N=7)		Overall (N=20)	
	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events
‡‡								
Any treatment-emergent pregnancies	0	0	0	0	0	0	0	0
Any TEAEs considered symptomatic overdose	0	0	0	0	0	0	0	0
Any TEAEs for dose limiting toxicity criteria met								
DLT1: Any increase in AST, ALT, total bilirubin, or alkaline phosphatase (AP) >3x baseline (prior to olipudase alfa therapy) and > the upper limit of normal range >2x ULN	0	0	1 (11.1%)	1	1 (14.3%)	2	2 (10.0%)	3
DLT2: Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT above the normal range >2x ULN	0	0	2 (2.22%)	2	3 (42.9%)	4	5 (25.0%)	6

Adverse reaction	Adolescent (N=4)		Child (N=9)		Infant/Early child (N=7)		Overall (N=20)	
	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events
DLT 3: Any increase in ALT or AST >3x the upper limit of normal (ULN) combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>ULN)	0	0	0	0	1 (14.3%)	2	1 (5.0%)	2

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; AP, alkaline phosphatase; CI, confidence interval; SAE, serious adverse event; TEAE, treatment emergent adverse event; ULN, upper limit of normal
MedDRA version 22.0 has been used for coding the adverse events.
N=Number of patients treated within each age cohort, n (%) =number and % of patients with at least one TEAE in each category, Events=number of TEAEs.
† TEAEs = Treatment-emergent adverse events. Includes all adverse events that started during the on-treatment period, i.e. after the first infusion start till the end of study (for details, refer to SAP). If due to incomplete date/time, this determination could not be made unambiguously, the AE is assumed to be treatment-emergent.
‡ Includes TEAEs that are identified by the investigator as related or possibly related to the study treatment.
§ Include serious treatment-emergent adverse events that are identified by the investigator as 'related' or 'possibly related' to the study treatment.
¶ Any TEAEs leading to treatment discontinuation: Any TEAE for which the infusion was interrupted at that visit and not completed.
†† Any TEAEs leading to study treatment interruption: Any TEAE for which the infusion was paused until event resolution, and then completed.
‡‡ Protocol-defined infusion-associated reactions=all adverse events that are identified as an IAR by the investigator. Algorithm-defined infusion-associated reactions=all adverse events that start between the start of infusion and the end of infusion plus 24 hours.

Table 38: Summary of the most common treatment-emergent adverse events by SOC and PT in ASCEND-Peds safety population†

Primary System Organ Class (SOC) Preferred Term (PT)	Adolescent (N=4)		Child (N=9)		Infant/Early child (N=7)		Overall (N=20)	
	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events
All	4 (100%)	63	9 (100%)	457	7 (100%)	278	20 (100%)	798
Injury, poisoning and procedural complications								
Contusion	0	0	3 (33.3%)	55	3 (42.9%)	33	6 (30.0%)	88 (11.0%)
General disorders and administration site conditions								
Pyrexia	1 (25.0%)	3	7 (77.8%)	24	7 (100%)	29	15 (75.0%)	56 (7.0%)
Injury, poisoning and procedural complications								
Scratch	0	0	2 (22.2%)	36	2 (28.6%)	8	4 (20.0%)	44 (5.5%)
Nervous system disorder								
Headache	2 (50.0%)	12	5 (55.6%)	21	1 (14.3%)	5	8 (40.0%)	38 (4.8%)
Respiratory, thoracic, and mediastinal disorders								
Cough	2 (50.0%)	3	7 (77.8%)	15	5 (71.4%)	13	14 (70.0%)	31 (3.9%)
Nasal congestion	0	0	3 (33.3%)	5	3 (42.9%)	13	6 (30.0%)	18 (2.3%)
Epistaxis	0	0	3 (33.3%)	6	1 (14.3%)	11	4 (20.0%)	17 (2.1%)
Infections and infestations								
Nasopharyngitis	2 (50.0%)	4	5 (55.6%)	13	4 (57.1%)	11	11 (55.0%)	28 (3.5%)
Upper respiratory tract infection	0	0	3 (33.3%)	4	5 (71.4%)	13	8 (40.0%)	17 (2.1%)

Primary System Organ Class (SOC) Preferred Term (PT)	Adolescent (N=4)		Child (N=9)		Infant/Early child (N=7)		Overall (N=20)	
	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events
Skin and subcutaneous tissue disorders								
Urticaria	0	0	2 (22.2%)	20	2 (28.6%)	4	4 (20.0%)	24 (3.0%)
Rash	0	0	3 (33.3%)	13	3 (42.9%)	4	6 (30.0%)	17 (2.1%)
Gastrointestinal disorders								
Vomiting	2 (50.0%)	3	6 (66.7%)	21	4 (57.1%)	14	12 (60.0%)	38 (4.8%)
Diarrhoea	2 (50.0%)	5	5 (55.6%)	10	4 (57.1%)	7	11 (55.0%)	22 (2.8%)
Abdominal pain	0	0	5 (55.6%)	19	1 (14.3%)	1	6 (30.0%)	20 (2.5%)

Abbreviations: PT, preferred term; SOC, system organ class
† This table considers all adverse events that started during the on-treatment period, i.e. after the first infusion start till the end of study (for details, refer to SAP), and with percentage of events >=2% and number of patients >= 2. The table is first sorted by descending number of events, then alphabetically by Preferred Term.
MedDRA version 22.0 has been used for coding the adverse events.
N=Number of patients treated within each age cohort, n (%) = number and % of patients with at least one TEAE in each category, Events=number of TEAEs.

B.2.10.1.2 *Additional safety endpoints*

ASCEND

Change in physical observations

There were no clinically meaningful changes in physical examinations associated with olipudase alfa at Week 52 (full details in Appendix N.4).

Change in neurological observations

There were no clinically meaningful changes in neurological function associated with olipudase alfa treatment at Week 52 (full details in Appendix N.4).

Safety biomarkers

Safety biomarkers included hsCRP, ceramide, iron, ferritin, cardiac-specific troponin I, calcitonin, IL-6 and IL-8. Full results for safety biomarkers are provided in Appendix N.

- Mean hsCRP, iron, ferritin, calcitonin, cardiac Troponin I, and IL-8 [redacted].
- Plasma ceramide was used to monitor rapid debulking of sphingomyelin during dose escalation. Treatment with olipudase alfa resulted in increased plasma ceramide levels at 24 and 48 hours post-infusion, at Week 52. At 24 hours post-infusion, olipudase alfa treatment resulted in a 28.93% increase in ceramide from baseline, compared with a 2.34% increase in the placebo group. At 48 hours post-infusion, olipudase alfa treatment resulted in a 4.91% increase in ceramide from baseline, compared with a 3.48% decrease in the placebo group.

ASCEND-Peds

Change in physical observations

Abnormal abdomen and general appearance were [redacted] (Appendix N.4.). [redacted]:

- [redacted]

Onset of puberty (Tanner stage)

Tanner stage was [redacted].

Change in weight and height

Treatment with olipudase alfa resulted in a numerical increase in weight and height at Week 52 compared with baseline, although no statistical analysis was performed (Appendix N.5.)

Change in neurological observations

There were no clinically meaningful changes from baseline in neurological function associated with olipudase alfa treatment at Week 52 (full details in Appendix N.1.).

Safety biomarkers

Safety biomarkers included hsCRP, ceramide, iron, ferritin, cardiac-specific troponin I, calcitonin, IL-6 and IL-8. Full results for safety biomarkers are provided in Appendix N. Plasma ceramide was used to monitor rapid debulking of sphingomyelin during dose escalation, with mean ceramide levels increasing following olipudase alfa infusion compared with pre-infusion at 24 hours and 48 hours post infusion (13.56% and 6.34% change from baseline, respectively). [redacted].

B.2.10.2 *Additional studies*

The clinical systematic review, detailed in Appendix D, included adverse events, and did not identify any additional studies.

B.2.10.3 *Safety overview*

Overall, the available data show that treatment with olipudase alfa was generally well-tolerated during the one phase II/II ASCEND study and the phase I/II ASCEND-Peds study.

The majority of TEAEs reported were non-serious, and of mild or moderate severity. There were no TEAEs that led to treatment discontinuation of any patient in any of the olipudase alfa trials. No deaths were reported in any of the trials. Thus, olipudase alfa results in significant improvement in clinical efficacy endpoints with a favourable safety profile.

In the long-term LTS13632 study, the majority of TEAEs reported were non-serious, and of mild or moderate severity (Section B.2.11.3). No severe adverse events led to permanent treatment discontinuation or study withdrawal. Thus, olipudase alfa's favourable safety profile is maintained as of the current 78 months of data collected.

B.2.11 *Ongoing studies*

The LTS13632 study, a multinational, multicentre, non-randomised, open-label, long-term treatment study of olipudase alfa, is currently ongoing (Table 39). Results are expected after this submission, in July 2024. However, interim results (up to 2 years for paediatric patients and up to 6.5 years for adult patients) have been presented at international congresses (83, 84), and the latest available data (up to 4 years for paediatric patients and up to 6.5 years for adult patients as of 01 March 2021 data cut) are summarised in this section. Overall, interim results suggest that olipudase alfa is well-tolerated and clinical benefits are maintained or amplified in the long term.

Table 39: Clinical effectiveness evidence LTS13632

Study					
Study design	Phase II, multinational, multicentre, non-randomised, open-label, long term treatment study				
Population	Paediatric and adult patients with ASMD who already received olipudase alfa				
Intervention(s)	• Olipudase alfa (patients started at the same dose they were receiving at the end of their original study provided)				
Comparator(s)	• None				
Indicate if study supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale if trial not used in model	Not applicable.				
Reported outcomes specified in the decision problem	• Change in spleen volume • Change in lung function • Change in liver function and volume • Change in weight, height and onset of puberty in children and young people • Change in fatigue and exercise tolerance • Change in physical observations (including observations or measurements from examination of the eyes, nose and throat; heart, lungs, bone marrow, extremities and joints) • Change in neurological observations (including observations or measurements from examination of coordination; cranial nerves; extrapyramidal features; fundoscopy; gait; motor skills; peripheral nervous system; reflexes; sensory nervous system; strength and mental status) • Change in biomarkers (including high sensitivity C reactive protein; ceramide, cardiac troponin, ferritin chitotriosidase,				

Study	
	CCL18 levels, lysosphingomyelin, oxysterols, and lipid profile) • Mortality • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Bone disease assessments • Pulmonary imaging • Cycle ergometry • Physician's Global Assessment • Haematology • Bone biomarkers • Bone age by hand X-ray (DFI13803 Peds only) • Tanner Staging (DFI13803 Peds only)

Abbreviations: ASMD, Acid sphingomyelinase deficiency; CCL18, Chemokine ligand 18

B.2.11.1 *Methodology*

The design and methodology of Study LTS13632 are presented in Table 40.

Table 40: Summary of LTS13632

Trial number (acronym)	LTS13632
Settings and locations	2 sites across 2 countries (the UK and the US)
Trial design	Phase II, multinational, multicentre, non-randomised, open-label, long-term study Patients were enrolled from DFI1342 phase Ib and ASCEND-Peds study
Eligibility criteria for participants	Patients were included who had completed the treatment period of a previous study of olipudase alfa with an acceptable safety profile.
Sample size	N=25 enrolled and evaluated for efficacy and safety
Planned analysis	For continuous efficacy measures, change or % change from baseline was analysed with the ANCOVA method adjusting for baseline value and no multiplicity adjustment was conducted
Trial drugs	• Olipudase alfa (patients started at the same dose they were receiving at the end of their original study) Formulation: Olipudase alfa is a sterile, non-pyrogenic white to off-white lyophilised cake supplied in single use, 20 cc Type 1 glass vials. Each vial contained 20 mg of extractable olipudase alfa. The lyophilized powder was reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL olipudase alfa, which

	was further diluted in 0.9% sodium chloride solution to a specific volume based on the dose to be administered. Route(s) of administration: Intravenous Dose regimen: Once every 2 weeks
Permitted and disallowed concomitant medication	Prohibited medications included those that may decrease olipudase alfa activity (e.g., fluoxetine, chlorpromazine, tricyclic antidepressants). Cationic amphiphilic antihistamines, such as loratadine, desloratadine, astemizole, ebastine, terfenadine, and clemastine, may decrease olipudase alfa activity. Therefore, the need for their use in oral or intravenous administration was to be carefully considered. Medications or herbal supplements that can cause or prolong bleeding and the use of medications or herbal supplements with potential hepatotoxicity were to be withheld as per local institution guidance/practice around the scheduled liver biopsies.
Method of randomisation and blinding	Not applicable
Primary outcomes (including scoring methods and timings of assessments)	• To obtain data regarding safety of olipudase alfa
Other outcomes	Secondary outcome • To obtain data regarding the efficacy of olipudase alfa and to characterise PD and PK variables Exploratory outcomes • Spleen and liver volume by abdominal magnetic resonance imaging • Pulmonary imaging by high resolution computed tomography • Chest X-ray • Pulmonary function testing • Cycle ergometry • Fasting profile • Efficacy biomarkers • Bone biomarkers • Haematology • Tanner staging (Peds only) • Height Z-score (Peds only) • Health outcome questionnaires • Physician's global assessment of change
Other outcomes used in the economic model/specified in the scope	Not applicable
Pre-planned subgroups	There were no pre-planned subgroup analyses. Subgroup analyses were added in 2019 for efficacy endpoints for patients ASCEND-Peds

Abbreviations: ANCOVA, analysis of covariance; cc, cubic centimetre; mL, millilitre; PD, pharmacodynamics; PK, pharmacokinetics;

B.2.11.2 *Clinical effectiveness*

The primary objective of LTS13632 was to obtain data regarding the safety of olipudase alfa in patients with ASMD who are exposed to long-term treatment with olipudase alfa. Efficacy was assessed as a secondary endpoint.

B.2.11.2.1 *Spleen volume and platelet count*

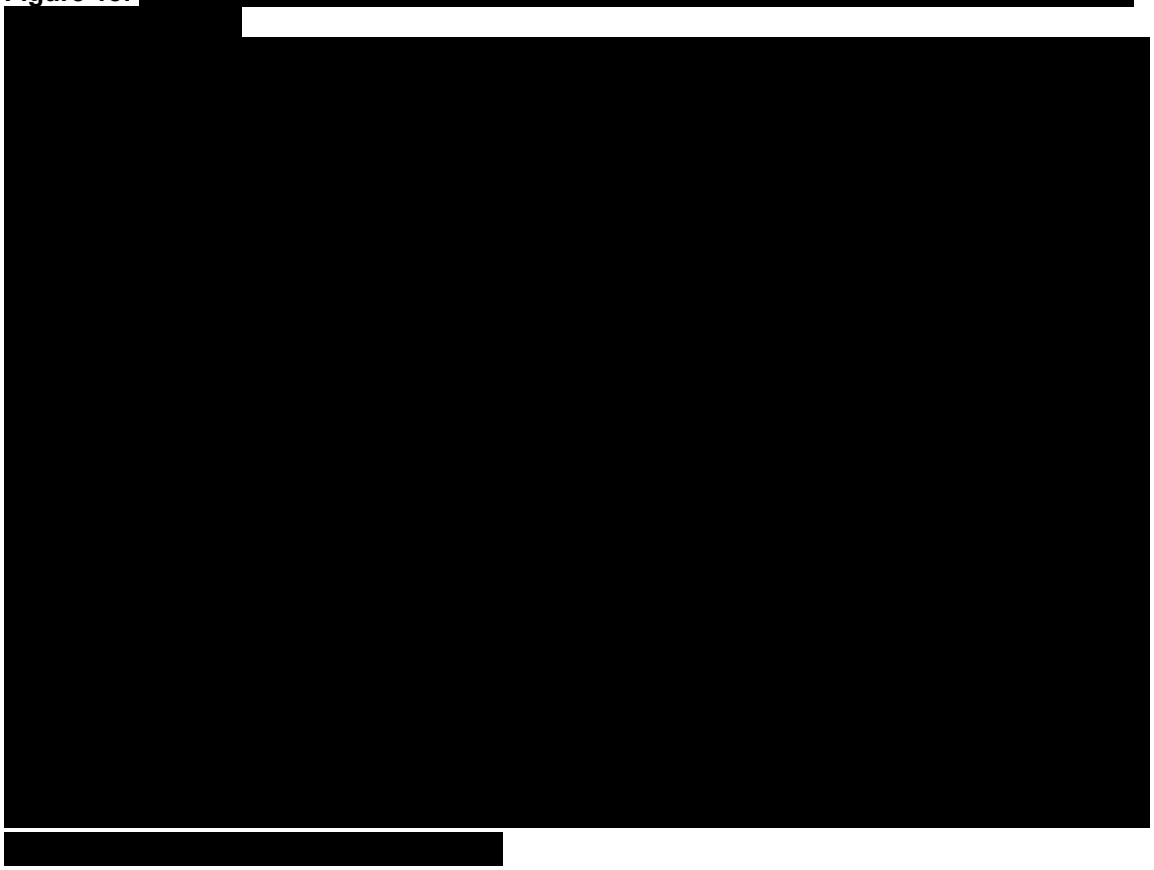
As of the latest date cut (01 March 2021), all patients treated with olipudase alfa demonstrated a reduction in spleen volume at all timepoints, starting as early as Month 6 and continuing up to Month 78 in the overall population (Figure 17). For adult patients (n=5), treatment with olipudase alfa resulted in a 59.46% reduction in spleen volume, on average, by Month 78 ($p<0.0001$). Olipudase alfa treatment resulted in a mean apercentage improvement of pre-infusion platelet count of 38.49% by Month 78 ($p=0.0093$). For paediatric patients (n=7), treatment with olipudase alfa resulted in a [redacted] reduction in spleen volume, on average, by Month 48 [redacted] By Month 48, the mean improvement in pre-infusion platelet count among paediatric patients (n=5) was 35.83% ($p=0.1917$).

Figure 17: [redacted]

B.2.11.2.2 *Liver volume*

Treatment with olipudase alfa resulted in a reduction in mean liver volume in all patients, as early as Month 6 and sustained up to Month 78 in adults and Month 66 in the paediatric population. For adult patients (n=5), treatment with olipudase alfa resulted in a [redacted] reduction in liver volume, on average, by Month 78 ([redacted]). For paediatric patients (n=7), treatment with olipudase alfa resulted in a [redacted] reduction in liver volume, on average, by Month 48 ([redacted]).

Figure 18: [redacted]



B.2.11.2.3 *% predicted DLCO*

Treatment with olipudase alfa resulted in improvement in the percent predicted DL_{CO}, with greater improvement over time (Figure 19). For adult patients (n=5), treatment with olipudase alfa resulted in a [redacted] improvement in % predicted DL_{CO}, on average, by Month 78 ([redacted]). For paediatric patients (n=5), treatment with olipudase alfa resulted in a 60.28% improvement in % predicted DL_{CO}, on average, by Month 48 ([redacted]).

Figure 19: [redacted]

[redacted]

B.2.11.3 *Additional efficacy endpoints*

Additional key efficacy endpoints in LTS13632 included % change from baseline in liver function tests, change in weight, height, and onset of puberty (paediatric population only), health related QoL, pulmonary function tests, fasting lipid profile, change in efficacy biomarkers, and exercise tolerance measured by cycle ergometry. These data are provided in Appendix O.

B.2.11.4 *Adverse reactions*

Overall, all patients experienced a TEAE in the LTS13632 study, with 99.7% of these events in both adult and paediatric patients reported as mild or moderate in severity. No severe adverse event led to permanent treatment discontinuation or study withdrawal and all patients recovered (Table 41).

Table 41: Overview of treatment-emergent adverse events in LTS13632, safety population

Adverse reactions	Patients from DFI3412 (Adults) (N=5)		Patients from DFI13803 (Paediatrics) (N=20)		All patients (N=25)	
	N (%)	Events	N (%)	Events	N (%)	Events
Any treatment-emergent adverse events (TEAEs)[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs potentially related to study drug[‡]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-emergent AEs by severity						
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAEs potentially related to study drug[§]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-emergent adverse events leading to permanent treatment discontinuation	0	0	0	0	0	0
Any TEAEs leading to study withdrawal	0	0	0	0	0	0
Any TEAEs leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to study treatment interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs leading to death	0	0	0	0	0	0

Adverse reactions	Patients from DFI3412 (Adults) (N=5)		Patients from DFI13803 (Paediatrics) (N=20)		All patients (N=25)	
	N (%)	Events	N (%)	Events	N (%)	Events
Any protocol-defined infusion-associated reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any algorithm-defined infusion-associated reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-emergent pregnancies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs considered symptomatic overdose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs for dose limiting toxicity criteria met						
DLT1: Any increase in AST, ALT, total bilirubin, or alkaline phosphatase (AP) >3x baseline (prior to olipudase alfa therapy) and > the upper limit of normal range >2x ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLT2: Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT above the normal range >2x ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLT 3: DLT3: Any increase in ALT or AST >3x the upper limit of normal (ULN) combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse reactions	Patients from DFI3412 (Adults) (N=5)		Patients from DFI13803 (Paediatrics) (N=20)		All patients (N=25)	
	N (%)	Events	N (%)	Events	N (%)	Events
of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>ULN)						

Abbreviations: AE, adverse event; ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; CI, confidence interval; DLT, dose limiting toxicity; n, number; PAP, primary analysis period; SAE, serious adverse event; TEAE, treatment emergent adverse event; ULN, upper limit of normal

† TEAEs = Treatment-emergent adverse events. Includes all adverse events that started during the treatment epoch of the primary analysis period (for details, refer to SAP). If due to incomplete date/time, this determination could not be made unambiguously, the AE is assumed to be treatment-emergent.

‡ Includes TEAEs that were identified by the investigator as related or possibly related to the study treatment in the primary analysis period.

§ Includes serious TEAEs that were identified by the investigator as related or possibly related to the study treatment in the primary analysis period.

MedDRA version 23.1 has been used for coding the adverse events.

N=Number of patients treated within each treatment group, n (%)=number and % of patients with at least one TEAE in each category,

Events=number of TEAEs.

Analysis based on 01 March 2021 data cut off

B.2.11.5 *Additional safety endpoints*

Additional safety efficacy endpoints in LTS13632 included change in physical observation, change in neurological observations, and change in key safety biomarkers. These data are provided in Appendix O.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 *Principal findings from the clinical evidence highlighting the clinical benefits of the technology*

The results of the olipudase alfa studies, including the randomised, double-blind, phase II/III ASCEND trial (73), the single-arm phase I/II ASCEND-Peds trial (74), and the long-term LTS13621 study (76), demonstrate that olipudase alfa is an effective treatment option in adult and paediatric patients with ASMD type B and type A/B. Olipudase alfa demonstrated efficacy as an enzyme replacement therapy for patients with ASMD, significantly improving clinical and patient-relevant outcomes versus placebo in adult patients, and versus baseline in paediatric patients. Furthermore, the clinical benefits of olipudase alfa have been validated by clinical expert advisors in a 2022 advisory board, with olipudase alfa described as a '*lifesaving treatment'* with clear improvement in several clinical outcomes, which are surrogate markers for mortality in ASMD (37). The improvement in surrogate markers for mortality was '*expected to be due to the reversal of the disease with olipudase alfa treatmen*t' (37).

Pulmonary impairment is common in patients with ASMD, with respiratory disease a leading cause of death in patients with ASMD type B and A/B (6). Abnormal diffusing capacity is consistent with interstitial lung disease (43), which may manifest with coughing, breathlessness, fatigue and recurrent respiratory infections including pneumonia (25), which has a significant impact on their ability to carry out daily activities and QoL (9, 22). Treatment with olipudase alfa resulted in a significant improvement in DL_{CO} in adults (% predicted) compared with placebo at Week 52 (19.01%; $p<0.001$) (73). A greater number of responders, defined as % predicted DL_{CO} ≥15% at Week 52, were observed with olipudase alfa treatment compared with placebo (27.8% vs 0% respectively) (73). The Connective Tissue Disease- associated interstitial lung disease (CTD-ILD)-OMERACT CTD-ILD working group consensus guideline highlights that a relative 15% change in DL_{CO} constitutes a clinically meaningful change (86). International guidelines indicate a decrease of >15% DL_{CO} in absolute values is associated with increased risk of mortality (91, 92). Treatment with olipudase alfa also resulted in a significant improvement in percent predicted DL_{CO} adjusted for haemoglobin for children at Week 52 (mean increase of 32.94%, relative change from baseline) (74). In patients who were able to perform the test at baseline; improvement was also observed on percent predicted FVC, FEV1, and total lung capacity (74). The improvement in DL_{CO} reflects an improvement in lung function and may prevent manifestations such as shortness of breath, difficulty breathing, chest pain, and recurrent respiratory infections. The improvements in lung function following olipudase alfa treatment would also enable patients to carry out daily activities and fully participate in school/ work.

Significant enlargement of the spleen is often observed in patients with ASMD type B and A/B; it can be indicative of underlying metabolic and haematological pathologies and overall disease severity (2, 40). Patients with an enlarged spleen are at increased risk of splenic rupture, with abdominal pain, eating difficulty and worsening clinical outcomes (6, 7, 25, 38). Furthermore, a patient's QoL is severely impaired due to restricted participation in activities, social exclusion, and bullying (especially for children) (52). In adults, treatment with olipudase alfa resulted in a statistically significant reduction in spleen volume at Week 52 in the olipudase alfa group compared with the placebo group (-39.93%; p<0.0001). Treatment with olipudase alfa resulted in a statistically greater number of responders (≥30% reduction in spleen volume (MN) at Week 52), compared with placebo (94.4% vs 0%, respectively, p=0.002). Gaucher disease is another LSD which has similar symptoms to ASMD. In Gaucher disease, therapeutic goals for splenomegaly include a reduction in spleen volume of 30–50% within Year 1 of enzyme replacement therapy (90). Based on this goal, treatment with olipudase alfa resulted in a clinically meaningful reduction in spleen volume. In the single-arm phase I/II ASCEND-Peds trial, olipudase alfa demonstrated a statistically significant improvement in spleen and liver volume at Week 52, compared with baseline (mean decrease (in MN) of 49.21% and 40.56% for overall paediatric patients, respectively). The improvement in spleen volume may be indicative of an overall reduced severity of ASMD, with a reduced risk of splenic rupture and bleeding. The patient's QoL would also be improved due to no longer looking different to others and being more able to carry out daily activities due to a reduction in the size of the abdomen.

Patients with ASMD type B and A/B often have enlarged livers, which is associated with increased risk of liver dysfunction, cirrhosis, liver failure, portal hypertension, upper GI bleeding and premature death (personal communication; [redacted]) (6). As with an enlarged spleen, an enlarged liver often results in abdominal pain, eating difficulty, and reduced QoL. Treatment with olipudase alfa resulted in a statistically significant reduction in liver volume for adults at Week 52 compared with placebo (-26.60%; p<0.0001) (73). Olipudase alfa also demonstrated a statistically significant improvement in liver volume at Week 52, compared with baseline (mean decrease of 40.56% in MN for overall paediatric patients) (74). Olipudase alfa also improved liver function in adults at Week 52 (ALT: LS mean difference of -33.60%; p=0.006, AST: LS mean difference of -31.60%; p=0.0003) and children, which may result in a reduced risk of complications such as liver failure.

Children with ASMD experience poor growth and development, which can result in delayed bone age, which is indicative of delayed puberty (25). Patients with ASMD also have decreased bone mineral density which can result in skeletal fracture, and results in joint or limb pain (10). Olipudase alfa demonstrated an improvement in height z-scores in children, with a mean overall increase of 0.56 at Week 52, and 0.78 at the end of study at Week 64 in the ASCEND-Peds trial (74). The improvement in height z-scores with olipudase alfa treatment may also indicate normal bone development and reduced risk for skeletal fractures or bone pain. The improvement in height z-scores in paediatric patients following olipudase alfa treatment would greatly improve patients' QoL, as demonstrated with statistically significant improvements in PedsQL subtests. Treatment

with olipudase alfa also significantly improved the QoL of parents. The significant improvement in QoL for children was not reflected in the adult population, which may be due to an increased severity in the paediatric population, and maybe a reduction in 'coping' with their condition over time.

Olipudase alfa has also demonstrated improvement in lipid profiles, including total cholesterol and LDL levels within recommended ranges, which would potentially reduce the risk of CVD, and prevent long-term effects of high cholesterol such as stroke or heart attack (93).

In the ongoing LTS13632 study, currently available long-term follow up data demonstrates durability of olipudase alfa effect. Improvements in spleen volume, liver volume and mean DL_{CO} following olipudase alfa treatment are maintained for adult patients treated up to 7 years and children treated up to 5 years. Olipudase alfa represents an innovative and potentially transformative treatment which will revolutionise the treatment of adults and children with this disease. Olipudase alfa specifically targets the underlying pathology of ASMD and has demonstrated the ability to reverse clinical manifestations of the disease, such as inflammation in the liver and lungs (37). Liver and lung disease are major causes of death in patients with ASMD (37), with the reversal of disease with olipudase alfa treatment potentially delaying the onset of complications, and ultimately death. As there is currently no treatment available for ASMD, olipudase alfa offers patients who otherwise would be given BSC, and continue to deteriorate, a substantial improvement of their condition and the ability to live a more normal life.

Treatment with olipudase alfa could also have a transformative effect for caregivers and patient's families, who would otherwise have reduced QoL as a result of the burden of caring for a person with ASMD and the fear of losing their loved one.

Treatment with olipudase alfa was generally well-tolerated during the phase II/III ASCEND study and the phase I/II ASCEND-Peds study. The majority of TEAEs reported were non-serious, and of mild or moderate severity. There were no TEAEs that led to treatment discontinuation of any patient in any of the olipudase alfa trials. No deaths were reported in any of the trials. Thus, treatment with olipudase alfa results in significant improvement in clinical efficacy outcomes with a favourable safety profile.

B.2.12.2 *Strengths and limitations of the clinical evidence base for the technology*

The clinical development programme for olipudase alfa comprises a series of phase I–III clinical trials in patients with ASMD. To date, one phase II/III study, one phase I/II study, and one phase I study has been completed and one study is ongoing. The clinical development programme for olipudase alfa addresses the decision problem:

- The patient population in the studies includes those of the final scope, including adult and paediatric patients with ASMD type B and type A/B.
- Olipudase alfa is directly compared with placebo in ASCEND, with best supportive care identified as the most relevant comparator in the NICE scope.

- The key outcomes, as outlined in the NICE scope have been evaluated in patients with ASMD, i.e. change in spleen volume, change in lung function, change in liver function, change in neurological observations, change in physical observations, change in biomarkers, mortality, adverse effects of treatment and HRQoL.
- The ASCEND-Peds trial was designed as a single arm trial and is considered relevant to the decision problem as it includes paediatric patients with ASMD types A/B and B. ASMD is a very rare disease with a severely limited number of patients available for this study, as reflected in the 20 patients recruited for the trial. Additionally, paediatric onset of ASMD is often more severe and rapidly progressing , with a significant risk of mortality (7). ASMD is also a progressive disease, for which there is currently no treatment available. Taking all these considerations into account, a single arm trial was deemed appropriate, with the alternative of providing no treatment for these children considered unethical.

The clinical evidence for olipudase alfa has demonstrated the important benefits of this disease-modifying treatment compared with placebo and baseline in several clinically and patient-relevant outcomes including interstitial lung disease and spleen volume. The primary efficacy endpoints included changes in spleen volume and DL_{CO}. Both primary efficacy endpoints are clinically meaningful endpoints in ASMD trials as they are common clinical features of ASMD, contributing to a reduced QoL and increased disease burden (44). The primary endpoint of spleen volume is relevant to the clinical need of patients with ASMD as an enlarged spleen is associated with abdominal pain/discomfort, eating difficulty and diarrhoea, and worsening clinical outcomes for patients. An enlarged spleen is also indicative of underlying metabolic and haematological pathologies, with an increased risk of splenic rupture, bleeding, and ultimately early death. The use of DL_{CO} as a relevant endpoint was also considered appropriate by clinical expert advisors consulted during a 2022 advisory board (37). Furthermore, a targeted literature review conducted in 2020, including publications from the last 5–10 years, supported the use of lung function and spleen volume as clinically meaningful endpoints in ASMD trials (44). Although there is currently no ASMD-specific evidence for the association of a decrease in predicted DL_{CO} and increased mortality, data from other diseases such as chronic lung disease and pulmonary hypertension suggest that the risk of mortality increases 31% with every 10% decrease in predicted DL_{CO} (94); suggesting the primary endpoint of DL_{CO} is relevant to the clinical need of patients with ASMD.

The instruments used to measure HRQoL in the ASCEND study (including EQ-5D-5L and SF-36) may be insensitive to the ASMD population (95). As ASMD is a chronic disease, patients with ASMD may learn to cope with their condition over time, which may limit the responsiveness of the anxiety and depression domain on the EQ-5D-5L and the mental health domain on the SF-36. Patients may also adjust expectations of their usual activities (EQ-5D-5L), kinds of work (SF-36), and levels of accomplishment (SF-36), which may affect the sensitivity of these items.

Interviews of participants in the ASCEND trial show that patients learn to cope with their condition, with one patient stating, “[redacted] (41). Another patient reported, [redacted]” *(41).* The lack of sensitivity with HRQoL instruments for patients with ASMD was validated at the recent global advisory board, with challenges raised including the rare and slow progressive nature of ASMD, hedonic

adaptation, and the small number of patients available (37). Lack of sensitivity with HRQoL instruments in this submission may also be due to the time of follow-up of 52 weeks, with one patient stating “[redacted]” (41). One patient also highlighted that they were unsure whether some of their symptoms improved in the first year (time of measurement) and that they only realised they had improved on reflection at a later date, “[redacted]”” (41). Additionally, patients expressed that the demands of the trial, such as travel and undertaking assessment, may have masked the improvement in fatigue that they then later felt after the trial (41).

ASCEND is a phase II/III randomised, placebo-controlled, double-blinded, multicentre trial with balanced treatment arms, and is therefore robustly designed to assess the safety and efficacy of olipudase alfa. Patients included in the study were equally distributed across treatment groups (n=18 for both treatment groups). However, the placebo treatment group included a greater percentage of females compared with the olipudase alfa treatment group (72% vs 50%). This would not be expected to alter the effect of olipudase alfa treatment on the primary outcomes. Only one patient did not complete the PAP (placebo treatment group) due to poor compliance. The majority of patients included in the study were Caucasian (89%), which closely resembles that of the UK (84.8% in 2019) (96).

While the evidence base clearly demonstrates the clinical value of olipudase alfa in adults and paediatric patients with ASMD, it has some limitations. ASCEND-Peds is a single arm open-label trial, with no comparison to placebo potentially introducing uncertainty to the efficacy of olipudase alfa. However, paediatric onset of ASMD is associated with a poorer prognosis compared to adult onset, with no improvement of the condition expected without an efficacious treatment. Hence, it was considered unethical to include placebo for this population of patients. Treatment with olipudase alfa resulted in the reversal of disease progression, which would be highly unlikely without an efficacious treatment.

While results from the ASCEND and ASCEND-Peds trials were limited to 52 weeks and 64 weeks, respectively, patients previously treated with olipudase alfa are enrolled into a phase II long-term study (LTS13632). The LTS13632 study provides long-term evidence and durability of effect of olipudase alfa. The results of the LTS13632 study to date indicate that the effects of olipudase alfa are maintained up to 6.5 years for adults, and 5 years for paediatric population (76). Although the long-term efficacy of olipudase alfa beyond this timeframe is currently unknown, long-term efficacy and safety follow-up will be performed for LTS13632 up to 9 years or until marketing approval, whichever is sooner.

While the evidence base for olipudase alfa clearly demonstrates the clinical value of olipudase alfa in patients with ASMD, the small number of patients treated with olipudase alfa in ASCEND (n=18), and ASCEND-Peds (n=20), may be considered a limitation. However, despite the small size of the patient population, a clear benefit of treatment with olipudase alfa was demonstrated in adults (compared with placebo) and paediatrics (compared with baseline). Furthermore, the small number of patients is a common limitation with rare diseases, with the number of patients included in the ASCEND and ASCEND-Peds trials comparable to the number of known patients in the UK.

B.3. Cost effectiveness

- A cohort-based Markov model was developed in Excel to evaluate the cost-effectiveness of olipudase alfa for the treatment of ASMD from the perspective of the UK NHS/PSS. Spleen volume and DL_{CO} were used to determine health states.
- Paediatric and adult populations were modelled separately due to difference in natural history. The paediatric only base case compared olipudase alfa with BSC in paediatric patients utilising the ASCEND-Peds trial as the source of clinical characteristics. The adult base case compared olipudase alfa with BSC in adult patients utilising the ASCEND trial as the source of clinical characteristics. An overall combined ICER for both populations was also included.
- The structure of the model and inputs was validated in an advisory board meeting with key UK clinical experts (physicians treating ASMD) (3).
- Deterministic ICERs for olipudase alfa compared with BSC were £103,227 per QALY gained and £194,360 per QALY gained for the paediatric and adult populations respectively (£133,311 per QALY gained across both populations). ICERs were substantially lower when a more severe subgroup was considered: £48,305 per QALY gained and 164,736 per QALY gained for the paediatric and adult populations respectively.
- The model predicts impressive discounted QALY gains of 24.95 in paediatric patients and 16.44 in adult patients despite likely conservative assumptions regarding mortality and patient and family/carer utilities.
- As would be expected, probabilistic sensitivity analyses show a high level of uncertainty. This is inevitable for such a rare disease and as stated in the new NICE manual, there can now be a greater acceptance of uncertainty in specific circumstances: for rare diseases, for medicines treating peadiatric populations and for innovative or complex treatments. As olipudase alfa is an innovative, ultra-orphan medicine that can be used to treat children with ASMD, all three of these circumstances are relevant.
- As stated in NICE's principles (principle 7), recommendations should not be based on the evidence of costs and benefits alone (i.e. cost per QALY). Given the challenges in collecting evidence for such a rare disease, including those associated with the additional burden of collecting evidence from patients and their families, it is not possible for a cost-effectiveness analysis to truly reflect the value of olipudase alfa. The ICERs presented above must be considered alongside the benefits for patients, their families and society that are not captured in the QALY estimates (for example the ability to fully participate in work or education).
- Olipudase has the potential to address a critical unmet need, offering substantial health benefits for a population with high mortality and morbidity where no treatment is currently available. Given the small number of ASMD patients in the UK, decision risk and budget impact are manageable.

- A positive recommendation for olipudase alfa would support innovation (NICE principle 8) and would allow further evidence to be collected to strengthen the evidence base in ASMD.

B.3.1 *Published cost-effectiveness studies*

A SLR was conducted to identify relevant economic evaluations of treatments for patients with ASMD type B and A/B, described in Appendix D. No economic evaluations of treatments for ASMD were identified in the SLR.

B.3.2 *Economic analysis*

The base case evaluates the cost-effectiveness of olipudase alfa versus BSC and is informed primarily by the ASCEND and ASCEND-Peds clinical trials.

B.3.2.1 *Patient population*

The population considered in the base case analysis includes both children (<18 years) and adults (≥18 years) with ASMD types A/B and B, using ASCEND-Peds and ASCEND as the source of clinical characteristics, respectively (Section B.2.3.4).

B.3.2.2 *Intervention technology and comparators*

The intervention of interest to this submission is olipudase alfa. This treatment corresponds to the treatment arm of the ASCEND and ASCEND-Peds trial. Following a dose escalation phase (Table 42), olipudase alfa is administered as an intravenous infusion (IV) at a recommended maintenance dose of 3 mg/kg every 2 weeks. In line with the decision problem, BSC is considered a relevant comparator to this submission.

Table 42: Dose escalation regimen in adult and paediatric patients

Adverse reaction	Adult patients (≥18 years old)	Paediatric patients (0 to <18 years old)
First dose (Day 1/Week 0)	0.1 mg/kg†	0.03 mg/kg†
Second dose (Week 2)	0.3 mg/kg†	0.1 mg/kg†
Third dose (Week 4)	0.3 mg/kg†	0.3 mg/kg†
Fourth dose (Week 6)	0.6 mg/kg†	0.3 mg/kg†
Fifth dose (Week 8)	0.6 mg/kg†	0.6 mg/kg†
Sixth dose (Week 10)	1 mg/kg†	0.6 mg/kg†
Seventh dose (Week 12)	2 mg/kg†	1 mg/kg†
Eighth dose (Week 14)	3 mg/kg† (recommended maintenance dose)	2 mg/kg†
Ninth dose (Week 16)	-	3 mg/kg† (recommended maintenance dose)

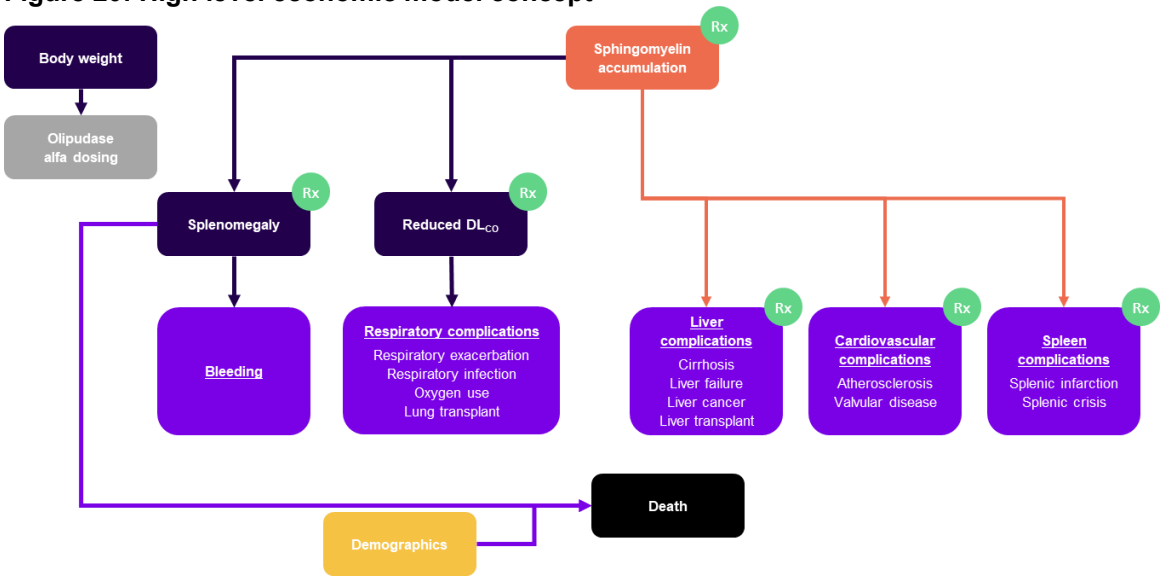
Abbreviations: kg, kilogram; mg, milligram

† Actual body weight will be used for patients with a BMI ≤30. For patients with a BMI >30, an optimal body weight will be used as calculated by: Body weight (kg) to be used for dose calculation = 30 × (actual height in m)^2

B.3.2.3 *Model structure*

A cohort-based Markov model was developed in Microsoft Excel. The model uses a Markov structure with health states defined by patients' spleen volume (SV) and DL_{CO}. Spleen volume and DL_{CO} form the core of the model as they are important predictors of disease progression, with a severe impact on the level of disability and QoL of patients, and thus are the primary efficacy endpoints from the ASCEND trial (2, 7, 44). The clinical relevance of spleen volume and DL_{CO} as primary endpoints for ASMD has also been supported in a recent review by Jones et al, 2020 (44). The model is designed to reflect clinical practice and disease progression of ASMD, with the key aspects of ASMD and the relationships between them outlined in Figure 20. The structure was validated in an advisory board meeting with key UK clinical experts (physicians treating ASMD) (3).

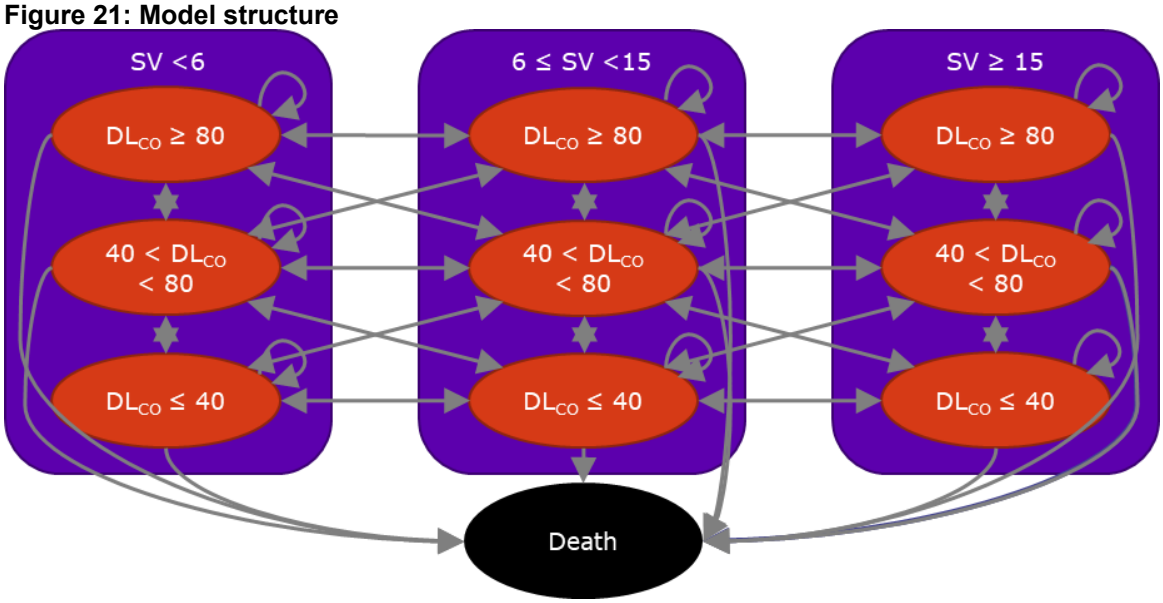
Figure 20: High level economic model concept



Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide

Three levels of SV were modelled: SV <6 MN (mild splenomegaly), 6–15 MN (moderate splenomegaly) and ≥15 MN (severe splenomegaly). Similarly, three levels of DL_{CO} were modelled: DL_{CO} percent predicted ≥80 (mild reduction), 40–80 (moderate reduction) and <40 (severe reduction). Health states in the model were a combination of the three levels each of SV and DL_{CO}, resulting in a total of nine alive health states plus death. A schematic of the model is shown in Figure 21.

Figure 21: Model structure



Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; SV, spleen volume

Patients enter the model distributed over the nine health states based on a combination of their SV and DL_{CO} as observed in the corresponding adult or paediatric clinical trial (ASCEND and ASCEND-Peds, respectively, in the base case) and, in each model cycle, can continue in the same health state or transition to a new health state that shows an improvement or worsening of their symptoms. In the base case, patients receiving olipudase alfa can only transition to a new health state for up to 2 years, after which they transition to the SV <6 / DL_{CO} >80 state until the end of the time horizon or death. Patients entering the model in the BSC group can also continue in the same health state or transition between health states in each cycle. However, in contrast to patients on treatment, those on BSC can transition in every cycle until the end of the time horizon or death. Patients in all health states can die at any point in time due to all-cause mortality, with the risk of death modified by the severity of splenomegaly, estimated by comparing observed mortality data from patients in the SPHINGO-100 study (stratified by spleen volume) to expected age- and sex-adjusted mortality rates in the general population, from US life tables (as the most representative population based on SPHINGO-100 demographics).

Patients receiving olipudase alfa start in a dose-escalation phase, during which their dose is gradually increased up to the highest tolerated dose. The distribution of highest tolerated dose for adults and children is based on the ASCEND (73) and ASCEND-Peds (74) clinical trials, respectively (0.6 mg/kg in 5.6% of adults, 3.0 mg/kg in 94.4% of adults and 100.0% of children). In each cycle, a proportion of patients experience disease-related complications, with the risk of these modified by treatment. The risks of respiratory and bleeding complications are stratified by DL_{CO} and SV, respectively. The risks of liver, spleen, and cardiovascular complications are not stratified by health state, but a direct treatment effect is applied each cycle for those patients on olipudase alfa treatment.

Patient utilities are determined primarily by their health state modified by age, DL_{CO}, and SV, with additional disutilities applied for patients experiencing complications. Caregiver disutilities are determined by treatment, using a proxy based on disutilities for caregivers of non-ventilator-dependent children with Pompe disease (97) due to unavailability of data for ASMD, with an additional caregiver disutility associated with the death of the patient. Caregiver disutility does not depend on the age of the patient, but the number of caregivers differs between children and adults. Costs accounted for in the model include olipudase alfa drug acquisition and administration costs, complication costs, costs of treatment-related AEs, and routine care costs, which are stratified by treatment.

3.2.3.1 Perspective

For this evaluation, a UK NHS/PSS perspective is employed, consistent with the NICE reference case (98).

3.2.3.2 Time horizon

All outcomes were evaluated over a lifetime time horizon in the base-case analysis, with the lifetime age limit set at 100 years of age. A lifetime time horizon was considered appropriate to capture the long-term clinical and economic impacts of olipudase alfa for the treatment of ASMD. The model uses a lifetime horizon of 100 years, after which point it was assumed all patients would have died.

3.2.3.3 Cycle length

To accurately model treatment effect in the first year during which clinical trial data were available, the first two cycles in the model are 6 months in length, with subsequent cycles 12 months in length. The cycle length is also reflective of anticipated UK clinical practice once treatment becomes available, where patients would initially be monitored every 6 months and every 12 months thereafter (personal communication; [redacted]).

3.2.3.4 Discounting

The model assumes an annual discount rate of 3.5% for costs and 1.5% for outcomes in the base case. This reflects the guidance on discount rates in the HM Treasury's Green Book (99) based on the fact that, whilst discounting of costs reflects both the time preference and a wealth effect, the same cannot apply to health and life where there is no wealth effect. In fact, it has been suggested that the value of health and societal expectations of health maintenance are increasing (100, 101), further justifying this approach. In addition, evidence suggests that differential discounting provides a less biased assessment in cases where the benefit are long-term, but the costs are accrued sooner (100, 102) – as in the case of olipudase.

In addition, a scenario analysis was carried out using a discount rate of 1.5% for both costs and effects, considered applicable when treatment restores people who would otherwise die or have very severely impaired life to full or near full health for a very long period (98)..

B.3.3 *Clinical parameters and variables*

B.3.3.1 *Incorporating the clinical data for olipudase alfa and BSC into the model*

3.3.1.1 Additional studies included in the model

A prospective, multicentre, natural history study (SPHINGO-100) was performed to characterise the clinical features, and disease burden over time in children and adults with ASMD (8). The SPHINGO-100 natural history study enrolled 59 patients (31 males and 28 females) with chronic ASMD types A/B and B, ranging from 7–64 years of age across 5 countries between May 2001 and June 2002. The median length of observation was 10.2 years (1.4–11.1). Assessments included patient medical histories, physical examinations, assessments of cardiorespiratory function, clinical laboratory data, liver and spleen volumes, radiographic evaluation of the lungs and bone, and QoL assessments (54)

3.3.1.2 Baseline patient characteristics

Baseline characteristics including age, weight, and the baseline distribution of patients' DL_{CO} and SV were informed by ASCEND-Peds and ASCEND for the adult and paediatric base cases, respectively. The impact of using different data sets was also explored in scenario analyses, with baseline characteristics informed by SPHINGO-100 trial data. A summary of the baseline characteristics used in the model is shown in Table 43.

Table 43: Baseline characteristics by subgroup

Description	ASCEND-Peds	ASCEND
Age (Years)	8	34
Weight (kg)	20.5	64.5
DL_{CO} ≥80%	0.0%	0.0%
DL_{CO} 40 – 80%	88.9%	80.6%
DL_{CO} ≤40%	11.1%	19.4%
Spleen volume <6 MN	0.0%	0.0%
Spleen volume 6–15 MN	40.0%	77.8%
Spleen volume ≥15 MN	60.0%	22.2%

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; kg, kilogram; MN, multiples of normal

Weight of the adult patients was informed by the ASCEND trial, and assumed to be constant over the time horizon (103). For paediatric patients, the Z-score function was derived from using data from the SPHINGO-100 trial for children at 8 years and written as below:

$$Zscore = 2.9625 + 0.0313 * Age^2 - 0.7709 * Age$$

Derived Z-scores were used to determine weight, which was calculated based on the general population mean weight informed by the UK growth chart and Z-score as a quadratic function of age. The average weight by age at 50th percentile was used as a proxy for mean weight

The weight of all children in the model was then derived as: $Mean_{gen\ pop} + SD_{gen\ pop} * Zscore$ (Table 44). Children were assumed to switch to adult weight calculations at 18 years of age, which remained constant thereafter.

Table 44: Children weight for age Z-score coefficients

Coefficient	Value
Intercept	2.9625
Age linear (years)	-0.7709
Age quadratic (years)	0.0313

3.3.1.3 Transition probabilities

Transition probabilities were calculated using multi-stage modelling of patient-level data for olipudase alfa and placebo from four clinical trials and one natural history study:

- DFI13412 – phase 1b trial including five adult patients for up to 26 weeks
- DFI13803 – ASCEND-Peds phase 1/2 trial including 20 paediatric patients for 64 weeks
- LTS13632 –long-term extension of DFI13412 and DFI13803 including 25 adult and paediatric patients for up to 9 years
- DFI12712 – ASCEND phase 2/3 trial including 36 adult patients for up to 52 weeks for the primary analysis, with a total duration of at least 3 years and up to 5 years, 3 months
- SPHINGO-100 – natural history study including 59 patients with ASMD type B, with data collected at baseline, 1 year, and a third time point varying from 5–11 years

The outcomes of the analysis were SV and DL_{CO}, with separate analyses conducted for adult and paediatric patients. Transition probabilities for SV in the first year were differentiated by the first 26 weeks (0–6 months), and subsequent 26 weeks (6–12 months) of the first annual cycle (6–12 months) due to the availability of SV data at these two time points. Transitions in DL_{CO} were not differentiated at 26 weeks, as only 52-week data were available, and an identity matrix was applied so that transitions in DL_{CO} were only differentiated from 52 weeks.

Multi-stage modelling is a method for analysing the movement of patients through different states. The observed outcome is a categorical variable denoting the different states (level of disease). The three states considered for SV were: SV <6 MN, SV 6–15 MN, SV ≥15 MN; and the three states for DL_{CO} were: DL_{CO} <40%, DL_{CO} 40–80%, DL_{CO} ≥80%. The analysis was conducted under the assumption that transitions between states between each cycle would depend only on their current state in that cycle. Transitions between SV and DL_{CO} states were assumed to be independent and were estimated separately.

Transition probabilities for the paediatric patients in the first year were calculated using ASCEND-Peds for olipudase alfa and SPHINGO-100 for BSC. In subsequent years, transition probabilities for olipudase alfa were determined using a combination of ASCEND-Peds and LTS13632, while SPHINGO-100 was used for BSC. Similarly, transition probabilities for adults in the first year were calculated using ASCEND and DF13412 for olipudase alfa and ASCEND and SPHINGO-100 for BSC. In subsequent years, transition probabilities for olipudase alfa were determined using a combination of ASCEND and LTS13632, while SPHINGO-100 was used for BSC.

Patients receiving olipudase alfa can only transition to a new health state for up to 2 years, after which they transition to the SV <6 / DL_{CO} >80 state until the end of the time horizon or death.

The full set of transition probabilities for olipudase alfa is shown in Table 45 and Table 46, and Table 47 and Table 48 for BSC.

Table 45: Transition probabilities SV–olipudase alfa

Start state		End state		
		<6 MN	**6–15 MN**	**≥15 MN**
0–6 Months				
Children	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	26.2%	73.8%	0.0%
	≥15 MN	7.9%	43.6%	48.5%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	36.2%	63.9%	0.0%
	≥15 MN	21.3%	64.5%	14.2%
6–12 Months				
Children	<6 MN	97.6%	2.4%	0.0%
	6–15 MN	11.3%	88.7%	0.0%
	≥15 MN	4.3%	59.3%	36.5%
Adult	<6 MN	97.5%	2.5%	0.0%
	6–15 MN	12.5%	87.5%	0.0%
	≥15 MN	3.5%	45.2%	51.3%
Year 2+				
Children	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	100.0%	0.0%	0.0%
	≥15 MN	100.0%	0.0%	0.0%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	100.0%	0.0%	0.0%
	≥15 MN	100.0%	0.0%	0.0%

Abbreviations: MN, multiples of normal; SV, spleen volume

Table 46: Transition probabilities DL_{CO}–olipudase alfa

Start state		End state		
		≥80%	**40–80%**	**≤40%**
0–6 Months				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
6–12 Months				
Children	≥80%	100.0%	0.0%	0.0%

Start state		End state		
		≥80%	40–80%	≤40%
	40–80%	24.7%	75.3%	0.0%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	6.3%	93.7%	0.0%
	≤40%	2.9%	72.0%	25.1%
Year 2+				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	100.0%	0.0%	0.0%
	≤40%	100.0%	0.0%	0.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	100.0%	0.0%	0.0%
	≤40%	100.0%	0.0%	0.0%

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide

Table 47: Transition probabilities SV–BSC

Start state		End state		
		<6 MN	**6–15 MN**	**≥15 MN**
0–6 Months				
Children	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	0.0%	100.0%	0.0%
	≥15 MN	0.0%	6.0%	94.0%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	6.7%	86.3%	7.0%
	≥15 MN	1.2%	30.4%	68.4%
6–12 Months				
Children	<6 MN	91.5%	8.5%	0.0%
	6–15 MN	0.0%	100.0%	0.0%
	≥15 MN	0.0%	3.1%	96.9%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	1.0%	96.9%	2.0%
	≥15 MN	0.0%	0.0%	100.0%
Year 2+				
Children	<6 MN	83.8%	16.2%	0.0%
	6–15 MN	0.0%	100.0%	0.0%
	≥15 MN	0.0%	6.2%	93.8%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	2.0%	94.0%	4.0%
	≥15 MN	0.0%	0.0%	100.0%

Abbreviations: BSC, best supportive care; MN, multiples of normal; SV, spleen volume

Table 48: Transition probabilities DL_{CO}–BSC

Start state		End state		
		≥80%	**40–80%**	**≤40%**
0–6 Months				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
6–12 Months				
Children	≥80%	52.7%	47.3%	0.0%

Start state		End state		
		≥80%	40–80%	≤40%
	40–80%	21.7%	78.3%	0.0%
	≤40%	8.1%	48.5%	43.3%
Adult	≥80%	38.2%	59.3%	2.5%
	40–80%	3.2%	90.3%	6.5%
	≤40%	0.5%	24.2%	75.3%
Year 2+				
Children	≥80%	93.2%	6.6%	0.2%
	40–80%	0.0%	94.4%	5.6%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	91.2%	8.6%	0.2%
	40–80%	0.0%	95.5%	4.5%
	≤40%	0.0%	8.3%	91.7%

Abbreviations: BSC, best supportive care; DL_{CO}, diffusing capacity for carbon monoxide

3.3.1.4 Mortality

Overall survival was derived using data from the SPHINGO-100 observational study. For patients aged 3 years onwards, a standardised mortality ratio (SMR)-adjusted mortality rate was used. The overall survival was modelled by applying the SMR derived for patients with ASMD with severe splenomegaly (defined as SV ≥15 MN) and patients without severe splenomegaly, from the SPHINGO-100 observational study. The overall SMR was 12.5 [95% CI: 4.3, 20.7], and for patients with and without severe splenomegaly the SMRs were 43.1 and 4.3, respectively. Each year, the risk of ASMD-related mortality was calculated separately for patients with severe splenomegaly (≥15 MN) and for patients without severe splenomegaly (<15 MN), by multiplying the corresponding SMR with the general population mortality at a specific age. Finally, the total mortality in each cycle was estimated based on the proportion of patients in health states with SV <15 MN (SV <6 MN and 6–15 MN) and ≥15 MN and the calculated mortality risk.

The SMRs[a] were estimated by comparing the observed mortality in the SPHINGO-100 natural history study with the expected mortality of the general population in the US (104). The US life tables were used to estimate the SMR since the majority of patients in the SPHINGO-100 study were from North America. The estimated SMR was then applied to the mortality rates of the general population of the UK (105), as a multiplier to calculate the adjusted survival probabilities as shown in Table 49. The full data set is included in Appendix N. This approach assumes that once the SMR is calculated, it is independent of the geographic region. It likely underestimates the impact of ASMD on

[a] The ratio of the observed number of deaths in a study population divided by the number of deaths that would be expected, based on the age- and sex-specific mortality rates in a general population.

mortality, as patients who died prior to the age of six years or diagnosis of ASMD were no accounted for in the analysis. This is in line with the clinical advice received during the advisory board and from communications with a clinical expert stating, that the impact of ASMD on mortality is likely more pronounced than what is predicted using the SMR approach, in particular in the paediatric population (personal communication; [redacted]) (3). In fact, a recent initial analysis based on US data confirms a higher impact of ASMD on mortality in paediatric patients than that shown by SPHINGO-100 (55).

Table 49: Calculation of adjusted survival probabilities for the UK

UK (2016–2018) general population							Survival probabilities-adjusted for ASMD population		
Age (years)	**Probability of dying between ages x and x + 1**	**Number surviving to age x**	**Number dying between ages x and x + 1**	**Person-years lived between ages x and x + 1**	**Total number of person-years lived above age x**	**Expectation of life at age x**	**Probability of dying between ages x and x + 1**	**Number surviving to age x**	**Adjusted Survival Prob**
	q_x	**l_x**	**d_x**	**L_x**	**T_x**	**e_x**	**q_x*SMR**	**lx (ASMD)**	**S_x**
0	0.003874*	100000.0	387.4	99806.30	8106543.8	81.07	0.003874*	100000.0	1.000000
1	0.000240*	99612.6	24.0	99600.62	8006737.5	80.38	0.000240*	99612.60	0.996126
2	0.000133*	99588.6	13.2	99582.02	7907136.9	79.40	0.000133*	99588.64	0.995886
3	0.000106	99575.4	10.6	99570.12	7807554.8	78.41	0.000106 x SMR	99575.40	0.995754
4	0.000086	99564.8	8.6	99560.56	7707984.7	77.42	0.000086 x SMR	99443.43	0.994434
5	0.000087	99556.3	8.7	99551.95	7608424.2	76.42	0.000087 x SMR	99336.51	0.993365
6	0.000077	99547.6	7.7	99543.76	7508872.2	75.43	0.000077 x SMR	99228.46	0.992285
7	0.000068	99539.9	6.8	99536.50	7409328.5	74.44	0.000068 x SMR	99132.31	0.991323
8	0.000065	99533.1	6.5	99529.83	7309792.0	73.44	0.000065 x SMR	99047.41	0.990474
…	…	…	…	…	…	…	…	…	…

Abbreviations: ASMD, acid sphingomyelinase deficiency; SMR, standardised mortality ratio; UK, United Kingdom
* SMR was not applied for age 0–3 years
† ellipses denote ‘and so on’

B.3.4 *Measurement and valuation of health effects*

ASMD has a severe impact on patients' QoL. Clinical manifestations associated with ASMD result in patients being unable to care for themselves, perform common daily activities, and take part in social activities (2, 5, 9). There is also a profound impact on a patient's self-esteem, with a risk of anxiety and depression (39). Children with ASMD experience poor growth and development, which can result in delayed puberty, and increased risk of bone fracture (10). The lack of a disease-modifying treatment, and having to cope with the symptoms of ASMD, results in poor functioning and affects the mental health of many patients.

Families and caregivers of patients with ASMD face a substantial QoL burden (9, 11-13). They have to deal with the worry and grief of the disease progressing and their loved one deteriorating or dying (12). They struggle to maintain relationships, and attend social activities (11). In addition, they face an extreme financial burden due to time spent caregiving and the inability to work (9).

With a view to factoring these patient considerations into the economic appraisal where possible, the following section sets out the data, methods and assumptions used to measure and value health effects.

B.3.4.1 *Health-related quality-of-life data from clinical trials*

HRQoL was estimated by assigning utilities to health states and disutilities to complications and AEs. Utilities assigned to health states (based on SV and DL_{CO}) were stratified by patient age (paediatric and adult). Utility decrements associated with complications and AEs were applied multiplicatively (by multiplying the utility by 1 – decrement).

3.4.1.1 Health state utilities

While EQ-5D-5L and SF-36 data were collected in the ASCEND trial, these instruments lack sensitivity in patients with ASMD. Neither instrument assesses important aspects of ASMD, such as deterioration in pulmonary function and symptoms related to SV (e.g. bleeding and bruising). The lack of sensitivity of these instruments in ASMD is demonstrated by baseline data from ASCEND, which shows that utilities derived from both instruments were lowest (worst) among patients with the least severe ASMD. This may, in part, be due to a lack of sufficiently large sample size to represent different health states within ASMD, which is a common problem in rare diseases as it is often not feasible to recruit large patient populations. Furthermore, as ASMD is a chronic disease, many patients may learn to cope with their condition over time, which may limit the responsiveness of the anxiety and depression domain on the EQ-5D-5L and the mental health domain on the SF-36. Patients may also adjust expectations of their usual activities, kinds of work and levels of accomplishment, which may further affect the sensitivity of these items.

Therefore, to obtain reliable utility estimates, as per NICE guidance (98), for use in cost-effectiveness modelling of treatment for patients with ASMD, health state utilities for children and adults were derived from a vignette study, including [redacted] participants in [redacted] (106). The utility study used health state vignettes based on existing literature reviews, clinical expert opinion, and clinical trial results. The cross-sectional study was conducted in two phases (pilot and main study phase) and involved in-person interviews to evaluate the health states. Based on the results of the pilot study, [redacted] Utility values associated with each health state were summarised with means and 95% CIs. Health state utilities for children and adults can be found in Table 50 and Table 51, respectively.

Table 50: Health state utilities from vignette study-children

Health state	Mean (95% CI)
A1: ASMD without impairment	[redacted]
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]
A4: Mild/moderate ASMD	[redacted]
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]
A9: Severe ASMD	[redacted]

Abbreviations: ASMD, acid sphingomyelinase deficiency; CI, confidence interval; DL_{CO}, diffusing capacity for carbon monoxide

Table 51: Health state utilities from vignette study-adults

Health state	Mean (95% CI)
A1: ASMD without impairment	[redacted]
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]
A4: Mild/moderate ASMD	[redacted]

Health state	Mean (95% CI)
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]
A9: Severe ASMD	[redacted]

Abbreviations: ASMD, acid sphingomyelinase deficiency; CI, confidence interval; DL_{CO}, diffusing capacity for carbon monoxide

3.4.1.2 Utility decrement for complications and adverse events

Disutilities due to complications were extracted from published literature and assumed to be assigned one time at the start of the event. Due to the limited availability of utility data specific to ASMD-related complications, disutilities for complications were sourced from literature on analogue diseases:

- For respiratory complications, a disutility for pneumococcal disease was chosen as a representative respiratory complication. The disutility for respiratory complications was based on the utility for hospitalised pneumonia from a published UK vignette study for pneumococcal and human papillomavirus diseases (107).
- For liver complications, the disutility for decompensated cirrhosis in hepatitis C was taken from a large meta-analysis drawing on data from multiple countries (108). It was also cited in the HST committee papers for ID737 (Sebelipase alfa for treating lysosomal acid lipase deficiency).
- For spleen complications, no utility data were identified for splenic infarction or splenic crisis. Therefore, splenectomy was the closest concept for which utility data were available. The disutility associated with splenectomy in patients with immune thrombocytopenic purpura was used to inform spleen complications (109).
- For cardiovascular complications, the disutility associated with cardiovascular disease was extracted from the published utilities for angina in patients with diabetes-related chronic conditions (110). The reference is widely used in models of cardiovascular disease, diabetes, and related conditions.
- For major bleeding, the utility associated with thrombocytopenia in patients with immune thrombocytopenic purpura in the UK was used to inform major bleeding (111). Immune thrombocytopenic purpura was chosen as the closest proxy as

bleeding in patients with ASMD is also related to thrombocytopenia resulting from splenomegaly.

The duration of hospitalised pneumonia was assumed to be 2 weeks, while for all other complications it assumed to be one year. Utility decrements for complications can be found in Table 52.

Participants in the UK advisory board commented, that these complications likely have long-term consequences for patients with ASMD (3). Modelling these as one-off events can therefore be considered a conservative assumption.

Disutilities due to AEs were not included in the base-case analysis, as the nature of these events (increased alanine aminotransferase, urticaria, rash, anaphylactic reaction, and hypersensitivity) were not assumed to have a long-term additional impact on patient quality of life on top of the SV, DL_{CO} and complication mediated differences in patient QoL (considering the multiplicative approach to utility estimation used in the model).

Table 52: Utility decrement for complications

Complication	Utility decrement	Source
Respiratory	-0.034	Galante et al, 2011(107)
Liver Disease	-0.237	McLernon et al, 2008 (108)
Spleen	-0.080	Snyder et al, 2008 (109)
Cardiovascular Disease	-0.230	Sullivan et al, 2016 (110)
Major Bleeding	-0.129	Szende et al, 2010 (111)

3.4.1.3 Utility decrement for caregivers

Caregiver disutilities are determined by treatment (Table 53), given the treatment-mediated impact on patients' symptoms and manifestations, and the potential reduction in caregiver burden this brings. No caregiver disutilities were identified in the SLR, and therefore conservative estimates were used. Caregiver disutility was assumed the same as for caregivers of non-ventilator-dependent infants with Pompe disease (an inherited LSD with similar symptoms to ASMD, including respiratory difficulties, reduced growth, and fatigue (112) (97). An additional caregiver disutility associated with death was also included and assumed to be -0.5; this specific disutility value was assumed using conservative estimates based on those associated with patient death as used in published cancer models (113).

The model assumes that patients under the age of 18 have an average of 1.8 caregivers per patient, based on the average number of caregivers per child in the UK (105) in line with previous HST appraisals (114, 115); this reduces to 1 caregiver per patient beyond the age of 18, to ensure caregiver disutility estimates are conservative when reflecting patients who have reached adulthood.

Table 53: Utility decrement to caregivers of patients with ASMD type B and A/B

Caregiver's disutility		Spleen volume (MN)		
		1–6	6–15	>15
Olipudase alfa				
DL_{CO}	100–80	0.000	0.000	0.000
	80–40	0.000	0.000	0.000
	<40	0.000	0.000	0.000
BSC				
DL_{CO}	100–80	-0.150	-0.150	-0.150
	80–40	-0.150	-0.150	-0.150
	<40	-0.150	-0.150	-0.150

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; MN, multiples of normal

B.3.4.2 *Mapping*

Mapping was not required, as utility values were directly available from the TTO method used in the vignette study.

B.3.4.3 *Health-related quality-of-life studies*

A SLR was conducted to identify HRQoL studies relevant to the decision problem. The following electronic databases were searched: Embase, MEDLINE, MEDLINE In-Process, and the Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials) databases via Ovid SP. Please see Appendix D for full details of the original search. In total, five studies reporting burden of disease and HRQoL were identified, of which four evaluated measures of HRQoL. No utility data were identified in the SLR. Details of the HRQoL studies identified are available in Appendix H.

B.3.4.4 *Adverse reactions*

The model considers the effects of serious AEs on costs only, as these would be the events assumed to materially impact the resource and cost of the treatment of patients. AEs were stratified by the initial year of treatment (i.e., Year 1) and subsequent years (Table 54). A separate set of AEs were considered for children and adults. The incidence rates of AEs for children were obtained from the ASCEND-Peds and the long-term extension trial, while AEs for adults were estimated from the ASCEND-PAP + ETS study.

The incidence of serious AEs in children was based on the incidence of five events in the ASCEND-Peds and long-term extension study. The events included were increased alanine aminotransferase, urticaria, rash, anaphylactic reaction, and hypersensitivity. The overall incidence was then calculated as an annual probability, based on the duration of each trial. The incidence of AEs for adults was based on the occurrence of serious extrasystoles in the ASCEND-PAP + ETS study, converted to an annual probability. The probability of serious AEs related to treatment can be found in Table 54 below.

Table 54: Serious AE related to treatment

Treatment-related AEs	Year 1	Subsequent Years	Source
Children	8.30%	8.30%	ASCEND-P CSR, LTS13632 CSR (74, 76)
Adults	1.02%	1.02%	ASCEND CSR (73)

Abbreviations: AE, adverse event

The model also considers the effects of disease-related complications on costs and health-related quality of life. The complications included in the model are respiratory, liver, spleen, cardiovascular, and bleeding complications (Table 55 and Table 56). The base annual rate of complications were derived from SPHINGO-302 (116) and odds ratios were derived from SPHINGO-100 (8).

Table 55: Rates of complications

Complications	Complication probabilities			
	Base Annual Rate (116)	RR	BSC	Olipudase Alfa
Liver complications	0.035	0.10	3.4%	2.4%
Spleen complications	0.035	1.00	2.3%	1.6%
Cardiovascular complications	0.023	1.00	3.0%	2.1%

Abbreviations: BSC, best supportive care; RR, relative risk

Table 56: Rates of respiratory and bleeding complications

Respiratory and bleeding complications	Base Annual Rate (116)	OR (8)	Complication probabilities
Respiratory complications			
DL_{CO} ≥80%	0.141	-	13.1%
DL_{CO} 40–80%	-	2.14	26.0%
DL_{CO} ≤40%	-	3.12	35.6%
Bleeding complications			
SV <6 MN	0.027	-	2.7%
SV 6–15 MN	-	1.00	2.7%
SV ≥15 MN	-	2.56	6.7%

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; MN, multiples of normal; OR, odds ratio; SV, spleen volume

B.3.4.5 *Health-related quality-of-life data used in cost-effectiveness analysis*

A summary of the utility data used in the economic model for each health state is provided in Section B.3.4.1.

Table 57: Summary of utility values for cost-effectiveness analysis

State	Utility value	95% confidence interval	Reference in submission (section and page number)	Justification
Health state utilities - children				
A1: ASMD without impairment	[redacted]	[redacted]	Section 3.4.1.1	Health states included were observed in the ASCEND trials, with SV and DL_{CO} affecting clinical outcomes
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]	[redacted]	Section 3.4.1.1	
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A4: Mild/moderate ASMD	[redacted]	[redacted]	Section 3.4.1.1	
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A9: Severe ASMD	[redacted]	[redacted]	Section 3.4.1.1	
Health state utilities – adults				
A1: ASMD without impairment	[redacted]	[redacted]	Section 3.4.1.1	Health states included were observed in the ASCEND trials, with SV and DL_{CO}
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]	[redacted]	Section 3.4.1.1	

State	Utility value	95% confidence interval	Reference in submission (section and page number)	Justification
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	affecting clinical outcomes
A4: Mild/moderate ASMD	[redacted]	[redacted]	Section 3.4.1.1	
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]	[redacted]	Section 3.4.1.1	
A9: Severe ASMD	[redacted]	[redacted]	Section 3.4.1.1	
Utility decrement for complications				
Respiratory	-0.034	NR	Section 3.4.1.2	The complications included are common in patients with ASMD and have been identified as having the most impact on valued quality of life
Liver Disease	-0.237	NR	Section 3.4.1.2	
Spleen	-0.080	NR	Section 3.4.1.2	
Cardiovascular Disease	-0.230	NR	Section 3.4.1.2	
Major Bleeding	-0.129	NR	Section 3.4.1.2	

Abbreviations: ASMD, acid sphingomyelinase deficiency; DL_{CO}, diffusing capacity for carbon monoxide; MN, multiples of normal; NR, not reported; SV, spleen volume
Source: Sanofi data on file

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

B.3.5.1 *Resource identification, measurement and validation studies*

A SLR was conducted to identify resource use and costs data relevant to the decision problem. The following electronic databases were searched: Embase, MEDLINE, MEDLINE In-Process, and the Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials) databases via Ovid SP. Please see Appendix D for full details of the original search. In total, one study (5) identified in the SLR reported baseline annual resource utilisation for the following categories (as detailed in Appendix I):

- Hospital admissions
- Emergency room visits
- Outpatient service use
- Surgical procedures
- Medication/therapy use

B.3.5.2 *Intervention and comparators' costs and resource use*

NHS reference costs (2019–2020) have been used to inform cost inputs for administration costs, monitoring costs, and adverse event management (117).

3.5.2.1 Acquisition costs

Drug unit cost and package information are provided in Table 58. Two vial options, 4 mg and 20 mg were provided in the model. The 4 mg vial is anticipated to become available in the first half of 2023, with an equivalent per mg cost as the 20 mg vial.

Table 58: Drug acquisition costs

Drug name	Unit cost	Unit strength	Package size	Cost per mg
Olipudase alfa	[redacted]	4 mg	1	[redacted]
Olipudase alfa	[redacted]	20 mg	1	[redacted]

Abbreviations: mg, milligram

Annual drug acquisition costs are provided in Table 59. A compliance of 90% for all years was assumed in the model, in line with available trial data (73) and clinical expert opinion (personal communication; [redacted]). Child weight was also assumed to not changed in Year 1. In subsequent years, drug costs are calculated each cycle based on weight.

Table 59: Annual drug acquisition cost

Description	Compliance	Total annual dose	Annual Cost
Children			
Year 1 (escalation + maintenance)	90.0%	1,265 mg	[redacted]
Subsequent years (maintenance)	90.0%	-	-
Adults			
Year 1 (escalation + maintenance)	90.0%	3,822 mg	[redacted]
Subsequent years (maintenance)	90.0%	4,824 mg	[redacted]

3.5.2.2 Administration costs

Cost of dose escalation

During dose escalation, the annual administration cost was calculated from the biweekly cost of dose escalation consisting of a physician visit and any monitoring tests required for dose escalation until HTD was achieved.

Table 60: Cost of annual administration cost during dose escalation (biweekly)

Description	Value
Cost per visit of dose escalation and monitoring (biweekly)	£135.00

Cost of maintenance (subsequent years)

In subsequent years, administration cost was calculated as the weighted average cost based on location of administration, with no cost assumed for independent administration (Table 61). Cost of administration by a nurse was assumed post escalation in Year 1. Cost per administration by nurse was calculated based on a weighted average of mean duration of infusion by dose (Table 62) and the distribution of highest tolerated dose (HTD) patients achieved to estimate the overall mean duration and applied hourly cost. Hourly cost for nurse visit, cost per physician, and hospital outpatient clinic visit was extracted from Unit Costs of Health & Social Care 2020 (118).

Table 61: Cost of maintenance

Location	Children	Adults	Cost per admin/hourly cost
Hospital outpatient clinic	0.0%	0.0%	£135.00
Physicians' office	0.0%	0.0%	£39.00
Home with nurse present	100.0%	100.0%	-
Hourly administration cost for the first 60 min	-	-	£44.00

Location	Children	Adults	Cost per admin/hourly cost
Hourly admin cost after the first 60 min	-	-	£44.00
Independent administration	0.0%	0.0%	£0.00
Other	0.0%	0.0%	£0.00

Source: Unit Costs of Health & Social Care 2020 (118)
Abbreviations: min, minute

Table 62: Mean duration of infusion during maintenance

HTD	Duration of infusion (minutes)	
	Children	Adults
0.03 mg/kg	18	N/A
0.10 mg/kg	35	35
0.30 mg/kg	60	220
0.60 mg/kg	80	220
1.00 mg/kg	100	220
2.00 mg/kg	160	220
3.00 mg/kg	220	220
Mean duration of infusion (minutes)	220	220

Abbreviations: HTD, highest tolerated dose; kg, kilogram; mg, milligram

Annual administration cost

The annual administration cost for Year 1 (escalation and maintenance) and subsequent years (maintenance) is provided in Table 63.

Table 63: Annual administration costs

Description	Annual cost
Children†	
Year 1 (escalation + maintenance)	£3,561.90
Subsequent years (maintenance)	£3,778.16
Adults‡	
Year 1 (escalation + maintenance)	£3,567.87
Subsequent years (maintenance)	£3,778.16

Abbreviations: mg, milligram
† based on ASCEND-Peds
‡ based on ASCEND

B.3.5.3 *Health-state costs and resource use*

Medical management of ASMD is associated with costs that are additional to those directly related to treatment, due to regular or unexpected visits to healthcare providers. Unit costs were informed by National Schedule of Reference Costs 2019–2020 (117). Annual frequencies of resource use were derived from a retrospective cohort analysis conducted using IQVIA Open Claims for patients with confirmed and potential (high probability) ASMD type B. Frequencies of resource use were validated by a UK clinical expert (personal communication; [redacted]). Resource utilisation for treatment of ASMD with either olipudase alfa or BSC are found in Table 64 and Table 65. All resource utilisation estimates were assumed to be the same for patients treated with olipudase alfa and BSC.

Table 64: Annual number of visits and tests

Medical services	Olipudase alfa		BSC		Unit cost
	Children	Adults	Children	Adults	
Healthcare professional visits					
Primary care physician	[redacted]	[redacted]	[redacted]	[redacted]	£39.52
Nurse visits	[redacted]	[redacted]	[redacted]	[redacted]	£42.31
Neurologist	[redacted]	[redacted]	[redacted]	[redacted]	£188.54
Other specialist	[redacted]	[redacted]	[redacted]	[redacted]	£139.31
Physical therapist	[redacted]	[redacted]	[redacted]	[redacted]	£111.30
Other healthcare professional	[redacted]	[redacted]	[redacted]	[redacted]	£0.00
Laboratory tests					
Hepatic function panel	[redacted]	[redacted]	[redacted]	[redacted]	£8.46
Lipid panel	[redacted]	[redacted]	[redacted]	[redacted]	£4.84
Complete blood count	[redacted]	[redacted]	[redacted]	[redacted]	£2.55
Hormone panel (FSH, LH, oestradiol, testosterone, TSH, Free T3, T4)	[redacted]	[redacted]	[redacted]	[redacted]	£1.21
Monitoring tests					
Pulmonary function tests	[redacted]	[redacted]	[redacted]	[redacted]	£157.89
Electrocardiogram	[redacted]	[redacted]	[redacted]	[redacted]	£131.21
Abdominal ultrasound	[redacted]	[redacted]	[redacted]	[redacted]	£94.95
Echocardiogram	[redacted]	[redacted]	[redacted]	[redacted]	£119.09
MRI (abdomen)	[redacted]	[redacted]	[redacted]	[redacted]	£308.78
Chest X-ray	[redacted]	[redacted]	[redacted]	[redacted]	£32.96

Medical services	Olipudase alfa		BSC		Unit cost
	Children	Adults	Children	Adults	
High-resolution computed tomography	[redacted]	[redacted]	[redacted]	[redacted]	£213.02
Coronary angiography	[redacted]	[redacted]	[redacted]	[redacted]	£259.51
Dual-energy X-ray absorptiometry	[redacted]	[redacted]	[redacted]	[redacted]	£77.57
Bone age study	[redacted]	[redacted]	[redacted]	[redacted]	£32.96
Other					
Molecular pathology procedure	[redacted]	[redacted]	[redacted]	[redacted]	£36.85
Ophthalmological exam	[redacted]	[redacted]	[redacted]	[redacted]	£110.93
Pulse oximetry	[redacted]	[redacted]	[redacted]	[redacted]	£205.06
Developmental screening	[redacted]	[redacted]	[redacted]	[redacted]	£332.22

Source: Sanofi (65); National Schedule of NHS costs, 2019 (117)
Abbreviations: BSC, best supportive care; FSH, follicle stimulating hormone; LH, luteinising hormone; MRI, magnetic resonance imaging; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin

Table 65: Proportion of medication and vaccinations

Medical services	Olipudase alfa		BSC		Annual cost per patient
	Children	Adults	Children	Adults	
Medication and vaccinations					
Statins	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bisphosphonates for osteoporosis in adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza vaccine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumococcal pneumonia vaccine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medical services	Olipudase alfa		BSC		Annual cost per patient
	Children	Adults	Children	Adults	
Ace Inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aldosterone Antagonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticoagulants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta Blockers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory impairment					
Bronchodilators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oxygen therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenomegaly					
Wheelchair	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer's Allowance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hoist and home adjustments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spleen Guard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other treatments					
Liver transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Sanofi (65); National Schedule of NHS costs, 2019 (117)
Abbreviations: BSC, best supportive care

Annual cost of routine care by population and treatment arm are shown in Table 66. Unit costs were informed by National Schedule of Reference Costs 2019–2020 (117).

Table 66: Average annual cost of routine care

Care	Olipudase alfa		BSC	
	Children	Adults	Children	Adults
Healthcare professional visits	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring and laboratory tests	[redacted]	[redacted]	[redacted]	[redacted]
Other routine care	[redacted]	[redacted]	[redacted]	[redacted]
Medications and vaccinations	[redacted]	[redacted]	[redacted]	[redacted]
Other treatments	[redacted]	[redacted]	[redacted]	[redacted]
Lung transplant	[redacted]	[redacted]	[redacted]	[redacted]
Liver transplant	[redacted]	[redacted]	[redacted]	[redacted]

Source: National Schedule of NHS costs, 2019 (117)
All costs were inflated to 2021
Abbreviations: BSC, best supportive care

B.3.5.4 *Adverse reaction unit costs and resource use*

B.3.5.4.1 *Adverse reaction costs*

Adverse reaction costs for children were based on the weighted average of national average unit cost and number of events of alanine aminotransferase increase, rash, anaphylactic reaction, urticaria and hypersensitivity. Cost for adults was based on the cost of extrasystoles. Unit costs were informed by National Schedule of Reference Costs 2019–2020 (117). Table 67 shows annual cost of treatment-related AEs.

Table 67: Annual cost of treatment-related AEs

Treatment	Olipudase alfa	BSC
Children		
Year 1	£25.66	£0.00
Subsequent years	£25.66	£0.00
Adults		
Year 1	£10.51	£0.00
Subsequent years	£10.51	£0.00

Source: National Schedule of NHS costs (117)
Abbreviations: AE, adverse event; BSC, best supportive care

3.5.4.2 Complication costs

Complication costs are applied when a specific complication of the disease occurs. Costs were stratified by medical vs. pharmaceutical costs (Table 68). Medical costs were based on weighted average of national average unit cost of events associated with each complication extracted from National Schedule of Reference Costs 2019–2020 and number of events informed from the SPHINGO-302 study. Unit cost of events was derived from the average of cost associated with their HRG codes. Pharmaceutical costs were based on average cost of common treatments used for each complication. Unit costs were extracted from Monthly Index of Medical Specialities Drug Database.

Table 68: Complication costs

Complication	Event cost
Respiratory complication—medical	£694.18
Respiratory complication—pharmaceutical	£1.28
Spleen complication—medical	£1,533.37
Spleen complication—pharmaceutical	£0.00
Liver disease—medical	£1,692.72
Liver disease—pharmaceutical	£35.35
Cardiovascular disease—medical	£1,798.47
Cardiovascular disease—pharmaceutical	£59.26
Major bleeding—medical	£327.64

Source: National Schedule of NHS costs (117)

B.3.6 *Uncertainty*

ASMD is a very rare disease, with approximately 36 patients in the UK. Robust epidemiological data for ASMD are scarce, with no published studies of ASMD epidemiology in the UK. However, personal communication with clinical experts was used to reduce the uncertainty surrounding ASMD epidemiology in the UK (personal communication; [redacted] These estimates have been further supported by the NICE final scope (4), and an advisory board conducted by Sanofi (3).

Uncertainty is inherent in very rare diseases such as ASMD, with the common challenge of generating evidence from sufficiently large cohorts of patients. The low number of patients within clinical trials may affect the reflection of treatment effect. However, the clinical trial results (ASCEND and ASCEND-Peds) show unequivocally the large benefit of olipudase alfa treatment for both adults and children with ASMD. Furthermore, as with many rare diseases, the availability of evidence and published studies is sparse, as evident from the SLR. No economic evaluations of treatments for ASMD were identified in the SLR, with only one study identified that reported economic outcomes. Therefore, UK clinical experts provided validation for assumptions throughout the model, via advisory boards and personal communication. Input from UK clinical experts provides a realistic view of what is occurring in the UK for this condition and enables a greater understanding of the wide range of symptoms and healthcare interventions for this condition within the UK. The natural history of ASMD was also investigated, including long-term outcomes and mortality, using a number of sources, including the Sanofi sponsored SPHINGO-100 study (8, 54).

Measuring HRQoL for patients with ASMD is also challenging. Generic QoL instruments such as EQ-5D and SF-36, do not appear to fully capture the effect of ASMD on patients' QoL (as discussed in Section B.3.4). Although some measurements included in the instruments are relevant, such as pain, symptoms specifically related to patients with ASMD such as SV, which can dramatically affect a patient's life, are missing from these instruments. Patients have expressed that symptoms with the most impact to their QoL include a distended abdomen, which may not be included in the generic instruments, with one patient stating, [redacted] (41). However, to account for the uncertainty of the HRQoL data obtained from ASMD clinical trials, and to obtain reliable utility estimates for use in the cost effectiveness model, health state utilities were derived from a vignette study. This allowed for a greater number of participants to be included, and also to include ASMD specific measurements.

B.3.7 *Managed access proposal*

Not applicable.

B.3.8 *Summary of base-case analysis inputs and assumptions*

A summary of all the inputs used in the economic model is provided in Table 69. Base case results are reported in tables and figures.

B.3.8.1 *Summary of base-case analysis inputs*

A list of all variables used in the economic analysis is provided in Table 69 and Table 70.

Table 69: Summary of variables applied in the economic model for paediatric base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
Baseline patient characteristics			
Age (Years)	8	Normal	Table 43
Weight (kg)	20.5	Normal	
DL_{CO} >80%	0.0%	Normal	
DL_{CO} 40–80%	88.9%	Normal	
DL_{CO} ≤40%	11.1%	Normal	
Spleen volume <6 MN	0.0%	Normal	
Spleen volume 6–15 MN	40.0%	Normal	
Spleen volume ≥15 MN	60.0%	Normal	
Children weight for age Z-score coefficients			
Intercept	2.9625312	Normal	Table 44
Age linear (years)	-0.7708681	Normal	
Age quadratic (years)	0.0313266	Normal	
Transition probabilities			
Spleen volume 0-6 months Olipudase alfa			Table 45 - Table 48
Start state	**End state**		
	<6 MN	**6–15 MN**	**≥15 MN**
<6 MN	100.0%	0.0%	0.0%
6–15 MN	26.2%	73.8%	0.0%
≥15 MN	7.9%	43.6%	48.5%
Spleen volume 6-12 months Olipudase alfa			
Start state	**End state**		

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
	<6 MN	**6–15 MN**	**≥15 MN**	
<6 MN	97.6%	2.4%	0.0%	
6–15 MN	11.3%	88.7%	0.0%	
≥15 MN	4.3%	59.3%	36.5%	
Spleen volume year 2+ Olipudase alfa				
Start state	**End state**			
	<6 MN	**6–15 MN**	**≥15 MN**	
<6 MN	100.0%	0.0%	0.0%	
6–15 MN	100.0%	0.0%	0.0%	
≥15 MN	100.0%	0.0%	0.0%	
Spleen volume 0-6 months BSC				
Start state	**End state**			
	<6 MN	**6–15 MN**	**≥15 MN**	
<6 MN	100.0%	0.0%	0.0%	
6–15 MN	0.0%	100.0%	0.0%	
≥15 MN	0.0%	6.0%	94.0%	
Spleen volume 6-12 months BSC				
Start state	**End state**			
	<6 MN	**6–15 MN**	**≥15 MN**	
<6 MN	91.5%	8.5%	0.0%	
6–15 MN	0.0%	100.0%	0.0%	
≥15 MN	0.0%	3.1%	96.9%	
Spleen volume year 2+ BSC				
Start state	**End state**			
	<6 MN	**6–15 MN**	**≥15 MN**	
<6 MN	83.8%	16.2%	0.0%	
6–15 MN	0.0%	100.0%	0.0%	
≥15 MN	0.0%	6.2%	93.8%	
DL_{CO} 0-6 months Olipudase alfa				Table 45 - Table 48

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	100.0%	0.0%	0.0%	
40–80%	0.0%	100.0%	0.0%	
≤40%	0.0%	0.0%	100.0%	
DL_{CO} 6-12 months Olipudase alfa				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	100.0%	0.0%	0.0%	
40–80%	24.7%	75.3%	0.0%	
≤40%	0.0%	0.0%	100.0%	
DL_{CO} year 2+ Olipudase alfa				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	100.0%	0.0%	0.0%	
40–80%	100.0%	0.0%	0.0%	
≤40%	100.0%	0.0%	0.0%	
DL_{CO} 0-6 months BSC				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	100.0%	0.0%	0.0%	
40–80%	0.0%	100.0%	0.0%	
≤40%	0.0%	0.0%	100.0%	
DL_{CO} 6-12 months BSC				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	52.7%	47.3%	0.0%	
40–80%	21.7%	78.3%	0.0%	
≤40%	8.1%	48.5%	43.3%	

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
DL_{CO} year 2+ BSC				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	93.2%	6.6%	0.0%	
40–80%	0.0%	94.4%	5.6%	
≤40%	0.0%	0.0%	100.0%	
Health state utilities				
A1: ASMD without impairment	[redacted]		Beta	Table 50
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]			
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]			
A4: Mild/moderate ASMD	[redacted]			
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]			
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]			
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]			
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
A9: Severe ASMD	[redacted]		
Utility decrement for complications			
Respiratory	-0.034	Beta	Table 52
Liver Disease	-0.237		
Spleen	-0.080		
CVD	-0.230		
Major Bleeding	-0.129		
Caregiver's disutility			
Caregiver disutility: olipudase alfa	0.000	Beta	Table 53
Caregiver disutility: BSC	-0.150		Table 53
Caregiver disutility associated with death	-0.500	Beta	Section 3.4.1.3
Serious AE related to treatment			
Treatment related AE Year 1	8.30%	Normal	Table 54
Treatment related AE subsequent years			
Rates of complications			
Liver complications BSC	3.4%	Normal	Table 55
Liver complications olipudase alfa	2.4%		
Spleen complications BSC	2.3%		
Spleen complications olipudase alfa	1.6%		
Cardiovascular complications BSC	3.0%		
Cardiovascular complications olipudase alfa	2.1%		
Respiratory complication probabilities			
DL_{CO} ≥80%	13.1%	Normal	Table 56
DL_{CO} 40–80%	26.0%		
DL_{CO} ≤40%	35.6%		
Bleeding complication probabilities			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
SV <6 MN	2.7%	Normal	Table 56
SV 6–15 MN	2.7%		
SV ≥15 MN	6.7%		
Complication costs			
Respiratory complication—medical	£694.18	Gamma	Table 68
Respiratory complication—pharmaceutical	£1.28		
Spleen complication—medical	£1,533.37		
Spleen complication—pharmaceutical	£0.00		
Liver disease—medical	£1,692.72		
Liver disease—pharmaceutical	£35.35		
Cardiovascular disease—medical	£1,798.47		
Cardiovascular disease—pharmaceutical	£59.26		
Major bleeding—medical	£327.64		
Drug acquisition unit costs			
Olipudase alfa 4 mg	[redacted]	Constant	Table 58
Olipudase alfa 20 mg	[redacted]		
Cost of maintenance			
Hospital outpatient clinic	£135.00	Gamma	Table 61
Physicians' office	£39.00		
Home with nurse present	-		
Hourly admin cost for the first 60 min	£44.00		
Hourly admin cost after the first 60 min	£44.00		

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
Independent administration	£0.00			
Other	£0.00			
Annual administration costs				
Year 1 (escalation + maintenance)	£3,561.90		Gamma	Table 63
Subsequent years (maintenance)	£3,788.16			
Routine care costs				
	Olipudase alfa	**BSC**	Gamma	Table 66
Healthcare professional visits	[redacted]	[redacted]		
Monitoring and laboratory tests	[redacted]	[redacted]		
Other routine care	[redacted]	[redacted]		
Medications and vaccinations	[redacted]	[redacted]		
Other treatments	[redacted]	[redacted]		
Lung transplant	[redacted]	[redacted]		
Liver transplant	[redacted]	[redacted]		
Treatment related AE cost				
Year 1	£25.66		Gamma	Table 67
Subsequent years	£25.66			

Abbreviations: AE, adverse event; ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; CI, confidence interval; DL_{CO}, diffusing capacity for oxygen; kg, kilogram; mg, milligram; MN, multiples of normal;

Table 70: Summary of variables applied in the economic model for adult base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
Baseline patient characteristics			
Age (Years)	34	Normal	Table 43
Weight (kg)	64.52	Normal	
DL_{CO} >80%	0.0%	Normal	

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
DL_{CO} 40–80%	80.6%		Normal	
DL_{CO} ≤40%	19.4%		Normal	
Spleen volume <6 MN	0.0%		Normal	
Spleen volume 6–15 MN	77.8%		Normal	
Spleen volume ≥15 MN	22.2%		Normal	
Transition probabilities				
Spleen volume 0-6 months Olipudase alfa				Table 45 - Table 48
	End state			
Start state	**<6 MN**	**6–15 MN**	**≥15 MN**	
<6 MN	100.0%	0.0%	0.0%	
6–15 MN	36.2%	63.9%	0.0%	
≥15 MN	21.3%	64.5%	14.2%	
Spleen volume 6-12 months Olipudase alfa				
	End state			
Start state	**<6 MN**	**6–15 MN**	**≥15 MN**	
<6 MN	97.5%	2.5%	0.0%	
6–15 MN	12.5%	87.5%	0.0%	
≥15 MN	3.5%	45.2%	51.3%	
Spleen volume year 2+ Olipudase alfa				
	End state			
Start state	**<6 MN**	**6–15 MN**	**≥15 MN**	
<6 MN	100.0%	0.0%	0.0%	
6–15 MN	100.0%	0.0%	0.0%	
≥15 MN	100.0%	0.0%	0.0%	
Spleen volume 0-6 months BSC				
	End state			
Start state	**<6 MN**	**6–15 MN**	**≥15 MN**	
<6 MN	100.0%	0.0%	0.0%	

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
6–15 MN	6.7%	86.3%	7.0%	
≥15 MN	1.2%	30.4%	68.4%	
Spleen volume 6-12 months BSC				
Start state	**End state**			
	<6 MN	**6–15 MN**	**≥15 MN**	
<6 MN	100.0%	0.0%	0.0%	
6–15 MN	1.0%	96.9%	2.0%	
≥15 MN	0.0%	0.0%	100.0%	
Spleen volume year 2+ BSC				
Start state	**End state**			
	<6 MN	**6–15 MN**	**≥15 MN**	
<6 MN	100.0%	0.0%	0.0%	
6–15 MN	2.0%	94.0%	4.0%	
≥15 MN	0.0%	0.0%	100.0%	
DL_{CO} 0-6 months Olipudase alfa				Table 45 - Table 48
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	100.0%	0.0%	0.0%	
40–80%	0.0%	100.0%	0.0%	
≤40%	0.0%	0.0%	100.0%	
DL_{CO} 6-12 months Olipudase alfa				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	100.0%	0.0%	0.0%	
40–80%	6.3%	93.7%	0.0%	
≤40%	2.9%	72.0%	25.1%	
DL_{CO} year 2+ Olipudase alfa				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
≥80%	100.0%	0.0%	0.0%	
40–80%	100.0%	0.0%	0.0%	
≤40%	100.0%	0.0%	0.0%	
DL_{CO} 0-6 months BSC				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	100.0%	0.0%	0.0%	
40–80%	0.0%	100.0%	0.0%	
≤40%	0.0%	0.0%	100.0%	
DL_{CO} 6-12 months BSC				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	38.2%	59.3%	2.5%	
40–80%	3.2%	90.3%	6.5%	
≤40%	0.5%	24.2%	75.3%	
DL_{CO} year 2+ BSC				
Start state	**End state**			
	≥80%	**40–80%**	**≤40%**	
≥80%	91.2%	8.6%	0.2%	
40–80%	0.0%	95.5%	4.5%	
≤40%	0.0%	8.3%	91.7%	
Health state utilities				
A1: ASMD without impairment	[redacted]		Beta	Table 50
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]			
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]			
A4: Mild/moderate ASMD	[redacted]			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]		
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]		
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]		
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]		
A9: Severe ASMD	[redacted]		
Utility decrement for complications			
Respiratory	-0.034	Beta	Table 52
Liver Disease	-0.237		
Spleen	-0.080		
CVD	-0.230		
Major Bleeding	-0.129		
Caregiver's disutility			
Caregivers disutility olipudase alfa	0.000		Table 53
Caregivers disutility BSC	-0.150		Table 53
Caregivers disutility associated with death	-0.500		Section 3.4.1.3
Serious AE related to treatment			
Treatment related AE Year 1	1.02%	Normal	Table 54
Treatment related AE subsequent years			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
Rates of complications			
Liver complications BSC	3.4%	Normal	Table 55
Liver complications olipudase alfa	2.4%		
Spleen complications BSC	2.3%		
Spleen complications olipudase alfa	1.6%		
Cardiovascular complications BSC	3.0%		
Cardiovascular complications olipudase alfa	2.1%		
Respiratory complication probabilities			
DL_{CO} ≥80%	13.1%	Normal	Table 56
DL_{CO} 40–80%	26.0%		
DL_{CO} ≤40%	35.6%		
Bleeding complication probabilities			
SV <6 MN	2.7%	Normal	Table 56
SV 6–15 MN	2.7%		
SV ≥15 MN	6.7%		
Complication costs			
Respiratory complication—medical	£694.18	Gamma	Table 68
Respiratory complication—pharmaceutical	£1.28		
Spleen complication—medical	£1,533.37		
Spleen complication—pharmaceutical	£0.00		
Liver disease—medical	£1,692.72		
Liver disease—pharmaceutical	£35.35		
Cardiovascular disease—medical	£1,798.47		

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
Cardiovascular disease—pharmaceutical	£59.26			
Major bleeding—medical	£327.64			
Drug acquisition unit costs				
Olipudase alfa 4 mg	[redacted]		Constant	Table 58
Olipudase alfa 20 mg	[redacted]			
Cost of maintenance				
Hospital outpatient clinic	£135.00		Gamma	Table 61
Physicians' office	£39.52			
Home with nurse present	-			
Hourly admin cost for the first 60 min	£44.00			
Hourly admin cost after the first 60 min	£44.00			
Independent administration	£0.00			
Other	£0.00			
Annual administration costs				
Year 1 (escalation + maintenance)	£3,561.90		Gamma	Table 63
Subsequent years (maintenance)	£3,788.16			
Routine care costs				
	Olipudase alfa	**BSC**	Gamma	Table 66
Healthcare professional visits	[redacted]	[redacted]		
Monitoring and laboratory tests	[redacted]	[redacted]		
Other routine care	[redacted]	[redacted]		
Medications and vaccinations	[redacted]	[redacted]		
Other treatments	[redacted]	[redacted]		
Lung transplant	[redacted]	[redacted]		

Variable	Value (reference to appropriate table or figure in submission)		Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to table/figure in submission
Liver transplant	[redacted]	[redacted]		
Treatment related AE cost				
Year 1	£10.51		Gamma	Table 67
Subsequent years	£10.51			

Abbreviations: AE, adverse event; ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; CVD, cardiovascular disease; DL_{CO}, diffusing factor for carbon monoxide; kg, kilogram; mg, milligram; MN, multiples of normal; SV, spleen volume.

B.3.8.2 *Assumptions*

Assumptions used in the economic model and the rationale for each assumption are provided in Table 71.

Table 71: Assumptions used in the economic model

Area	Assumption	Justification
Time horizon	Lifetime time horizon with cut off at 100 years	A lifetime time horizon was considered appropriate to capture the long-term clinical and economic impacts of olipudase alfa for the treatment of ASMD, as per the NICE guide to the methods of technology appraisal (98). The lifetime horizon was set at 100 years, after which point it was assumed all patients would have died.
Model cycle length	6 months for the first two model cycles and 1 year for subsequent cycles	The model cycle length was 6 months for the first two model cycles to accurately model treatment effect in the first year during which clinical trial data were available. The cycle length is also reflective of anticipated UK clinical practice once treatment becomes available, where patients would initially be monitored every 6 months and then every year (personal communication; [redacted]).
Discount rate	3.5% for costs and 1.5% for outcomes	Based on stipulations in HM Treasury's Green Book and potentially increasing value of health (99) .
Patient population and characteristics	Children assumed to switch to adult weight at 18 years of age	This is in line with the SmPC for olipudase alfa, which assumes a switch to adult dosing at 18 years of age. Children are assumed to have clinically developed into adulthood by age 18. This was a simplifying assumption.
Transition probabilities	Transitions between SV and DL_{CO} states assumed to be independent	This was a simplifying assumption designed to reduce the number of parameters needing to be estimated.

Area	Assumption	Justification
	Patients receiving olipudase alfa only transition to a new health state for up to 2 years, after which they transition to the SV <6 / DL_{CO} >80 state until the end of the time horizon or death	Two years of data are available from clinical trial data for olipudase alfa (ASCEND (73) and ASCEND-Peds (74)), after which assumption is used to reallocate patients to states. Two years of data are available from clinical trial data for olipudase alfa (ASCEND (73) and ASCEND-Peds (74)), after which assumption is used to reallocate patients to states.
Overall survival vs general population	SMR of 4.3 and 43.1 used for patients without and with severe splenomegaly, respectively	Best available data comes from an analysis of data from the observational natural history study SPHINGO-100 (54). In line with advice from clinical experts, this likely underestimates the impact of ASMD on mortality and therefore is a conservative assumption.
Treatment duration	Lifetime	This is in line with the SmPC for olipudase alfa.
	No discontinuation, 90% compliance	As olipudase alfa is administered in a healthcare setting, compliance is assumed to be 90%, in line with trial data. This was validated by a UK clinical expert (personal communication; [redacted]).
Caregiver utilities	Caregiver disutility value is assumed the same as Pompe disease and cancer	Conservative assumption on caregiver disutility based on published cancer models: • Caregiver -0.16 (79) • Due to death -0.6 (119)
	Caregiver disutility assumed relevant for adult patients, but number of caregivers reduced to 1.0 versus 1.8 in children	This is a conservative assumption. 1.8 paediatric caregivers based on ONS data and used in HST11 (120) 1 adult caregiver has been used previously in published studies for other diseases

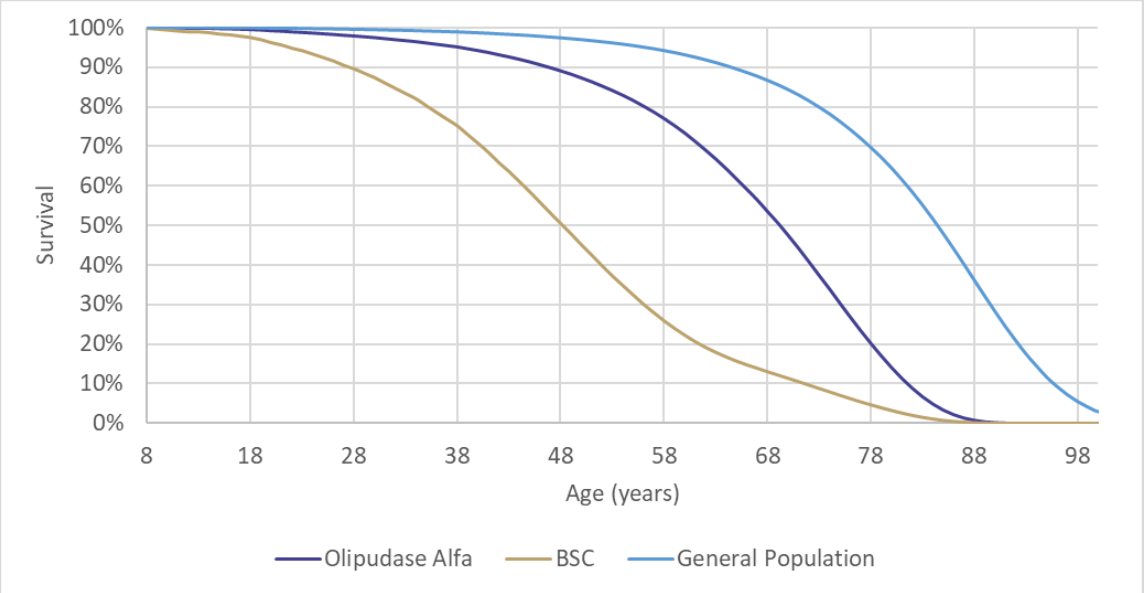
Area	Assumption	Justification
Resource utilisation	Resource utilisation estimates were assumed to be the same for patients treated with olipudase alfa or BSC in the base case	The assumption for medication costs is considered conservative as treatment with olipudase alfa would be expected to decrease these. Frequencies for resource utilisation were validated by a UK clinical expert (personal communication; [redacted]).
Costs	Cost of administration by a nurse was assumed post escalation in Year 1	Cost was calculated based on location of administration. The escalation phase includes a physician visit and any monitoring tests required for dose escalation. During the maintenance phase of treatment, olipudase alfa may be administered at home with an HCP present.

Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; DL_{CO}, diffusing capacity for carbon monoxide; HCP, healthcare practitioner; NICE, National Institute for Health and Care Excellence; SmPC, summary of product characteristics; SV, spleen volume; UK, United Kingdom

B.3.9 *Base-case results*

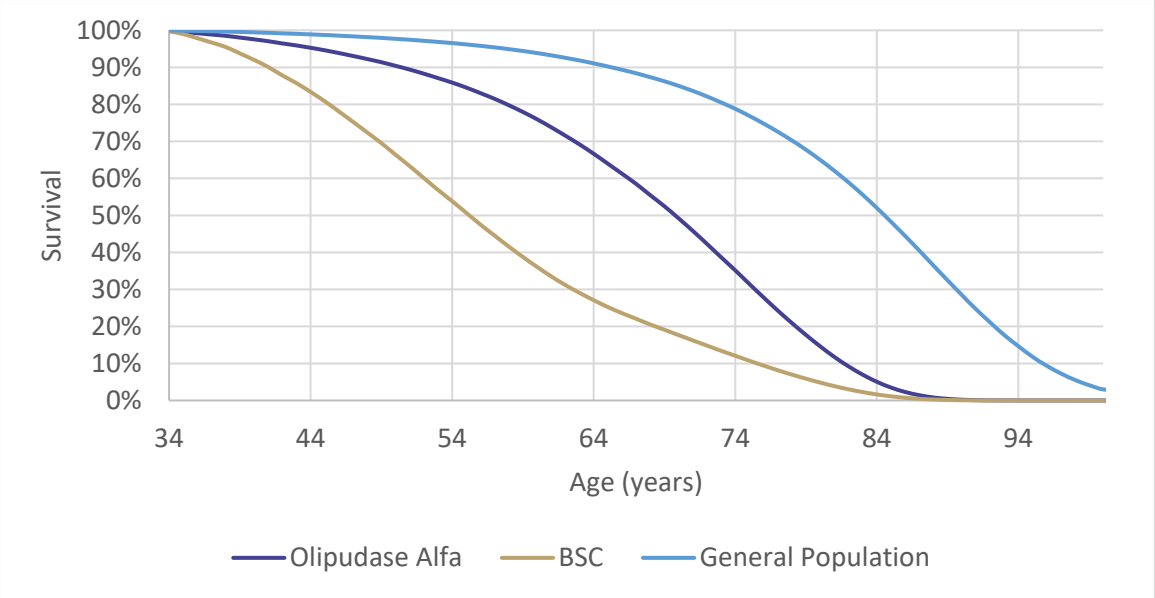
Overall survival curves for the base case paediatric and adult populations are presented in Figure 22 and Figure 23: respectively.

Figure 22: Model projections of survival for children treated with olipudase alfa, BSC, and the general population



Abbreviations: BSC, best supportive care

Figure 23: Model projections of survival for adults treated with olipudase alfa, BSC, and the general population



Abbreviations: BSC, best supportive care

B.3.9.1 *Base-case incremental cost effectiveness analysis results*

Base case results for the paediatric, adult, and combined overall population are presented in Table 72.

Table 72: Base-case (deterministic) results

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/QALY)	ICER (£/Weighted QALY
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Weighted QALYs		
Paediatric	Olipudase alfa	[redacted]	[redacted]	24.41	[redacted]	[redacted]	24.95	74.86	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-0.54	[redacted]	[redacted]	–	–		
Adult	Olipudase alfa	[redacted]	[redacted]	6.66	[redacted]	[redacted]	16.44	36.89	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-9.77	[redacted]	[redacted]	–	–		
Combined	Olipudase alfa	[redacted]	[redacted]	15.54	[redacted]	[redacted]	20.69	55.88	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-5.16	[redacted]	[redacted]	–	–		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

In the combined population, olipudase alfa is estimated to offer a high per-patient incremental health benefit. Base case results discounted at 3.5% for costs and 1.5% for outcomes show that olipudase alfa provides an increase in life years (LYs) and QALYs compared to BSC ([redacted] LYs and 15.54 QALYs for olipudase alfa vs [redacted]LYs and -5.16 QALYs for BSC). The estimated incremental cost-effectiveness ratio (ICER) for olipudase alfa vs BSC is [redacted] per unweighted QALY gained and [redacted] per weighted QALY gained.

Clinical outcomes from the model and estimated disaggregated results are presented in Appendix J.

B.3.10 *Exploring uncertainty*

B.3.10.1 *Probabilistic sensitivity analysis*

3.10.1.1 Inputs

In order to assess the overall effect of parameter uncertainty on the model outcomes, probabilistic sensitivity analysis (PSA) was conducted. Key model parameters were assigned to statistical distributions based on the parameter type and the expected uncertainty around the default parameter values. A total of one thousand simulations were performed during the PSA as this quantity of simulations proved to be sufficient in producing convergent results. The distributions used are presented in Table 73.

Table 73: Distributions used for model parameters in PSA

Model parameter	Distributions used
Patient baseline characteristics	• Starting age: normal distribution • Adult weight: normal distribution
Children weight for age Z-score parameters	Children weight for age Z-score parameters were varied assuming a normal distribution
Transition probabilities	Sampled from a Dirichlet distribution
Highest tolerated dose	Highest tolerated dose for children and adults was sampled from a Dirichlet distribution
Drug acquisition costs	Compliance-maintenance for children and adults was sampled from a beta distribution
Administration costs	• Cost per visit of dose escalation and monitoring (biweekly): Gamma • Admin cost by nurse - first 60 min: Gamma • Admin cost by nurse - after first 60 min: Gamma • Admin cost - hospital outpatient clinic: Gamma • Admin cost - physicians office: Gamma • Admin cost - independent admin: Gamma • Admin cost – other: Gamma
Complications rates	• Respiratory base rate - DL_{CO} ≥80%: Normal • Respiratory OR - DL_{CO} 40-80%: Normal • Respiratory OR - DL_{CO} ≤40%: Normal

Model parameter	Distributions used
	• Bleeding base rate - SV <6 MN: Normal • Bleeding OR - SV 6-15 MN: Normal • Bleeding OR - SV ≥15 MN: Normal • base rate - Liver complications: Normal • base rate - Spleen complications: Normal • base rate - CV complications: Normal • RR - Liver complications: Normal • RR - Spleen complications: Normal • RR - CV complications: Normal
Complication costs	• Respiratory complication – medical: Gamma • Respiratory complication – pharmaceutical: Gamma • Spleen complication – medical: Gamma • Spleen complication – pharmaceutical: Gamma • Liver disease – medical: Gamma • Liver disease – pharmaceutical: Gamma • CVD – medical: Gamma • CVD – pharmaceutical: Gamma • Major bleeding – medical: Gamma
Treatment related adverse events	• TRAE rates: Normal • TRAE costs- SAEs related to treatment – child: Gamma • TRAE costs – SAEs related to treatment – adult: Gamma
Routine care costs	Routine care costs including healthcare professional visits, monitoring and laboratory tests, other routine care, medications and vaccinations, other treatments, lung transplant, liver transplant were sample from gamma distributions
Health state utilities	Health state utilities for children and adults were sampled from a beta distribution
Complication and adverse events disutilities	Complication disutilities and AE disutilities were sampled from a beta distribution
Caregivers disutilities	Caregiver disutilities were sampled from a beta distribution
Mortality	SMR with and without severe splenomegaly were varied using a normal distribution

Abbreviations: AE, adverse events; CV, cardiovascular; CVD, cardiovascular disease; DL_{CO}, diffusing capacity for carbon monoxide; MN, multiples of normal; SAE, serious adverse event; SMR, standardised mortality ratio; SV, spleen volume; TRAE, treatment related adverse event;

3.10.1.2 Results

Paediatric population

The PSA cost-effectiveness plane, and the cost effectiveness acceptability for the paediatric population is presented in Figure 24 and Figure 25, respectively. With a

willingness to pay threshold of [redacted], the CE probability was [redacted] for the paediatric population.

Figure 24: [redacted]

Figure 25: [redacted]

Adult population

The PSA cost-effectiveness plane, and the cost effectiveness acceptability for the paediatric population is presented in Figure 26 and Figure 27, respectively. With a willingness to pay threshold of [redacted], the CE probability was [redacted] for the adult population.

Figure 26: [redacted]

Figure 27: [redacted]

As would be expected, the probabilistic sensitivity analyses show a high level of decision uncertainty. This is inevitable for such a rare disease and as per the new NICE manual there can now be a greater acceptance of uncertainty in specific circumstances. This can be considered for rare diseases, for medicines treating paediatric populations and for innovative or complex treatments. As olipudase alfa is an innovative, ultra-orphan medicine that can be used to treat children with ASMD, all three of these circumstances are relevant to this appraisal.

B.3.10.2 *Deterministic sensitivity analysis*

Deterministic sensitivity analyses (DSAs) were conducted to explore the impact of changing assumptions concerning key model parameter values on the plausible ICER. Tornado diagrams, in which a numerical variable is varied over a specified range in order to measure its impact on cost-effectiveness, were generated. Parameters included in tornado diagrams were varied by ±20% of the base case in order to assess the relative impact of these parameters on the cost-effectiveness estimates.

Parameters varied in the univariate sensitivity analysis were:

- Patient baseline characteristics
- Drug acquisition costs
- Administration costs
- Complication costs
- Treatment related adverse events
- Routine care costs
- Utilities
- Mortality

The results for the DSA for the overall paediatric and adult populations for olipudase alfa vs BSC are presented in Figure 28 and Figure 29, respectively. Drivers of the cost-effectiveness model that had the greatest effect on ICER outcomes for both the paediatric and adult population included drug unit cost, adult weight, compliance of adults during the maintenance phase, and health state utilities for adults and children. In comparison, the remaining parameters are seen to have a much smaller effect on cost-effectiveness model outcomes.

Figure 28: [redacted]

Figure 29: [redacted]

B.3.10.3 *Scenario analysis*

Scenarios evaluated are summarised in Table 74.

Table 74: Scenario analyses conducted in the paediatric and adult population, and rationale

Scenario	Rationale
1.5% discount rate for costs	The NICE guide to the methods of technology appraisal specifies that, when treatment restores people who would otherwise die or have very severely impaired life to full or near full health for a very long period, a discount rate of 1.5% may be used (98).
Alternative mortality assumptions based on McGovern et al (2013) (7)	To assess the impact of alternative mortality assumptions and modelling based on data in published literature
Discontinuation in Week 80 of rate of 5.56%	To reflect the patients in the ASCEND trial who discontinued during the extended trial period in the adult portion of the cohort.
Patient compliance increased to 95%	To determine the effect of a higher compliance rate on results as compliance in clinical trials was affected by Covid-19. This is a conservative scenario analysis, as it does not account for the additional benefit from higher compliance.

Abbreviations: CE, cost effectiveness; QALY, quality adjusted life years

3.10.3.1 Summary of scenario analyses results

Results of scenario analyses are shown in Table 75.

Table 75: Summary of scenario analyses (weighted average of paediatric and adult cohort)

Scenario	Incremental (olipudase alfa vs BSC)			ICER per QALY (£) versus BSC (unweighted)	ICER per QALY (£) versus BSC (weighted)
	Costs (£)	LYG	QALYs		Costs (£)
1.5% discount rate for costs in paediatric cohort	[redacted]	[redacted]	20.69	[redacted]	[redacted]
1.5% discount rate for costs in adult cohort	[redacted]	[redacted]	20.69	[redacted]	[redacted]
1.5% discount rate for costs in paediatric and adult cohort	[redacted]	[redacted]	20.69	[redacted]	[redacted]
Mortality modelled through parametric fit of data from McGovern et al. (2013) (7)	[redacted]	[redacted]	29.33	[redacted]	[redacted]
Discontinuation at 80 weeks of 5.56% (zero thereafter)	[redacted]	[redacted]	15.89	[redacted]	[redacted]
Patient compliance increased to 95%	[redacted]	[redacted]	20.69	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year

B.3.11 *Subgroup analysis*

A subgroup analysis was conducted based on a population of patients with severe disease, in whom the following additional characteristics/assumptions were modelled:

- All patients are assumed to start in the most severe health state within the model: DLco ≤40% and SV ≥15 MN.
- Paediatric patients start at age 2 years and adults at 34 years: this was the average age at diagnosis for paediatric patients; average age at start of ASCEND trial for adults.
- Rather than SMRs (with and without severe splenomegaly), mortality is modelled by treatment using a parametric fit (Weibull distribution) to extrapolate survival data from McGovern *et al*. (2013) (7)

Table 76: Summary of subgroup analysis – severe patients

Population	Incremental (olipudase alfa vs BSC)			ICER per QALY (£) versus BSC (unweighted)	ICER per QALY (£) versus BSC (Weighted)
	Costs (£)	LYG	QALYs		
Children	[redacted]	[redacted]	47.42	[redacted]	[redacted]
Adults	[redacted]	[redacted]	17.83	[redacted]	[redacted]
Combined	[redacted]	[redacted]	32.62	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year

In this analysis, the ICER was reduced markedly, mainly through increased incremental QALY gains with olipudase alfa.

A PSA was run in both the paediatric and adult populations of the severe patient subgroup. The PSA cost-effectiveness plane, and the cost effectiveness acceptability for the paediatric population is presented in Figure 30 and Figure 31, respectively. With a willingness to pay threshold of [redacted], the CE probability was [redacted] for the paediatric population.

Figure 30: [redacted]

Figure 31: [redacted]

Adult population

The PSA cost-effectiveness plane, and the cost effectiveness acceptability for the adult population is presented in Figure 32 and Figure 33, respectively. With a willingness to pay threshold of [redacted], the CE probability was [redacted] for the adult population.

Figure 32: [redacted]

[redacted]

Figure 33: [redacted]

B.3.12 *Benefits not captured in the QALY calculation*

The clinical manifestations of ASMD have a severe impact on patients' QoL, including their emotional well-being (Section 0). Given the multi-organ involvement, patients require multiple medical appointments to manage their symptoms and monitor disease progression. The need to coordinate these has a profound impact on the lives of people with ASMD and their families, already struggling with the everyday impact of the condition. As there is currently no disease-modifying treatment available for patients with ASMD, they suffer from feelings of anxiety, depression, frustration, and the fear of not knowing how their disease will progress. Due to the lack of available treatment, patients also struggle to plan for the future due to the uncertainty of the disease, with one patient stating: "[redacted]"" (13). Olipudase alfa is the first disease modifying treatment available, paving the way for improvements in how ASMD is treated. The technology will provide hope for patients with ASMD and enable them to look forward to the future without the worry of their disease progressing.

The clinical manifestations of ASMD, such as respiratory impairment, and liver complications, are included as short-term events in the QALY calculation. However, these complications likely have long-term consequences for patients with ASMD, including the need for supplemental oxygen which can substantially limit people's ability to lead normal lives (3). As these complications have been modelled as one-off events for the QALY calculation, it can be considered a conservative estimation, with additional benefits from the prevention of long-term consequences not fully captured. The evidence

for the long-term improvement of patient and caregiver utilities due to olipudase alfa continues to evolve.

Children with ASMD often miss school due to their symptoms, or medical appointments, which has a detrimental effect on their future career prospects and earning potential. In addition, the high risk of bleeding and bone fractures can result in requirements for additional support at school, limit participation in normal play and sports, leading to feelings of social exclusion and poor mental health. Adult patients with olipudase alfa struggle to maintain full-time jobs due to symptoms such as fatigue, with one patient stating "[redacted]" (39). The difficulty to attend school would also result in negative outcomes for the patient's future, with reduced school absence negatively linked to attainment (50), and potential loss of lifetime income for patients (51). Olipudase alfa treatment would enable children and adults to attend school/work completely thereby improving their economic situations and quality of life.

Caregivers of patients with ASMD have difficulties maintaining their emotional and mental health, as well as maintaining social activity and relationships. The care needed by children with ASMD will also likely have a negative impact on their siblings, who may feel like they are not given sufficient attention. They may also have difficulty maintaining full-time work due to caregiving commitments, and therefore face extreme financial burdens and feelings of low self-worth. The reduced income is particularly important, given that it has been estimated that families with a disabled person face close to £600 per month additional costs compared to the average family (121). Olipudase alfa treatment would improve caregiver's productivity, enabling them to work and reduce their loss of income. The impact of olipudase alfa treatment on carer and family QoL is likely to be underestimated in the QALY calculation. The impact of high mortality for children with severe phenotypes in paediatric populations is especially likely to be underestimated. The literature on caregiver anticipatory grief is only now evolving, but the impact in a disease like ASMD is likely substantial.

There are also wider societal benefits of treatment including for social care, education and allied health profession budgets, productivity of caregivers and patients and utilisation of hospice care. These elements could be important in the evolving integrated care system (ICS) structures within the NHS.

B.3.13 *Validation*

B.3.13.1 *Validation of cost-effectiveness analysis*

The cost-effectiveness model has undergone validation within a UK advisory board conducted in May 2022 by Sanofi (3). Five clinical experts participated in the advisory board.

Any issues identified were considered in the final model and discussed with a clinical expert.

The model approach, methodology, parameters and data sources, calculations and programmed functionality, and internal and external validity of outcomes were evaluated by two external health economists separate to the model development process.

B.3.14 *Interpretation and conclusions of economic evidence*

B.3.14.1 *Interpretation of economic evidence*

In the overall ASMD population, using base case assumptions, the weighted ICER was estimated to be [redacted] per QALY gained (accounting for QALY weighting). In the paediatric population, the weighted ICER was estimated to be [redacted] per QALY gained (accounted for QALY weighting). In the adult population, the weighted ICER was estimated to be [redacted] per QALY gained. This decreased substantially in the severe subpopulation (ICER of [redacted] per QALY gained, accounting for QALY weighting).

Sensitivity analyses conducted supported the results of the base case. In deterministic sensitivity analyses, for which input parameters were varied by +/-20% of base case value, the ICER for olipudase alfa vs BSC was most sensitive to varying the olipudase alfa medication cost. The drivers that most affected the ICER included adult weight, compliance of adults during the maintenance phase, and health state utilities for adults and children. The mean ICER from the probabilistic sensitivity analysis for both paediatric and adult population was slightly higher than the deterministic ICER.As would be expected, the probabilistic sensitivity analyses showed a high level of decision uncertainty, inevitable for such a rare disease. As indicated in the new NICE manual, there can now be a greater acceptance of uncertainty in rare diseases, for medicines treating paediatric populations and for innovative or complex treatments – all of which apply to olipudase alfa.

All ICERs should be interpreted in the context of value not captured in the QALY. This relates both to the healthcare system (for example avoiding future long-term complications and need for additional treatment), as well as to patients and their family (including impacts such as being able to fully participate in school, work, social activities). A more detailed description is presented in section B.3.12.

The cost-effectiveness model does not capture all benefits that would be expected with olipudase alfa treatment, such as the cost saving associated with the long-term improvement of symptoms. The model also does not capture the impact of olipudase alfa on broader societal costs such as education, employment, and future earning potential.

In spite of some benefits not captured in the QALY calculation, the ICER for the combined adult and paediatric population reduced to [redacted] per QALY gained (accounting for QALY weighting) in the severe subgroup of patients. It is likely that this analysis using parametric extrapolation of survival data from McGovern et al. 2013 (7) could be closer to capturing the actual impact on ASMD on patients' life expectancy than that based on SPHINGO-100. Clinical opinion suggests the approach using SPHINGO-100 is underestimating the impact of ASMD on mortality. This is likely due to the inclusion criteria in SPHINGO-100 (age of at least six years) and the potential for the most severe patients to die prior to diagnosis.

B.3.14.2 *Consistency with published economic literature*

As no treatment is currently available for ASMD, no economic evaluations of treatments for ASMD were identified.

B.3.14.3 *Relevance to all groups of patients who could potentially use the technology*

The cost-effectiveness analysis was considered relevant to all groups of patients in England that could potentially use olipudase alfa. The economic evaluation included both children (<18 years) and adults (≥18 years) with ASMD and included data from the ASCEND and ASCEND-Peds trials, as well as sensitivity analyses to include natural history cohort (SPHINGO-100).

B.3.14.4 *Strengths and limitations of the economic evaluation*

The strengths and limitations of the economic evaluation include:

- Robust data from a randomised controlled trial was used to inform the efficacy of olipudase alfa in the adult population. The effect of olipudase alfa seen in the paediatric trial was consistent with that for adult patients and was modelled separately to account for, amongst others, the differences in prognosis.
- Sensitivity analyses and several scenario analyses were conducted to test the robustness of the economic evaluation.
- Due to the rare nature of ASMD, data used to inform comparisons in some populations were limited, with small numbers of patients within trials available. However, this is common in very rare diseases, and efforts have been made to source natural history data for long-term outcomes and mortality. The olipudase alfa trials demonstrated an unequivocal benefit of treatment in spite of the small patient numbers inherent in a very rare disease.
- A robust vignette study, including [redacted] participants, was used to obtain reliable utility estimates for children and adults as the EQ-5D and SF-36 instruments used in the ASCEND trial had substantial limitations for estimating utilities for patients with ASMD in the cost effectiveness analysis. The vignette study was built on existing literature reviews, expert clinical opinion, and clinical trial results. A pilot phase was also conducted to ensure the comprehensibility and feasibility of the health state and methodology. The vignette study also enabled a larger cohort of participants to be included ([redacted] versus 36 from the ASCEND trial).
- The natural history study utilised for mortality curves within the cost effectiveness analysis was conducted in the US. However, adjusted survival probabilities were calculated by applying the mortality rates of the general population of the UK, and were conservative in nature (compared to alternative mortality rates based on other studies as tested in scenario analyses).
- The impact of ASMD on mortality was likely underestimated, therefore providing a conservative estimate of the benefits of olipudase. This is being further

investigated (55), with initial results suggesting higher mortality in ASMD patients than derived from SPHINGO-100.

- The US natural history SPHINGO-302 study was used to inform complications and number of events in the cost effectiveness analysis. However, American monitoring guidelines may not be truly reflective of UK clinical practice.
- UK clinical opinion was sought via advisory boards and individual conversations with experts to ensure validity of the assumptions and data inputs in the economic analysis.

A disease modifying treatment for ASMD would allow patients to lead a more normal life, improving their ability to attend school/work, and alleviating the burden on caregivers, with large benefits beyond the QALY. It is clear that a large number of potential benefits of olipudase to the patients, their families and the society could not be quantified and included in the economic model. However, as highlighted in the statements from patients treated with olipudase, it is likely to offer patients and their families large benefits at a relatively small budget impact for the NHS.

B.3.15 Cost to the NHS and Personal Social Services

B.3.15.1 *State how many patients are eligible for treatment in England. Present results for the full marketing authorisation and any subgroups considered. Also present results for the subsequent 5 years.*

Olipudase alfa is indicated in paediatric and adult patients for the treatment of non-CNS manifestations of ASMD (type B or A/B). The estimated prevalence and incidence of ASMD in England, and the estimated number of patients with the condition, are shown in Table 77. In the absence of published estimates, prevalence estimates for Year 1 were based on clinical expert estimates that 33 patients are currently diagnosed with ASMD type B or A/B in the England (personal communication; [redacted]. An annualised five-year mortality rate of 0.053% from the CEM was applied to the prevalence estimate in Year 1 (as detailed in Section 3.3.1.4). There are limited published data available regarding incidence figures, but it is estimated that around 1 to 2 patients are diagnosed with ASMD each year in England (4).

Prevalence and incidence estimates for year 2–5 were based on assumptions applied to the year 1 data. Incidence was assumed to remain constant from year 1–5 and was applied to the previous year's prevalence to obtain the following years prevalence.

Table 77: ASMD prevalence and incidence England

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalence	33	35	36	38	39
Incidence	2	1	2	1	2
Estimated number of patients with the condition	35	36	38	39	41

Abbreviations: ASMD, acid sphingomyelinase deficiency

B.3.15.2 *Describe the expected uptake of the technology and the changes in its demand over the next 5 years.*

Olipudase alfa is expected to be available for all patients with ASMD in England. As there is currently no treatment available for ASMD, olipudase alfa is expected to be used for 100% of ASMD patients in England. Based on the estimated number of patients with the condition, olipudase alfa is expected to be used for 35 patients in Year 1, up to 42 patients by Year 5 (Table 78).

Table 78: Estimate eligible ASMD population and olipudase alfa uptake

	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible population	35	36	38	39	41
Total % uptake of olipudase alfa	100%	100%	100%	100%	100%
Patients treated with olipudase alfa, n	35	36	38	39	41

Abbreviations: ASMD, acid sphingomyelinase deficiency

B.3.15.3 *In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).*

The costs considered in the analysis include drug acquisition and administration, in addition to adverse event management, complication and bronchodilator costs. Aligned with the accompanying cost-effectiveness model, costs for dose escalation were calculated biweekly until the HTD was achieved. Maintenance dose cost was then calculated dependent on location of administration. Please refer to Section B.3.5.2 for further details.

B.3.15.4 *Describe any estimates of resource savings associated with the use of the technology, including any other opportunities for resource savings or redirection of resources that it has not been possible to quantify*

Patients treated with olipudase alfa experience a reduction in the frequency of spleen, liver, respiratory, cardiovascular and bleeding complications versus BSC. The reduction in complications results in resource savings as all complications incur treatment costs. The full impact of avoided complications was unable to be accurately quantified. The reduction in complications patients experience from treatment is expected to subsequently reduce the need for other treatments (including surgeries) which carry a risk of further complications. Patients using olipudase alfa also require bronchodilators less often than BSC, resulting in further resource savings (Appendix K.1.2.).

Patients treated with olipudase alfa would be able to live more independently due to improvement in symptoms of ASMD, with a new hope of improvement in their condition now that a treatment for their condition is available. This would thereby improve their mental health and lower the need for mental health support. As there is currently no treatment currently available for ASMD, the effect of a treatment on resource use is difficult to estimate.

B.3.15.5 *Describe any costs or savings associated with the technology that are incurred outside of the NHS and Personal Social Services*

No costs or savings associated with the technology incurred outside of the NHS/PSS were included in the analysis. It should be noted that this is a conservative assumption, as there is the potential for the use of olipudase alfa to reduce indirect (societal) costs associated with productivity losses for adult patients and caregivers, in addition to the impact of loss of income and earnings for the patients and caregivers themselves.

B.3.15.6 *State the estimated budget impact for the NHS and Personal Social Services over the first year of uptake of the technology, and over the next 5 years*

Table 79 shows the annual budget impact to the NHS of olipudase alfa reimbursement at assumed list prices.

Table 79: Total budget impact of olipudase alfa

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADD: Supportive medicines cost per patient per annum	£0	£0	£0	£0	£0
Gross additional medicines costs per patients per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines (savings)/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated in each year	35	36	38	39	41
Budget impact (new medicine and supportive medicine costs only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact – net medicine costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other (savings)/costs					
(Savings)	(51)	(79)	(79)	(79)	(79)
Costs (per patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total other (savings)/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.15.7 *Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc)*

Section B.3.14.4 provides details of the limitations of the cost-effectiveness analysis. The limitations relating to the cost-effectiveness analysis, in terms of the availability of the underlying data and any structural assumptions also apply to the budget impact analysis.

In addition to the cost-effectiveness analysis, the main limitations within the budget impact analysis include:

- Compliance is assumed to be 90% in the analysis; while an assumption, olipudase alfa will be administered by healthcare professionals this should be considered a reasonable estimation. This was validated by a UK clinical expert (personal communication; [redacted]).
- ASMD is a very rare disease, with no published studies of ASMD epidemiology in England or the UK. The lack of robust epidemiological data makes it difficult to accurately estimate the size of the population in England. However, personal communication with clinical experts in the UK have been used to inform assumptions by Sanofi on the number of patients who may be treated with olipudase alfa in the first 5 years (personal communication; [redacted]. These estimates have been further supported by the NICE final scope (4), and a 2022 advisory board conducted by Sanofi (3).
- It was not possible to model accurately the full impact of avoided complications. The reduction in complications that patients experience due to treatment is expected to subsequently reduce the need for other treatments (including surgeries) which carry a risk of further complications.

B.4. References

1. EMA. SmPC olipudase alfa. Available from: https://www.ema.europa.eu/en/documents/product-information/xenpozyme-epar-product-information_en.pdf. Last accessed August 2022.
2. McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). Orphanet J Rare Dis. 2017 Feb 23;12(1):41.
3. Sanofi. Understanding the clinical practice and characteristics of the ASMD patient population in the UK, evaluate the current evidence and gaps from the payer's perspective. Virtual scientific advisory board. 25th May 2022. Data on file.
4. NICE. Highly Specialised Technologies Evaluation. Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and A/B). Final scope. 2022.
5. Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of Illness in Acid Sphingomyelinase Deficiency: A Retrospective Chart Review of 100 Patients. JIMD Rep. 2018;41:119-29.
6. Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases. Molecular Genetics and Metabolism. 2016 2016/07/01/;118(3):206-13.
7. McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann-Pick disease. Genet Med. 2013 Aug;15(8):618-23.
8. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis. 2021 May 10;16(1):212.
9. Pokrzywinski R, Hareendran A, Nalysnyk L, Cowie S, Crowe J, Hopkin J, et al. Impact and burden of acid sphingomyelinase deficiency from a patient and caregiver perspective. Scientific Reports. 2021 2021/10/25;11(1):20972.
10. Wasserstein M, Godbold J, McGovern MM. Skeletal manifestations in pediatric and adult patients with Niemann Pick disease type B. Journal of Inherited Metabolic Disease. 2013 2013/01/01;36(1):123-7.
11. Evidera. A Qualitative Study to Better Understand Caregivers' Burden of Acid Sphingomyelinas Deficiency (ASMD). September 2020. Data on file.
12. Henderson SL, Packman W, Packman S. Psychosocial aspects of patients with Niemann-Pick disease, type B. Am J Med Genet A. 2009 Nov;149a(11):2430-6.
13. Sanofi. ASMD Patient Journey. Topline findings from US and LATAM interviews. January 2019. Data on file.
14. Wasserstein M, Dionisi-Vici C, Giugliani R, Hwu WL, Lidove O, Lukacs Z, et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Mol Genet Metab. 2019 Feb;126(2):98-105.
15. Lipiński P, Kuchar L, Zakharova EY, Baydakova GV, Ługowska A, Tylki-Szymańska A. Chronic visceral acid sphingomyelinase deficiency (Niemann-Pick disease type B) in 16 Polish patients: long-term follow-up. Orphanet J Rare Dis. 2019 Feb 22;14(1):55.
16. UniProt. UniProtKB - P17405 (ASM_HUMAN). 2021; https://www.uniprot.org/uniprot/P17405. .
17. McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. Genet Med. 2017 Sep;19(9):967-74.

18. Schuchman EH, Wasserstein MP. Types A and B Niemann-Pick disease. Best Pract Res Clin Endocrinol Metab. 2015 Mar;29(2):237-47.
19. Wasserstein MP, Aron A, Brodie SE, Simonaro C, Desnick RJ, McGovern MM. Acid sphingomyelinase deficiency: prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. J Pediatr. 2006 Oct;149(4):554-9.
20. McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. Neurology. 2006 Jan 24;66(2):228-32.
21. Pastores GM, Hughes DA. Non-neuronopathic lysosomal storage disorders: Disease spectrum and treatments. Best Pract Res Clin Endocrinol Metab. 2015 Mar;29(2):173-82.
22. Sanofi. Summary of Results of Concept Elicitation Interviews with ASMD Patients. Data on file. 2016.
23. Schuchman EH, Desnick RJ. Types A and B Niemann-Pick disease. Mol Genet Metab. 2017 Jan-Feb;120(1-2):27-33.
24. Oliva P, Schwarz M, Scott J, Sansen S, Mechtler T, Keutzer J, et al. The incidence of acid sphingomyelinase deficiency (ASMD) in cases of suspected Gaucher disease, genotype-phenotype correlation together with Lyso-SPM biomarker. Presented at 17th WORLDSymposium. Available at: https://www.archimedlife.com/incidence-of-asmd-in-suspected-gaucher-patients/. Last accessed May 2022. 2021.
25. McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics. 2008 Aug;122(2):e341-9.
26. Al-Jasmi FA, Tawfig N, Berniah A, Ali BR, Taleb M, Hertecant JL, et al. Prevalence and Novel Mutations of Lysosomal Storage Disorders in United Arab Emirates : LSD in UAE. JIMD Rep. 2013;10:1-9.
27. Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, et al. Newborn Screening for Lysosomal Storage Disorders in Illinois: The Initial 15-Month Experience. J Pediatr. 2017 Nov;190:130-5.
28. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. Jama. 1999 Jan 20;281(3):249-54.
29. Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, et al. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet. 2004 Feb;12(2):87-92.
30. Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet. 1999 Jul-Aug;105(1-2):151-6.
31. Poupetová H, Ledvinová J, Berná L, Dvoráková L, Kozich V, Elleder M. The birth prevalence of lysosomal storage disorders in the Czech Republic: comparison with data in different populations. J Inherit Metab Dis. 2010 Aug;33(4):387-96.
32. Hollak CE, de Sonnaville ES, Cassiman D, Linthorst GE, Groener JE, Morava E, et al. Acid sphingomyelinase (Asm) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. Mol Genet Metab. 2012 Nov;107(3):526-33.
33. Pavlů-Pereira H, Asfaw B, Poupctová H, Ledvinová J, Sikora J, Vanier MT, et al. Acid sphingomyelinase deficiency. Phenotype variability with prevalence of intermediate phenotype in a series of twenty-five Czech and Slovak patients. A multi-approach study. J Inherit Metab Dis. 2005;28(2):203-27.
34. Kingma SD, Bodamer OA, Wijburg FA. Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening. Best Pract Res Clin Endocrinol Metab. 2015 Mar;29(2):145-57.

35. Filocamo M, Morrone A. Lysosomal storage disorders: molecular basis and laboratory testing. Hum Genomics. 2011 Mar;5(3):156-69.
36. Simonaro CM, Desnick RJ, McGovern MM, Wasserstein MP, Schuchman EH. The demographics and distribution of type B Niemann-Pick disease: novel mutations lead to new genotype/phenotype correlations. Am J Hum Genet. 2002 Dec;71(6):1413-9.
37. Sanofi. ASMD Advisory Board, March 2022. Data on file. .
38. Wasserstein MP, Desnick RJ, Schuchman EH, Hossain S, Wallenstein S, Lamm C, et al. The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. Pediatrics. 2004 Dec;114(6):e672-7.
39. Sanofi. ASMD Patient Experience. Data on file. June 2022.
40. Chapman J, Bansal P, Goyal A. Splenomegaly. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430907/.
41. Sanofi. Qualitative Research Study of Acid Sphingomyelinase Deficiency – DFI12712 ASCEND Clinical Trial Treatment Experience (IQVIA). Data on file. July, 2022. .
42. UK AaL. Pulmonary fibrosis. Available at: https://www.blf.org.uk/support-for-you/pulmonary-fibrosis/what-is-pulmonary-fibrosis. Last accessed July 2022. 2022.
43. Mendelson DS, Wasserstein MP, Desnick RJ, Glass R, Simpson W, Skloot G, et al. Type B Niemann-Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. Radiology. 2006 Jan;238(1):339-45.
44. Jones SA, McGovern M, Lidove O, Giugliani R, Mistry PK, Dionisi-Vici C, et al. Clinical relevance of endpoints in clinical trials for acid sphingomyelinase deficiency enzyme replacement therapy. Mol Genet Metab. 2020 Sep-Oct;131(1-2):116-23.
45. Schuchman EH. Acid sphingomyelinase, cell membranes and human disease: lessons from Niemann-Pick disease. FEBS Lett. 2010 May 3;584(9):1895-900.
46. Wasserstein MP, Larkin AE, Glass RB, Schuchman EH, Desnick RJ, McGovern MM. Growth restriction in children with type B Niemann-Pick disease. J Pediatr. 2003 Apr;142(4):424-8.
47. Spurr L. The treatment burden of long-term home noninvasive ventilation. Breathe (Sheff). 2021 Mar;17(1):200291.
48. Cheng SL, Chan VL, Chu CM. Compliance with home non-invasive ventilation. Respirology. 2012 May;17(4):735-6.
49. Duchenne UK. Impact of respiratory symptoms in Duchenne Muscular Dystrophy. Data on file. 2021.
50. Department for Education. The link between absence and attainment at KS2 and KS4, 2012/2013 academic year. February 2015. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/412638/The_link_between_absence_and_attainment_at_KS2_and_KS4.pdf. Last accessed July 2022.
51. Hanushek E, Woessmann L. The Economic Impacts of Learning Losses. September 2020. Available at: https://www.oecd.org/education/The-economic-impacts-of-coronavirus-covid-19-learning-losses.pdf. Last accessed July 2022. .
52. Sanofi. Data on file. Sanofi Genzyme Market Research Insights. ASMD TPP Testing & Research Insights. 2020. .
53. Rini A, Loriz L. Anticipatory Mourning in Parents With a Child Who Dies While Hospitalized. Journal of Pediatric Nursing: Nursing Care of Children and Families. 2007;22(4):272-82.
54. Sanofi. CSR: MSC12840 (SPHINGO-001-00). A prospective, cross-sectional survey study to collect natural history data in patients with Niemann-Pick B disease. Data on file. 2015.

55. F. Laredo, M.V. Munoz-Rojas, G. Gusto, A. Chandak, A. Khachatryan, T. Banon, et al. Survival of Patients with Acid Sphingomyelinase Deficiency (ASMD) in the United States (US): A Retrospective Real-world Study. Sanofi data on file. . 2022.
56. Wang RY, Bodamer OA, Watson MS, Wilcox WR. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med. 2011 May;13(5):457-84.
57. npuk. UK specialist centres. Available from: https://www.npuk.org/niemann-pick-disease/uk-specialist-centres/?doing_wp_cron=1643204773.3096809387207031250000. Last accessed January 2022.
58. Wasserstein MP SE. Acid Sphingomyelinase Deficiency. 2006 Dec 7 [Updated 2021 Feb 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1370/.
59. Sanofi. Understanding UK and Ireland Clinical Practice in ASMD-Virtual Scientific Advisory Board. 26th June 2020. Data on file.
60. npuk. A guide to ASMD Niemann-Pick disease types A and B: Understanding acrid sphingomyelinase deficient Niemann-Pick diseases types A and B and their potential treatment. Available at: https://www.npuk.org/wp-content/uploads/2019/05/Understanding-ASMD-Niemann-Pick-A-B-booklet-for-Professionals.pdf. Last accessed February 2022. 2010.
61. Mercati O, Pichard S, Ouachée M, Froissart R, Fenneteau O, Roche B, et al. Limited benefits of presymptomatic cord blood transplantation in neurovisceral acid sphingomyelinase deficiency (ASMD) intermediate type. Eur J Paediatr Neurol. 2017 Nov;21(6):907-11.
62. O'Neill RS, Belousova N, Malouf MA. Pulmonary Type B Niemann-Pick Disease Successfully Treated with Lung Transplantation. Case Reports in Transplantation. 2019 2019/06/16;2019:9431751.
63. Tirelli C, Arbustini E, Meloni F. Bilateral Cystic Bronchiectasis as Novel Phenotype of Niemann-Pick Disease Type B Successfully Treated With Double Lung Transplantation. Chest. 2021 May;159(5):e293-e7.
64. Victor S, Coulter JB, Besley GT, Ellis I, Desnick RJ, Schuchman EH, et al. Niemann-Pick disease: sixteen-year follow-up of allogeneic bone marrow transplantation in a type B variant. J Inherit Metab Dis. 2003;26(8):775-85.
65. Sanofi. Data on file. IQVIA Open Claims.
66. Diaz GA, Jones SA, Scarpa M, Mengel KE, Giugliani R, Guffon N, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genetics in Medicine. 2021 2021/08/01;23(8):1543-50.
67. Wasserstein M, Arash-Kaps L, Barbato A, Gallagher R, Giugliani R, Guelbert N, et al. OP093 - One-year results of the placebo-controlled ASCEND trial of olipudase alfa enzyme replacement therapy in adults with chronic acid sphingomyelinase deficiency. Molecular genetics and metabolism. 2021 2021/04/01/;132:S64-S5.
68. NHS England. 2013/14 NHS STANDARD CONTRACT FOR LYSOSOMAL STORAGE DISORDERS SERVICE (CHILDREN). Available at: https://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf. Last accessed March 2022.
69. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.
70. NICE. Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template. Updated February 2022. Last accessed May 2022. .

71. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919.
72. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996 Aug 3;313(7052):275-83.
73. Sanofi. CSR: DFI12712 (ASCEND). A Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, repeat dose study to evaulate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency. Data on file. 2021.
74. Sanofi. CSR: DFI13803 (ASCEND-Peds). A Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency. Data on file. 2020.
75. Sanofi. CSR: DFI13412. An open-label, multicenter, ascending dose study of the tolerability and safety of recombinant human acid sphingmyelinase (rhASM) in patients with acid sphingomyelinase deficiency (ASMD). Data on file. 2014.
76. Sanofi. CSR: LTS13632. A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency. Data on file. 2021.
77. Wasserstein M, Lachmann R, Hollak C, Arash-Kaps L, Barbato A, Gallagher RC, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. Genet Med. 2022 Jul;24(7):1425-36.
78. Villarubia J, Wasserstein, M, Barbato, A, Gallagher, RC, Giugliani, R, Guelbert, NB et al. Olipudase alfa for adults with acid sphingmyelinase deficiency: improvements in crossover placebo patients and further improvements in original olipudase alfa patients after 2 years in ASCEND trial. HemaSphere. 2022;6:S3.
79. Diaz GA, Jones SA, Scarpa M, Mengel KE, Giugliani R, Guffon N, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genet Med. 2021 Aug;23(8):1543-50.
80. Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL, et al. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Mol Genet Metab. 2015 Sep-Oct;116(1-2):88-97.
81. Thurberg BL, Diaz GA, Lachmann RH, Schiano T, Wasserstein MP, Ji AJ, et al. Long-term efficacy of olipudase alfa in adults with acid sphingomyelinase deficiency (ASMD): Further clearance of hepatic sphingomyelin is associated with additional improvements in pro- and anti-atherogenic lipid profiles after 42 months of treatment. Mol Genet Metab. 2020 Sep-Oct;131(1-2):245-52.
82. Wasserstein MP, Diaz GA, Lachmann RH, Jouvin MH, Nandy I, Ji AJ, et al. Olipudase alfa for treatment of acid sphingomyelinase deficiency (ASMD): safety and efficacy in adults treated for 30 months. J Inherit Metab Dis. 2018 Sep;41(5):829-38.
83. Lachmann R, Diaz GA, Wasserstein MP, Rawlings AM, Yarramaneni A, Kim Y. Sustained and continued improvements in pulmonary function, hepatosplenomegaly, dyslipidemia, and disease biomarkers in 5 adults with chronic acid sphingomyelinase deficiency after 6.5 years of olipudase alfa enzyme replacement therapy. Molecular Genetics and Metabolism. 2022 2022/02/01/;135(2):S70.
84. Diaz G, Giugliani R, Guffon N. Continued improvement in pulmonary, visceral, biomarker and growth outcomes in children with chronic acid sphingomyelinase deficiency treated with olipudase alfa enzyme replacement therapy: 2-year results of ASCEND-Peds. Molecular Genetics and Metabolism. 2022;135(2):S37.

85. MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. European Respiratory Journal. 2005;26(4):720.
86. Khanna D, Mittoo S, Aggarwal R, Proudman SM, Dalbeth N, Matteson EL, et al. Connective Tissue Disease-associated Interstitial Lung Diseases (CTD-ILD) - Report from OMERACT CTD-ILD Working Group. J Rheumatol. 2015 Nov;42(11):2168-71.
87. National Gaucher Foundation. Gaucher Disease Symptoms. Available at: https://www.gaucherdisease.org/about-gaucher-disease/symptoms/. Last accessed June 2022.
88. Shankar S, Lukina E, Amato D, Dasouki M, Packman S, Pastores G. Engage: A Phase 3, randomized, double-blind, placebo-controlled, multicenter study to investigate the efficacy and safety of eliglustat in adults with Gaucher disease type 1: 9 month results. Blood. 2013;122(21)2275.
89. Zimran A, Brill-Almon E, Chertkoff R, Petakov M, Blanco-Favela F, Muñoz ET, et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease. Blood. 2011 Nov 24;118(22):5767-73.
90. Pastores GM, Weinreb NJ, Aerts H, Andria G, Cox TM, Giralt M, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004 Oct;41(4 Suppl 5):4-14.
91. Cottin V, Crestani B, Cadranel J, Cordier JF, Marchand-Adam S, Prévot G, et al. French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis - 2017 update. Full-length version. Rev Mal Respir. 2017 Oct;34(8):900-68.
92. Xaubet A, Molina-Molina M, Acosta O, Bollo E, Castillo D, Fernández-Fabrellas E, et al. Guidelines for the medical treatment of idiopathic pulmonary fibrosis. Arch Bronconeumol. 2017 May;53(5):263-9.
93. Abdullah SM, Defina LF, Leonard D, Barlow CE, Radford NB, Willis BL, et al. Long-Term Association of Low-Density Lipoprotein Cholesterol With Cardiovascular Mortality in Individuals at Low 10-Year Risk of Atherosclerotic Cardiovascular Disease. Circulation. 2018 Nov 20;138(21):2315-25.
94. Rose L, Prins KW, Archer SL, Pritzker M, Weir EK, Misialek JR, et al. Survival in pulmonary hypertension due to chronic lung disease: Influence of low diffusion capacity of the lungs for carbon monoxide. J Heart Lung Transplant. 2019 Feb;38(2):145-55.
95. Sanofi. Data on file. Limitations of the EQ-5D and SF-6D in Patients with ASMD. March 2021.
96. ONS. Population estimates by ethnic group and religion, England and Wales:2019. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/populationestimatesbyethnicgroupandreligionenglandandwales/2019. Last assessed March 2022.
97. Simon N-J, Richardson J, Ahmad A, Rose A, Wittenberg E, D'Cruz B, et al. Health utilities and parental quality of life effects for three rare conditions tested in newborns. Journal of Patient-Reported Outcomes. 2019 2019/01/22;3(1):4.
98. NICE. NICE health technology evaluations: the manual. Published 31 January 2022. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Last accessed April 2022
99. HM Treasury. The Green Book. Central Government Guidance on Appraisial and Evaluation. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1063330/Green_Book_2022.pdf. Last accessed August 2022. .

100. Khorasani E, Davari M, Kebriaeezadeh A, Fatemi F, Akbari Sari A, Varahrami V. A comprehensive review of official discount rates in guidelines of health economic evaluations over time: the trends and roots. The European Journal of Health Economics. 2022 2022/03/02.
101. O'Mahony JF, Paulden M, McCabe C. NICE's Discounting Review: Clear Thinking on Rational Revision Meets Obstacle of Industrial Interests. PharmacoEconomics. 2021 2021/02/01;39(2):139-46.
102. John J, Koerber F, Schad M. Differential discounting in the economic evaluation of healthcare programs. Cost Effectiveness and Resource Allocation. 2019 2019/12/17;17(1):29.
103. Royal College of Paediatrics and Child Health (RCPCH). Girls: UK Growth chart 2-18 years. 2012 [updated 2012; cited 2022 January 12]; Available from: https://www.rcpch.ac.uk/sites/default/files/Girls_2-18_years_growth_chart.pdf.
104. NCHS. National Vital Statistics System. In. Mortality.
105. Office for National Statistics. National life tables - life expectancy in the UK 2017 to 2019.
106. Sanofi. Data on file. Assessment of Health State Utilities Associated with Acid Sphingomyelinase Deficiency (ASMD). 2022.
107. Galante J, Augustovski F, Colantonio L, Bardach A, Caporale J, Marti SG, et al. Estimation and comparison of EQ-5D health states' utility weights for pneumococcal and human papillomavirus diseases in Argentina, Chile, and the United Kingdom. Value Health. 2011 Jul-Aug;14(5 Suppl 1):S60-4.
108. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making. 2008 Jul-Aug;28(4):582-92.
109. Snyder CF, Mathias SD, Cella D, Isitt JJ, Wu AW, Young J. Health-related quality of life of immune thrombocytopenic purpura patients: results from a web-based survey. Curr Med Res Opin. 2008 Oct;24(10):2767-76.
110. Sullivan PW, Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. Value Health. 2016 Dec;19(8):1002-8.
111. Szende A, Brazier J, Schaefer C, Deuson R, Isitt JJ, Vyas P. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. Curr Med Res Opin. 2010 Aug;26(8):1893-903.
112. Pompe Disease News. What is Pompe Disease? Available at: https://pompediseasenews.com/what-is-pompe-disease/. Last accessed July 2022. .
113. Hornberger J, Reyes C, Shewade A, Lerner S, Friedmann M, Han L, et al. Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. Leuk Lymphoma. 2012 Feb;53(2):225-34.
114. Pennington B, Wong R. Modelling carer Health-related Quality of Life in NICE Technology Appraisals and Highly Specialised Technologies. Sheffield: Decision Support Unit. 2019. http://nicedsu.org.uk/wp-content/uploads/2019/07/2019-04-03-NICE-carer-HRQL-v-2-0-clean.pdf.
115. NICE. Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. HST guidance, HST11. Published 9th October 2019. Available from: https://www.nice.org.uk/guidance/hst11. Last accessed July 2022.
116. Sanofi. Data on File. SPHINGO-302 Clinical Trial.
117. NHS. National Schedule of NHS costs - Year 2019-20 - NHS trust and NHS foundation trusts.
118. Curtis L, Burns A. Unit Costs of Health & Social Care 2020. Table 10.2. University of Kent, PSSRU; 2020. p. 185.
119. Wasserstein M, Barbato A, Gallagher R, Giugliani R, Guelbert N, Hennermann J, et al. Continued improvement in adults with acid sphingomyelinase deficiency

after 2 years of olipudase alfa in the ASCEND placebo-controlled trial. Genetics in Medicine. 2022 2022/03/01/;24(3, Supplement):S176-S7.
120. NICE. Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. HST guidance, HST11. Published 9th October 2019. Available from: https://www.nice.org.uk/guidance/hst11. Last accessed July 2022. .
121. John E, Thomas G, Touchet A. The Disability Price Tag 2019. Available at: https://www.scope.org.uk/scope/media/files/campaigns/disability-price-tag-report-2019.pdf. Last accessed August 2022. . 2019.
122. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700.
123. Bembi B, Comelli M, Scaggiante B, Pineschi A, Rapelli S, Gornati R, et al. Treatment of sphingomyelinase deficiency by repeated implantations of amniotic epithelial cells. Am J Med Genet. 1992 Nov 1;44(4):527-33.
124. Diaz G. A Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency; data on file. 2020.
125. Diaz G, Giugliani R, Guffon N, Jones S, Mengel E, Scarpa M, et al. Children treated with olipudase alfa for chronic acid sphingomyelinase deficiency show meaningful improvement on clinically relevant outcomes and an overall favorable safety profile: 1-year results of the ASCEND-Peds trial. Molecular Genetics and Metabolism. 2021 02/01;132:S33-S4.
126. Garside B, Ho JH, Kwok S, Liu Y, Dhage S, Donn R, et al. Changes in PCSK 9 and apolipoprotein B100 in Niemann–Pick disease after enzyme replacement therapy with olipudase alfa. Orphanet Journal of Rare Diseases. 2021 2021/02/27;16(1):107.
127. Giugliani R. A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency 2021.
128. Giugliani R, Diaz G, Guffon N. Two-year outcomes of the first trial of olipudase alfa enzyme replacement therapy in children with chronic acid sphingomyelinase deficiency show continued improvements in clinical parameters 2021.
129. Liu Y, Luo Y, Xia L, Qiu B, Zhou T, Feng M, et al. The Effects of Liver Transplantation in Children With Niemann-Pick Disease Type B. Liver Transpl. 2019 Aug;25(8):1233-40.
130. McGovern MM, Wasserstein MP, Kirmse B, Duvall WL, Schiano T, Thurberg BL, et al. Novel first-dose adverse drug reactions during a phase I trial of olipudase alfa (recombinant human acid sphingomyelinase) in adults with Niemann-Pick disease type B (acid sphingomyelinase deficiency). Genet Med. 2016 Jan;18(1):34-40.
131. Scarpa M, Arash-Kaps L, Barbato A. Olipudase alfa enzyme replacement therapy improves liver and lipid parameters in adults and children with chronic acid sphingomyelinase deficiency: 1-year results of the ASCEND and ASCEND-Peds trials 2021.
132. Scarpa M, Arash-Kaps L, Barbato A. Impact of olipudase alfa enzyme replacement therapy on pulmonary, visceral and hematologic manifestations of acid sphingomyelinase deficiency: 1-year results of clinical trials in children and adults. Hemasphere. 2021;5(Suppl 2):317-318.
133. Thurberg BL, Wasserstein MP, Jones SA, Schiano TD, Cox GF, Puga AC. Clearance of Hepatic Sphingomyelin by Olipudase Alfa Is Associated With Improvement in Lipid Profiles in Acid Sphingomyelinase Deficiency. Am J Surg Pathol. 2016 Sep;40(9):1232-42.

134. Thurberg BL, Wasserstein MP, Schiano T, O'Brien F, Richards S, Cox GF, et al. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). Am J Surg Pathol. 2012 Aug;36(8):1234-46.
135. Wasserstein M. A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency; data on file. 2021.
136. Wasserstein M, Arash-Kaps L, Barbato A, Gallagher RC, Giugliani R, Guelbert NB, et al. Adults with chronic acid sphingomyelinase deficiency show significant visceral, pulmonary, and hematologic improvements after enzyme replacement therapy with olipudase-alfa: 1-year results of the ASCEND placebo-controlled trial. Molecular Genetics and Metabolism. 2021;132(2):S110-S1.
137. Diaz. A Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency; data on file. 2020.
138. Wasserstein M. A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency; data on file. 2020.
139. Giugliani. R. A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency, final CSR 2021.
140. Guigliani R. A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency; data on file; interim CSR. 2020.
141. Heart UK. Understanding your cholesterol results. Available at: https://www.heartuk.org.uk/cholesterol/understanding-your-cholesterol-test-results-. Last accessed 2022

Appendices

Appendices associated with the submission are provided as a standalone document.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

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

Addendum to company evidence submission

April 2023

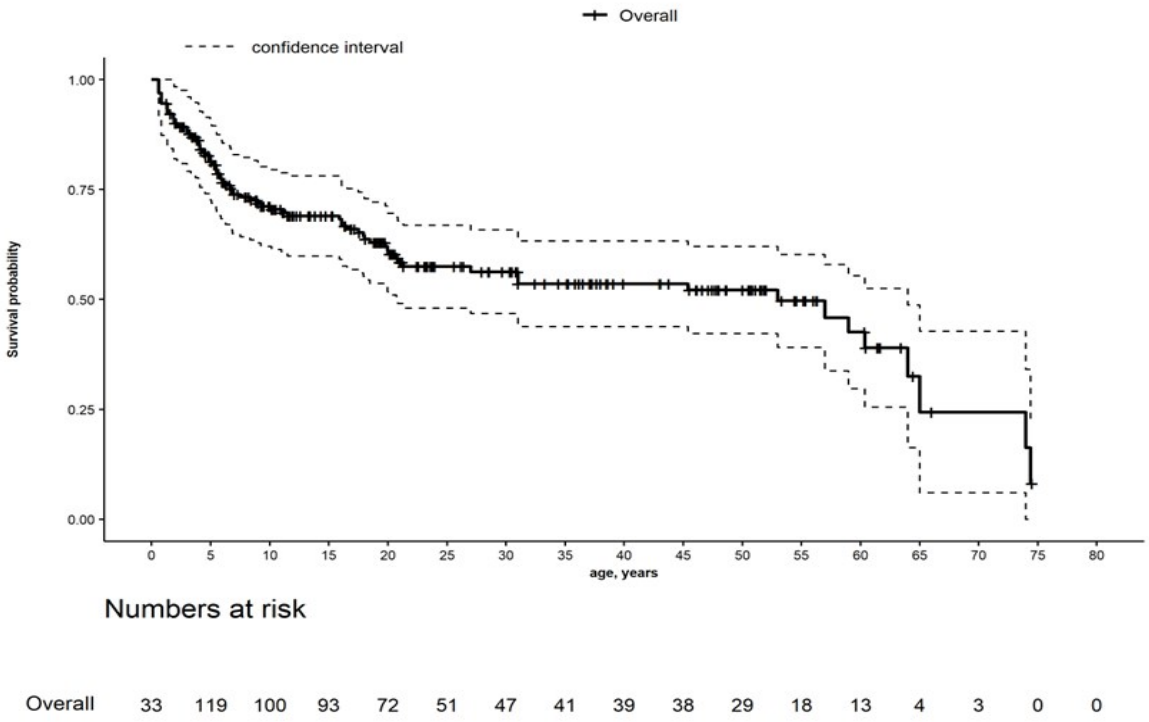
Version 1.0

File name	Version	Contains confidential information	Date
Addendum A	1.0	Yes	28th April 2023

Addendum to original HST submission to include new survival data for ASMD

After provision of the initial evidence submission to NICE in August 2022, further data relevant to the decision problem have become available. A chart review and subsequent pooled data analysis of ASMD patients (n=270) in Germany, France, the USA and Brazil[1] provides new survival estimates for adults and children with ASMD (Figure 1). Clinicians consulted by Sanofi confirmed that the population included in this study was generalisable to ASMD patients in the UK[2].

Figure 1: Kaplan Meier curve for survival (overall population), from birth date with risk adjustment (left truncation; n=270)



Median (95% CI): 53 (6.83-65)

Time (years)	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80
Number at risk	33	119	100	93	72	51	47	41	39	38	29	18	13	4	3	0	0
Number of censors	0	45	93	117	150	181	190	202	215	219	232	246	255	265	267	270	270
Number of events	17	16	3	10	4	1	2	0	0	1	1	2	2	1	2	0	0

*3 patients with missing first symptoms and diagnosis dates

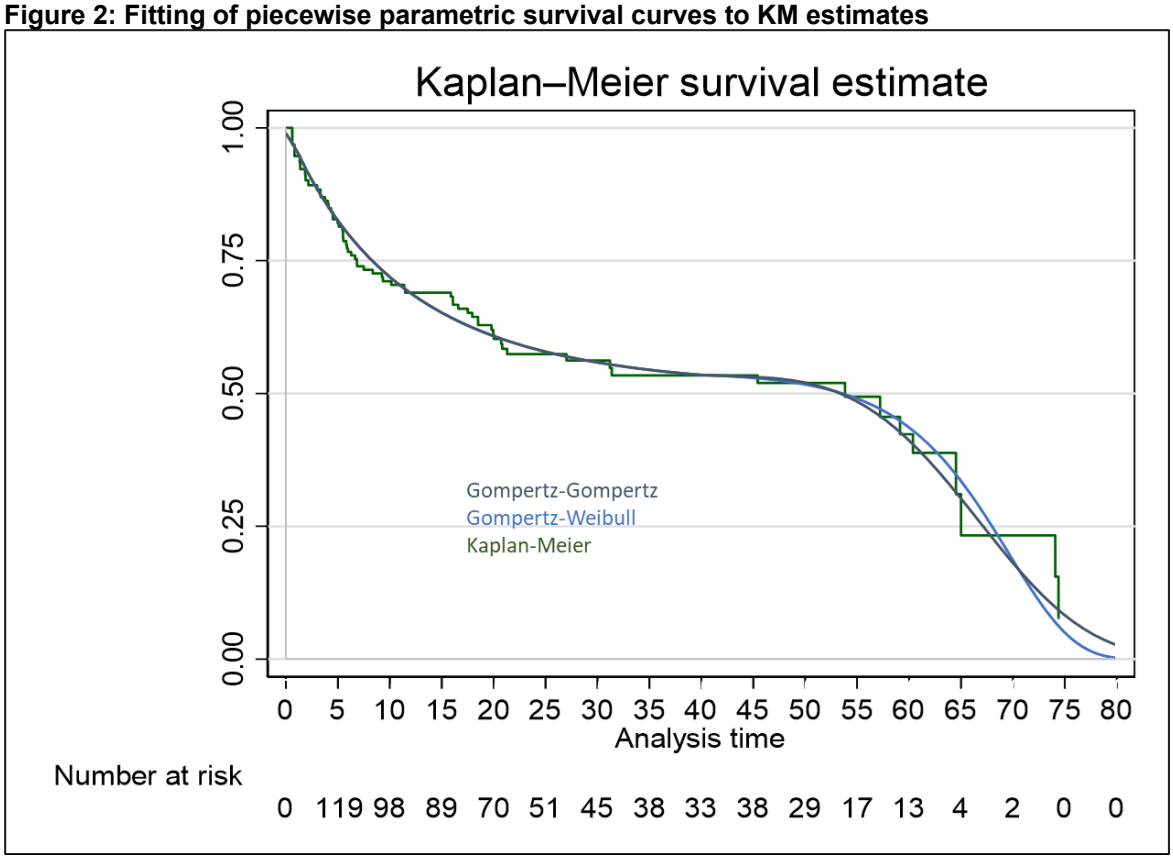
These data were used to conduct parametric survival analyses. Overall survival (OS) was modelled using both a single and piecewise-parametric approach. Goodness of fit was assessed via statistical methods – using Akaike information criterion (AIC) and Bayesian information criterion (BIC) methods (Table 1) – and assessment of visual fit (Figure 2). The piecewise parametric approach provided a better fit to the observed

Kaplan Meier data compared with a single fitted parametric survival curve. Gompertz distributions both before and after the splitting point of 40 years provided the lowest AIC/BIC statistics compared to other distributions. The first Gompertz distribution (i.e., before 40 years) provided a very close fit to the observed data. The second Gompertz distribution (i.e., after 40 years) provided both the best fit to the observed data but may be considered conservative as it predicted that all patients would be expected to die by age 80 (i.e., the earliest age predicted compared with all other distributions). The second-best fitting distribution in the second time-period was the Weibull distribution.

Table 1: Model fit testing and selection statistics

	Before piecewise split		After piecewise split	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential model	320.47746	323.97463	41.88031	43.8506
Weibull model	307.02703	314.02136	26.78161	30.7222
Gompertz model	303.3732	310.3675	25.73244	29.67302
Log-logistic model	305.6815	312.6758	28.69222	32.6328
Log-normal model	304.9689	311.9633	31.2049	35.14549
Generalised Gamma model	305.5933	316.0848	NA	NA

Figure 2: Fitting of piecewise parametric survival curves to KM estimates



Implementation into cost-effectiveness model (CEM)

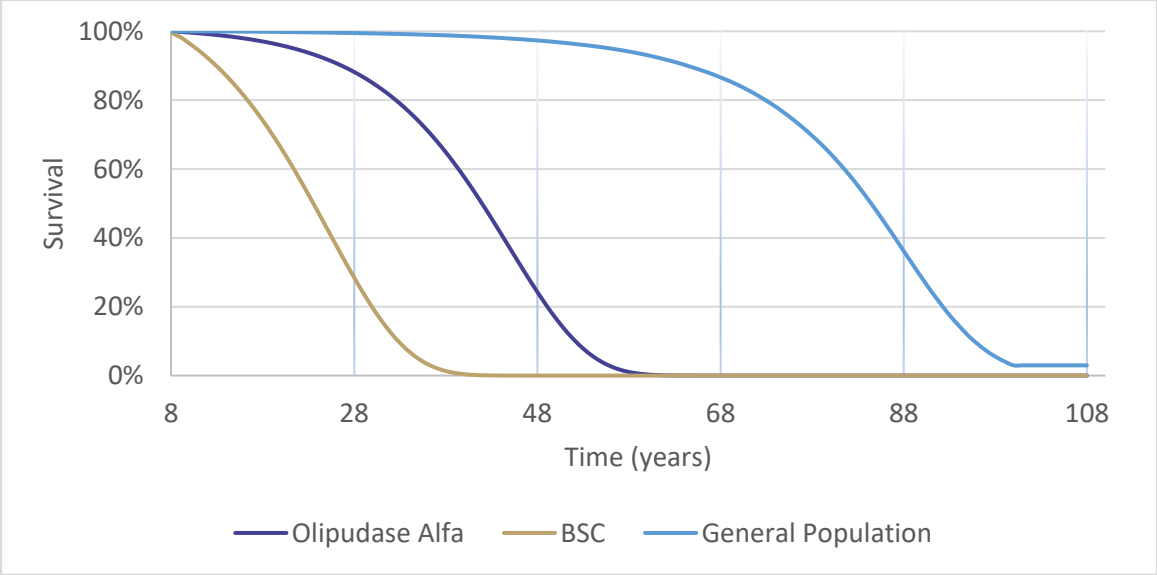
The generated curves have been used to update the model cited in the previous submission. The choice of curve for the base case and scenarios was informed by clinical opinion[2]. For children, base case overall survival was modelled using a single

parametric fit and for adults, overall survival was implemented in the CEM using the piecewise-parametric approach. In the paediatric base case, a Weibull distribution was used to model overall survival. In the adult base case, a Gompertz distribution was used to model OS before 40 years of age, and a Weibull distribution was used from age 40 years onwards. Alternative plausible parametric fits were also implemented in the CEM for scenario analyses.

Base-case survival traces

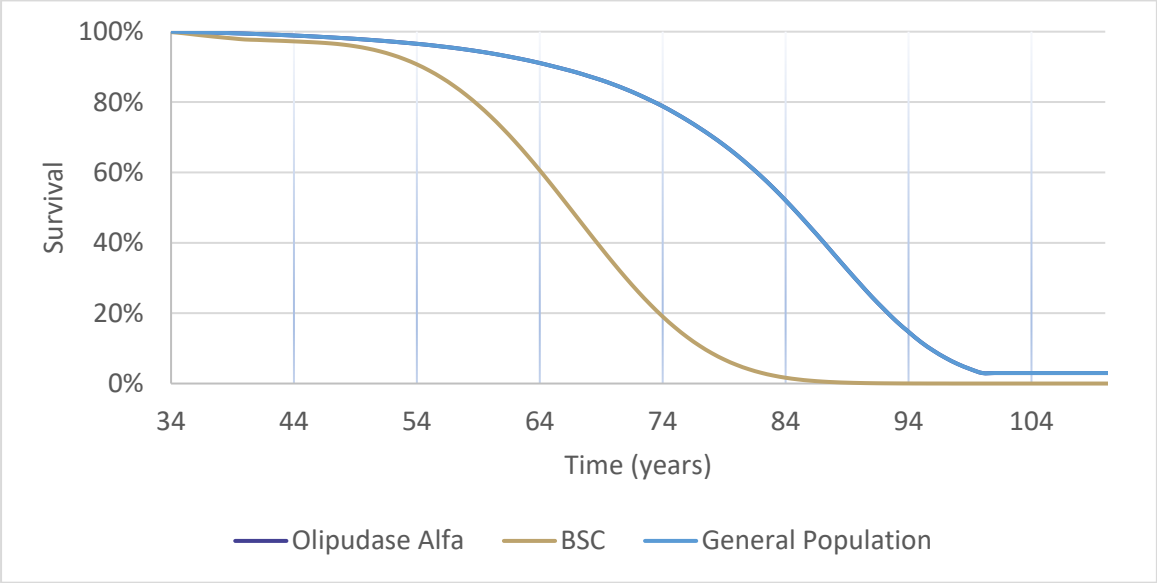
Overall survival curves using a one-piece Weibull distribution and piece-wise Gompertz-Weibull distributions to model survival in the paediatric and adult populations are presented in Figure 3 and Figure 4, respectively. Clinical opinion[2] confirmed that there is expected to be a relatively high early mortality in patients diagnosed in childhood, as these would be severe cases.

Figure 3: Model projections of survival for children treated with olipudase alfa, BSC, and the general population



Abbreviations: BSC, best supportive care

Figure 4: Model projections of survival for adults treated with olipudase alfa, BSC, and the general population



Abbreviations: BSC, best supportive care
* olipudase alfa curve is not visible as it overlaps with BSC curve

Base-case incremental cost effectiveness analysis results

Updated base case results for the paediatric and the adult population are presented in Table 2.

Table 2: Base-case results

Technologies		Total			Incremental (olipudase alfa vs BSC)			Weighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (weighted)	
Children	Olipudase alfa	[redacted]	[redacted]	25.13	[redacted]	[redacted]	108.87	[redacted]
	BSC	[redacted]	[redacted]	-11.15	–	–	–	
Adult	Olipudase alfa	[redacted]	[redacted]	16.55	[redacted]	[redacted]	62.55	[redacted]
	BSC	[redacted]	[redacted]	-4.30	–	–	–	
Combined	Olipudase alfa	[redacted]	[redacted]	20.84	[redacted]	[redacted]	85.71	[redacted]
	BSC	[redacted]	[redacted]	-7.73	–	–	–	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

In the combined paediatric and adult population, olipudase alfa is estimated to offer a high per-patient incremental health benefit, providing an increase in QALYs compared to BSC (20.84 unweighted QALYs with olipudase alfa vs -7.73 QALYs with BSC). With this clinical benefit, the estimated incremental cost-effectiveness ratio (ICER) for the combined population for olipudase alfa vs BSC is [redacted] per QALY gained.

Sensitivity analysis

Results from probabilistic sensitivity analyses are shown in **Figure 5**, **Figure 6**, **Figure 7** and **Figure 8**.

Figure 5: [redacted]

Figure 6: [redacted]

Figure 7: [redacted]

Figure 8: [redacted]

Outputs from one-way (deterministic) sensitivity analyses are shown in Figure 9 and Figure 10.

Figure 9: [redacted]

Figure 10: [redacted]

Scenario analysis

Scenarios in which mortality was modelled using alternative parametric distributions were evaluated to assess the impact of distributional selection on the ICER. Results from these scenarios analyses are shown in Table 3 and Table 4.

Table 3: Summary of scenario analyses (paediatric population)

Scenario	Incremental (olipudase alfa vs BSC)			ICER per QALY (£) versus BSC
	Costs (£)	LYG	QALYs (weighted)	
Piecewise: Gompertz-Gompertz	[redacted]	[redacted]	89.97	[redacted]
Piecewise: Gompertz-Weibull	[redacted]	[redacted]	93.00	[redacted]
One-piece fit: Gompertz	[redacted]	[redacted]	67.28	[redacted]
One-piece fit: Weibull	[redacted]	[redacted]	108.87	[redacted]

Abbreviations: BSC, best supportive care; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 4: Summary of scenario analyses (adult population)

Scenario	Incremental (olipudase alfa vs BSC)			ICER per QALY (£) versus BSC
	Costs (£)	LYG	QALYs (weighted)	
Gompertz-Gompertz	[redacted]	[redacted]	56.14	[redacted]
Gompertz-Weibull	[redacted]	[redacted]	62.55	[redacted]

Abbreviations: BSC, best supportive care; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year

References

1. ASMD Chart review pooled data analysis. Sanofi Genzyme, November 2022
2. Clinical opinion. Data on file. Sanofi, March 2023.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

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

Clarification questions

August 2022

File name	Version	Contains confidential information	Date
ID3913 EAG clarification questions.docx	1.0	Yes	15/09/2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. Please confirm whether additional searches were conducted to identify conference abstracts in Ovid Embase and if so, please provide details of the search strategy. The search strategy for Ovid MEDLINE & Embase reported in Table 80 (Appendix D) applies a limit of 'Article' or 'Article in Press' in line #12. This limit excludes conference abstracts from search results.

Additional hand searches of the following conferences were conducted to identify relevant abstracts in Ovid Embase from the past two meeting years:

- WORLDSymposium
- European Society of Human Genetics
- Annual Symposium of the Society for the Study of Inborn Errors of Metabolism

Details of the search strategy are provided in Table 1.

Table 1: Search procedure for grey literature sources

Conference, HTA Body or Organization Name	Search Information	Website Navigation Pathway	Search Terms
WORLDSymposium, 2021	https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/132/issue/2	Use ctrl + f	Acid Sphingomyelinase Deficiency
WORLDSymposium, 2022	https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/135/issue/2	Use ctrl + f	NA
European Society of Human Genetics, 2021	https://www.abstractsonline.com/pp8/#!/10372	Use search bar	Acid Sphingomyelinase Deficiency
European Society of Human Genetics, 2021	https://www.abstractsonline.com/pp8/#!/10372	Use search bar	Acid Sphingomyelinase Deficiency
European Society of Human Genetics, 2022	NA- has not occurred	NA	Acid Sphingomyelinase Deficiency
Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2021	https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12458	Use search bar	Niemann
Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2021	https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12458	Use search bar	Niemann
Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2022	NA- has not occurred	NA	Niemann
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click methods in basic search	Acid Sphingomyelinase Deficiency

Conference, HTA Body or Organization Name	Search Information	Website Navigation Pathway	Search Terms
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click ratios in basic search	Niemann
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click utility weights in basic search	Acid Sphingomyelinase Deficiency
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click methods in basic search	Niemann
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click ratios in basic search	Acid Sphingomyelinase Deficiency
Cost-Effectiveness Analysis Registry via Tufts Medical Center	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Click "View the CEA Registry", click utility weights in basic search	Niemann
Clinicaltrials.gov	https://clinicaltrials.gov/	Search in conditions, apply "with results" in filters	Acid Sphingomyelinase Deficiency
Clinicaltrials.gov	https://clinicaltrials.gov/	Search in conditions, apply "with results" in filters	NA

Conference, HTA Body or Organization Name	Search Information	Website Navigation Pathway	Search Terms
International Guideline Library	https://g-i-n.net/library/international-guidelines-library/international-guidelines-library	Use search bar	Acid Sphingomyelinase Deficiency
International Guideline Library	https://g-i-n.net/library/international-guidelines-library/international-guidelines-library	Use search bar	Acid Sphingomyelinase Deficiency
ECRI Guidelines Trust	https://guidelines.ecri.org/	Navigate to library at bottom of page, click "clinical specialties"	Acid Sphingomyelinase Deficiency
ECRI Guidelines Trust	https://guidelines.ecri.org/	Navigate to library at bottom of page, click "clinical specialties"	Niemann

Abbreviations: CEA, cost-effectiveness analysis; ECRI, Emergency Care Research Institute

A2. Please confirm whether the references from conference abstract searches and other grey literature searches were screened by 2 reviewers? Were any records identified from these grey literature searches excluded, and for what reasons?

Grey literature was screened by two reviewers (initial screening by one and validation by a second senior reviewer). A total of 27 conference abstracts were identified through keyword searching, of which 19 of those records were excluded due to the following:

- Population: 10
- Outcomes: 4
- Duplicate: 5

A3. Please provide the search strategies used to identify unpublished trials at ClinicalTrials.gov, and strategies used in the Cost Effectiveness Analysis Registry.

Unpublished trials were identified at ClinicalTrials.gov by searching in conditions “acid sphingomyelinase deficiency” as well as “Niemann”, the “with results” filter was selected to only identify trials with results.

As for the Cost-Effectiveness Analysis Registry, a similar approach was used wherein each overarching topic of the basic search (i.e. ratios, utility weights, and methods) were searched for both “acid sphingomyelinase deficiency” and “Niemann”. This methodology resulted in six hits, all of which were excluded due to population.

Systematic literature review methods

A4. Please provide justification for the exclusion of non-medical interventions as comparators in the SLR.

The inclusion criteria of the SLR were limited to medical interventions for ASMD due to the fact that non-medical interventions such as supplemental nutrition, occupational therapy, etc. are aimed at reducing symptom burden rather than treating ASMD. In addition, there were no potentially relevant studies identified through the searches of grey literature that were excluded for evaluating a non-medical intervention.

A5. Please provide justification for not using NCT00410566 to provide supporting evidence in the submission (with particular reference to safety data) despite providing critical appraisal ratings for this trial.

Study NCT00410566 did not include patients treated with the licensed maintenance dose (3.0 mg/kg) and was therefore deemed to be of limited relevance. An overview of the study is provided below:

Study NCT00410566 was a phase I, single-centre, open-label, nonrandomised, single-ascending-dose trial which evaluated the safety of olipudase alfa (administered IV) at a dose of 0.03, 0.1, 0.3, 0.6, or 1.0 mg/kg in 11 adults (18–65 years of age) with ASMD type B (1, 2). Overall, no serious adverse drug reactions occurred during the study. The maximum tolerated starting dose of olipudase alfa in patients with ASMD type B was identified to be 0.6 mg/kg, with results of the study supporting the use of a within-patient dose-escalation strategy.

The company has also provided the CSR for NCT00410566 (1) in the updated reference pack.

A6. The ROBINS-I tool for critical appraisal requires researchers to pre-specify the confounders that will be considered in the appraisal. Please state which confounders were selected for this purpose.

As discussed in the company submission, a mix of clinical and demographic confounders were selected: age, gender, weight, medical history (history of blood, lymphatic system, or hepatobiliary disorders), prior treatments (including history of surgical/medical procedures), concomitant medication, age at symptom onset, age at diagnosis, genotype/phenotype subtype, disease severity and symptoms at baseline, and family history.

A7. Please provide full critical appraisal ratings (i.e. across all signalling questions) for trials of olipudase alfa.

Full ratings for Cochrane AROB and the ROBINS-I assessment are provided as a separate document (3).

A8. Further justification is needed for critical appraisal ratings given for ASCEND-Peds. We further note that the ROBINS-I tool was primarily developed to evaluate

risk of bias in comparative studies, and therefore the appraisal should explicitly consider the additional risks presented by single-arm trials. Please provide a justification for your following statements:

Justification for critical appraisal ratings for ASCEND-Peds have been provided in Table 21 of the company submission. Justifications have been extracted below.

- That the cohort of ASCEND-Peds was “representative of the relevant targeted population” (CS p. 87, Table 21);

The cohort of ASCEND-Peds was considered “representative of the relevant targeted population” as all eligible patients meeting the protocol-defined inclusion criteria were enrolled and completed the study.

- That the trial design adequately accounted for confounding factors in the design and/or analysis;

The inclusion criteria were designed a priori to help minimise confounding factors. Results were adjusted as needed for any remaining confounders.

- That the findings were sufficiently precise.

For exploratory efficacy assessments, observed measures and changes from baseline values were analysed with a regression model using baseline as the covariate, least squares mean, 95% CIs and p-values were provided. In addition, any concerns with precision could be driven by the smaller sample size.

A9. Please confirm that the critical appraisal ratings reported for the included trials were attributed to all reported trial outcomes.

The company can confirm that this is correct.

Administration of olipudase alfa

A10. The EAG understands that there is no diagnostic test to confirm type of ASMD (i.e. type A, B, or A/B), and that diagnosis is based on clinical presentation. The licence for olipudase alfa does not specify a minimum age for use, however do you

consider there to be a minimum age for use to ensure that a diagnosis of type A ASMD has been ruled out?

The diagnosis of ASMD is established by detection of biallelic pathogenic variants in SMPD1 and/or residual acid sphingomyelinase enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts) (4, 5). In a study evaluating the natural history of 10 type A patients, the results revealed that the natural history of this disorder is very similar amongst affected patients and is characterised by a relentless neurodegenerative course that leads to death usually within 3 years (4). According to clinical opinion, the distinction between patients with ASMD type A and other phenotypes (type B, and A/B) is clear (6).

A11. Would you please provide further information about the packaging of olipudase alfa and the potential for wastage when used in clinical practice? Please also explain about the shelf life of the medication and whether there are specific storage requirements.

Packaging of olipudase alfa

Olipudase alfa is a white to off-white lyophilised powder for concentrate for solution for infusion (powder for concentrate). Each vial contains 20 mg of olipudase alfa. After reconstitution each vial contains 4 mg of olipudase alfa per mL (7).

Potential for wastage

Enzyme replacement therapy doses are routinely rounded to the nearest vial to avoid wastage, according to clinical experts from three different centres (personal communication: [redacted]. All three clinical experts confirmed that the standard procedure would be to round up or down to the nearest vial, if weight is halfway between two vials they would round down dose one week and up the next week to avoid wastage. Vial rounding is therefore expected to be the routine practice in England.

Shelf life and storage requirements (Section 6.3. of SmPC (7))

Unopened vials

Shelf life of unopened vials is 48 months.

Reconstituted medicinal product

After reconstitution with sterile water for injection, chemical, physical and microbiological in-use stability has been demonstrated for up to 24 hours at 2-8°C or 12 hours at room temperature (up to 25°C).

From a microbiological point of view, the reconstituted medicinal product should be used immediately. If not used for dilution immediately, in-use storage times and conditions prior to dilution are the responsibility of the user and should normally not be longer than 24 hours at 2°C - 8°C or 12 hours at room temperature (up to 25°C).

Diluted medicinal product

After dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, chemical, physical and microbiological in-use stability has been demonstrated between 0.1 mg/mL and 3.5 mg/mL for 24 hours at 2-8°C, and up to 12 hours (including infusion time) when stored at room temperature (up to 25°C).

From a microbiological point of view, the diluted medicinal product should be used immediately. If not used immediately after dilution, in-use storage times and conditions are the responsibility of the user and should normally not be longer than 24 hours at 2°C to 8°C followed by 12 hours (including infusion time) at room temperature (up to 25°C).

Methodology used for clinical trials of olipudase alfa

A12. The CS reports that 62 patients were screened for ASCEND but 38 patients were considered eligible for inclusion. Can you please provide a breakdown of why these 24 patients were considered ineligible, and confirm whether all patients considered ineligible had a diagnosis of ASMD B or A/B?

Please consider the screen failure list below.

[redacted]

[redacted]

[redacted]

A13. Please can you confirm whether any of the participants in the included trials had previously received treatment with olipudase alfa?

No participant in ASCEND and ASCEND-Peds had previously received olipudase alfa within 30 days before study enrolment, as stated on the protocol.

A14. Two participants discontinued from the olipudase alfa arm of ASCEND (11.1%) but the reasons for their discontinuation is unclear. Please can you provide further details, and/or confirm whether discontinuation was related to the efficacy or safety of olipudase alfa?

There were no discontinuations related to the efficacy or safety of olipudase alfa. The ID of the two ASCEND participants from the olipudase alfa arm that discontinued were [redacted]. Both participants discontinued after the primary analysis period (PAP) (did not complete the extension treatment period [ETP]).

[redacted]

[redacted]

A15. Please provide the number of participants in each trial and trial arm diagnosed with ASMD type B vs. type A/B.

At the time ASCEND was initiated, no clear diagnostic classification criteria were available and the subtypes were considered to represent a disease spectrum rather than discrete entities. Consequently, while the inclusion criteria in ASCEND stated ASMD type B the study enrolled both patients with a clinical diagnosis consistent with ASMD type B and type A/B. Considering this, the trial protocols did not require investigators to sub-classify patients according to ASMD Type A/B and B subtypes at enrolment.

A16. Please provide population eligibility criteria for the included clinical trials (please note that we have accessed these from the trial CSRs, but we cannot report these without redaction unless you present them in your submission).

Eligibility criteria for participants are presented in the submission for the included clinical trials as follows:

- ASCEND-Peds and ASCEND is provided in Table 13 of the company submission
- DFI13412 is provided in Table 101 of Appendix M
- LTS13632 is provided in Table 40 of the company submission

The eligibility criteria are not deemed confidential.

A17. PRIORITY. Please provide data for the treatments received by participants in all treatment arms of the trials, including:

- dose received
- mean dose duration
- dose modifications
- details of background care received.

Please see below data for the treatment received by participants in all treatment arms of the ASCEND study.

Table 2: Treatment received by participants in all treatment arms of ASCEND study

ASCEND	Placebo (N=15)	Olipudase alfa (N=18)
Cumulative dose (mg) on olipudase alfa in PAP		
Number of patients with value	0	[redacted]
Mean (SD)		[redacted]
Median		[redacted]

Abbreviations: mg, milligram; PAP, primary analysis plan; SD, standard deviation

Please see below data for the treatment received by participants in ASCEND-Peds.

Table 3: Treatment received by participants in all treatment arms of ASCEND-Peds study

ASCEND-Peds	Olipudase alfa (N=20)
Number of infusions received	
Number of patients with value	[redacted]
Mean (SD)	[redacted]
Median	[redacted]

Abbreviations: SD, standard deviation

Please see below a summary of concomitant medications in ASCEND PAP-mITT population.

Table 4: Summary of concomitant medications in ASCEND PAP-mITT

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Nervous System, n(%)	[redacted]	[redacted]
Analgesics	[redacted]	[redacted]
Psycholeptics	[redacted]	[redacted]
Anesthetics	[redacted]	[redacted]
Antiepileptics	[redacted]	[redacted]
Psychoanaleptics	[redacted]	[redacted]
Alimentary tract and metabolism, n(%)	[redacted]	[redacted]
Stomatological preparations	[redacted]	[redacted]
Mineral supplements	[redacted]	[redacted]
Vitamins	[redacted]	[redacted]
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	[redacted]	[redacted]
Antiemetics and antinauseants	[redacted]	[redacted]
Drugs for constipation	[redacted]	[redacted]
Other alimentary tract and metabolism products	[redacted]	[redacted]
Drugs for acid related disorders	[redacted]	[redacted]
Drugs for functional gastrointestinal disorders	[redacted]	[redacted]
Antiobesity preparations, excl. diet products	[redacted]	[redacted]

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Bile and liver therapy	[redacted]	[redacted]
Cardiovascular system, n(%)	[redacted]	[redacted]
Cardiac therapy	[redacted]	[redacted]
Lipid modifying agents	[redacted]	[redacted]
Agents acting on the renin-angiotensin system	[redacted]	[redacted]
Calcium channel blockers	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]
Vasoprotectives	[redacted]	[redacted]
Antihypertensives	[redacted]	[redacted]
Beta blocking agents	[redacted]	[redacted]
Dermatologicals, n (%)	[redacted]	[redacted]
Antipruritics, incl. antihistamines, anesthetics, etc.	[redacted]	[redacted]
Anti-acne preparation	[redacted]	[redacted]
Antibiotics and chemotherapeutics for dermatological use	[redacted]	[redacted]
Antifungals for dermatological use	[redacted]	[redacted]
Emollients and protectives	[redacted]	[redacted]
Other dermatological preparations	[redacted]	[redacted]
Respiratory system, n (%)	[redacted]	[redacted]
Cough and cold preparations	[redacted]	[redacted]
Antihistamines for systemic use	[redacted]	[redacted]
Nasal preparations	[redacted]	[redacted]
Drugs for obstructive airway diseases	[redacted]	[redacted]
Antiinfectives for systemic use, n (%)	[redacted]	[redacted]
Antibacterials for systemic use	[redacted]	[redacted]
Vaccines	[redacted]	[redacted]

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Antivirals for systemic use	[redacted]	[redacted]
Blood and blood forming organs, n (%)	[redacted]	[redacted]
Antihemorrhagics	[redacted]	[redacted]
Antianemic preparations	[redacted]	[redacted]
Blood substitutes and perfusion solutions	[redacted]	[redacted]
Antithrombotic agents	[redacted]	[redacted]
Musculo-skeletal system, n(%)	[redacted]	[redacted]
Antiinflammatory and antirheumatic products	[redacted]	[redacted]
Muscle relaxant	[redacted]	[redacted]
Drugs for treatment of bone diseases	[redacted]	[redacted]
Topical products for joint and muscular pain	[redacted]	[redacted]
Various, n (%)	[redacted]	[redacted]
All other therapeutic products	[redacted]	[redacted]
Allergens	[redacted]	[redacted]
Unspecified herbal and traditional medicine	[redacted]	[redacted]
Contrast media	[redacted]	[redacted]
General nutrients	[redacted]	[redacted]
Antiparasitic products, insecticides and repellents, n (%)	[redacted]	[redacted]
Anthelmintics	[redacted]	[redacted]
Genito urinary system and sex hormones, n (%)	[redacted]	[redacted]
Sex hormones and modulators of the genital system	[redacted]	[redacted]
Sensory organs, n (%)	[redacted]	[redacted]

ASCEND	Placebo	Olipudase alfa (N=20)
Summary of concomitant medication in PAP – mITT population		
Ophthalmologicals	[redacted]	[redacted]
Systemic hormonal preparations, excl. sex hormones and insulins, n (%)	[redacted]	[redacted]
Thyroid therapy	[redacted]	[redacted]
Corticosteroids for systemic use	[redacted]	[redacted]

Abbreviations: n, number; mITT, modified intention to treat; PAP, primary analysis period.

Please see below summary of concomitant medications in ASCEND-Peds safety population.

Table 5: Summary of concomitant medications in ASCEND-Peds safety population

ASCEND-Peds	Olipudase alfa (N=20)
Summary of concomitant medications – Safety Populations	
Respiratory system, n (%)	[redacted]
Antihistamines for systemic use	[redacted]
Nasal preparations	[redacted]
Cough and cold preparations	[redacted]
Drugs for obstructive airway diseases	[redacted]
Other respiratory system products	[redacted]
Throat preparations	[redacted]
Nervous system, n (%)	[redacted]
Analgesics	[redacted]
Anesthetics	[redacted]
Psycholeptics	[redacted]
Other nervous system drugs	[redacted]
Antiinfectives for systemic use, n (%)	[redacted]
Vitmains	[redacted]
Antiemetics and antinauseants	[redacted]
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	[redacted]
Mineral supplements	[redacted]
Drugs for constipation	[redacted]

ASCEND-Peds	Olipudase alfa (N=20)
Summary of concomitant medications – Safety Populations	
Drugs for functional gastrointestinal disorders	[redacted]
Stomatological preparations	[redacted]
Musculo-skeletal system, n (%)	[redacted]
Antiinflammatory and antirheumatic products	[redacted]
Muscle relaxants	[redacted]
Topical products for joint and muscular pain	[redacted]
Dermatologicals, n (%)	[redacted]
Antibiotics and chemotherapeutics for dermatological use	[redacted]
Emollients and protectives	[redacted]
Corticosteroids, dermatological preparations	[redacted]
Antifungals for dermatological use	[redacted]
Antipruritics, incl. antihistamines, anesthetics, etc.	[redacted]
Medicated dressings	[redacted]
Other dermatological preparations	[redacted]
Preparations for treatment of wounds and ulcers	[redacted]
Blood and blood forming organs, n (%)	[redacted]
Antianemic preparations	[redacted]
Blood substitutes and perfusion solutions	[redacted]
Antithrombotic agents	[redacted]
Various, n (%)	[redacted]
Unspecified herbal and traditional medicine	[redacted]
All other therapeutic products	[redacted]
Homeopathic preparation	[redacted]
Cardiovascular system, n (%)	[redacted]
Lipid modifying agents	[redacted]
Cardiac therapy	[redacted]
Vasoprotectives	[redacted]

ASCEND-Peds	Olipudase alfa (N=20)
Summary of concomitant medications – Safety Populations	
Sensory organs, n (%)	[redacted]
Ophthalmologicals	[redacted]
Otologicals	[redacted]
Ophthalmological and otological preparations	[redacted]
Systemic hormonal preparations, excl. sex hormones and insulins, n (%)	[redacted]
Corticosteroids for systemic use	[redacted]
Thyroid therapy	[redacted]
Antiparasitic products, insecticides and repellents, n (%)	[redacted]
Anthelmintics	[redacted]
Antineoplastic and immunomodulating agents, n (%)	[redacted]
Immunostimulants	[redacted]
Genito urinary system and sex hormones, n (%)	[redacted]
Sex hormones and modulators of the genital system	[redacted]

Abbreviations: n, number

Mean dose duration and dose modifications are not available at this time, this may be provided at a later date if required by the EAG.

A18. Please confirm the number of participants available at reported follow-up timepoints in the extension period of ASCEND, and can you explain why sample size varies across outcome for the same time point?

The number of participants available at reported follow-up timepoints in the extension period of ASCEND are presented in Table 6.

Table 6: Number of participants available at follow-up timepoints in the extension period - ASCEND

Outcome	Follow-up timepoint	Number of participants available	
		Placebo/olipudase alfa	Olipudase alfa/olipudase alfa
% predicted DL_{CO}	Year 1	17	17
	Year 2	10	10
Spleen volume (MN)	Year 1	17	18
	Year 2	11	14
Liver volume (MN)	Year 1	17	17
	Year 2	11	14
Platelet count (10^9/L)	Year 1	16	18
	Year 2	15	13
Lung HRCT ground glass appearance score	Year 1	17	18
	Year 2	14	16
ALT (IU/L)	Year 1	16	18
	Year 2	15	12
HDL cholesterol (mg/dL)	Year 1	16	18
	Year 2	14	12
LDL cholesterol (mg/dL)	Year 1	15	18
	Year 2	14	12

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; MN, multiples of normal
Source: Villarubia et al, 2022 (8)

For the same visit (timepoint) the assessments (such as MRI or PFT) could be scheduled during a 7 day window from the visit date and could be performed separately of the infusion. For some reasons, patients could miss one assessment and perform the other for a given visit. Some assessments performed at a given visit were not included in the database due to technical reasons (assessments partially done or not readable).

A19. Please report descriptive statistics for the length of follow-up available in the included trials.

Please see below data on the duration of study treatment in ASCEND and ASCEND-Peds (Table 7 and Table 8, respectively). The duration of exposure is defined as the number of weeks between first infusion and disposition dates (i.e. end of study).

Table 7: Duration of study treatment - ASCEND

ASCEND	Placebo (N=18)	Olipudase alfa (N=18)
Duration (weeks) on study treatment in PAP		
Number of patients with value	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]

Abbreviations: PAP, primary analysis plan; SD, standard deviation

Table 8: Duration of study treatment – ASCEND-Peds

ASCEND-Peds	Olipudase alfa (N=20)
Duration (weeks) on study treatment	
Number of patients with value	[redacted]
Mean (SD)	[redacted]
Median	[redacted]

Abbreviations: SD, standard deviation

A20. For clarity, can you please confirm whether any data points reported in the CS or used in the model were derived from analysis sets other than the mITT set (for clinical data) or safety set (for safety data)?

In the economic model, no other analysis sets than the mITT or safety set from the clinical trials were used.

- The EAG understands that the mITT and safety populations are the same, since no participant received a treatment other than the treatment they were allocated to receive. Can you please confirm this is the case?

In ASCEND and ASCEND-Peds, mITT and safety populations are indeed the same. In study DFI13412 no mITT population was defined.

Clinical outcomes reported for trials of olipudase alfa

A21. A number of clinical data points are provided without accompanying variance data (i.e. SD, SE or 95% Cis). Moreover, several clinical data points are described in text without accompanying data (e.g. “significant improvement in exercise capacity” CS Doc B, p. 93). Please provide missing data points and variance data for all

clinical outcomes reported in the CS. Please ensure that baseline data for all reported outcomes are also reported as these are missing for some outcomes/trials.

Further data on the exploratory endpoints listed on page 93 of the company submission (liver function, lipid profiles, pulmonary function, and efficacy biomarkers (ACE, CCL18, and chitotriosidase) are provided in Appendix N.6. LS mean change from baseline and p-values for treadmill ergometry are provided in Table 26 of the company submission. However, additional data for treadmill ergometry including baseline mean (SD), LS mean change from baseline (SE), and 95% CIs are provided in Table 9.

Table 9: Treadmill ergometry (exercise capacity) – ASCEND PAP mITT population

Test	Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
O_2 uptake (mL/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 52	LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Calculate percent predicted O_2 uptake (%)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 52	LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]
Calculated maximal O_2 uptake (mL/min/kg)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Week 52	LS mean change from baseline (SE)	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value for the difference between groups†	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; O_2, oxygen; SD, standard deviation; SE, standard error.
† The 95% CI and p-values are based on a mixed model repeated measures approach with baseline test, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates

A22. In the CS Section B2.11.3 it is stated that the additional endpoints measured in LTS13632 are reported in Appendix O, however not all these data points are reported. Please provide complete data for missing endpoints.

Please see Table 10, Table 11, and Table 12 for the requested additional endpoints measured in LTS13632 as reported in Appendix O in the company submission (pulmonary function tests, fasting lipid profile, and exercise tolerance, respectively).

Table 10: Summary of pulmonary function tests in LTS13632 safety population

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
Pulmonary function tests					
% Change in FEV1 (% predicted)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 78 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]
% Change in FVC (% predicted)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 78 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
% Change in TLC (% predicted)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 78 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; dl, decilitre; FEV1, forced expiratory volume; FVC, forced vital capacity; mg, milligram; LS, least squares; SD, standard deviation; SE, standard error; TLC, total lung capacity.
† From ANCOVA model: change (or percentage change) from baseline = age group cohorts + baseline value. P-value is for the age effect
‡ From Wilcoxon-Signed Rank test

Table 11: Summary of fasting lipid profile in LTS13632 safety population

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
Lipid profile					
Total cholesterol (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]
HDL cholesterol (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
LDL cholesterol (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]
Triglycerides (mg/dL)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (% change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		LS Mean (SE) †	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
		P-value‡	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; dl, decilitre; HDL, high density lipoprotein; LDL, low density lipoprotein; LS, least squares; mg, milligram; SD, standard deviation; SE, standard error
† From ANCOVA model: change (or percentage change) from baseline value. P-value is testing of change or percentage change from baseline is different from zero.
‡ From Wilcoxon-Signed Rank test

Table 12: Summary of exercise tolerance measured by cycle ergometry in LTS13632 safety population

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
Cycle ergometry (exercise capacity)					
Workload	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Percent predicted maximum workload	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 36 (%	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
	change from baseline)	95% CI†	[redacted]	[redacted]	[redacted]
Working time (min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum heart rate (breaths/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum percent predicted heart rate (%)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum O_2 saturation (%)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum respiratory rate (breaths/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum ventilation (L/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum O_2 uptake (mL/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]

Test	Visit	Statistic	Patients from DFI13412 (Adults) (N=5)	Patients from DFI13803 (Paediatrics) (N=20)	All patients (N=25)
Maximum percent predicted O_2 saturation (%)	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum CO_2 output (mL/min)	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]
Maximum respiratory exchange ratio	Baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Month 66 (change from baseline)	Mean (SD)	[redacted]	[redacted]	[redacted]
		P-value†	[redacted]	[redacted]	[redacted]
		95% CI†	[redacted]	[redacted]	[redacted]

Abbreviations: CO_2, carbon dioxide; CI, confidence interval; dl, decilitre; L, litre; ml, millilitre; O_2, oxygen; SD, standard deviation
† Based on regression of change from baseline with baseline value as covariate

A23. Data points for outcomes in LTS13632 are reported at different timepoints and the rationale for this is unclear. For example, for spleen volume the CS states that follow-up in paediatric participants is available at 66 months but the data point is provided for month 48 (p. 150). Please can you:

- Clarify if a rule was used to select timepoints reported in the CS

As patients entered the LTS13632 study at different times, the timepoint chosen for analysis was the latest assessment with at least 5 patients (adults and paediatrics separately), which was the number of patients deemed necessary for a meaningful analysis. For most outcome measures this timepoint was Month 78 in adult patients and Month 48 in paediatric patients. In a few cases, an earlier timepoint was used to obtain the minimum of 5 patients for analysis.

- Clarify the length of follow-up available for adult and paediatric participants for each outcome of LTS13632, including the available sample size.

The length of follow-up available for adult and paediatric participants for each outcome of LTS13632 are as follows:

Table 13: Length of follow-up for reported outcomes in LTS13632

Outcome	Population	Length of follow-up reported in CS (available sample size)	Maximum length of follow-up recorded (available sample size)
Spleen volume	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]
Platelet count	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]
Liver volume	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]
% predicted DL_{CO}	Adult	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide

- Please include outcomes at final available follow-up in your response to clarification question A21

The outcomes at final available follow-up have been provided by the company in response to question A21.

- On p.169 of the CS it is stated that data up to 9-years is available from LTS13632 to inform transition probabilities in the model. Can you please explain this assertion?

Data up to 9 years is available from LTS13632, however, patients receiving olipudase alfa can only transition to a new health state for up to 2 years.

A24. Please can you confirm whether a responder analysis was conducted for data gathered within the ASCEND extension period, and report these data if so?

As per the statistical analysis plan, responder analyses were carried out exclusively for the PAP.

A25. The CS states that all subgroup analyses conducted were post hoc. Please provide a rationale for the selection of subgrouping categories, including a rationale for why these were selected over other prognostic markers (e.g. those identified in

Eskes 2020) or demographic markers such as age of onset/diagnosis and type B vs. type A/B.

These subgroup analyses were requested by the FDA who did not provide a rationale for the populations that they requested.

A26. The HRQoL results show that treatment results in a benefit for generic HRQoL in paediatric but not adult participants treated with olipudase alfa. In the CS, it is suggested that generic HRQoL measures in adults may be insensitive to change in HRQoL for people with ASMD. Do you have a rationale for why this may be different in the adult vs. the paediatric populations?

The concerns around the sensitivity of HRQoL measures apply to both adult and paediatric populations. The paediatric trial did not have a control arm, preventing evaluation of the treatment related benefit on quality of life.

Section B: Clarification on cost-effectiveness data

Cost-effectiveness evidence

B1. PRIORITY QUESTION. The CS contains deterministic ICERs only. Please provide the probabilistic ICERs for the paediatric, adult and overall populations. It would be helpful if you could present these in a table outlining incremental, costs, LYs and QALYs.

The company have run an additional probabilistic analysis to provide the requested data as shown in Table 14.

Table 14: Base-case (probabilistic) results

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/QALY)	ICER (£/Weighted QALY
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Weighted QALYs		
Paediatric	Olipudase alfa	[redacted]	[redacted]	24.22	[redacted]	[redacted]	24.07	71.64	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	0.15	[redacted]	[redacted]	-	-		
Adult	Olipudase alfa	[redacted]	[redacted]	6.56	[redacted]	[redacted]	15.39	33.79	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-8.83	[redacted]	[redacted]	-	-		
Combined	Olipudase alfa	[redacted]	[redacted]	15.39	[redacted]	[redacted]	19.73	52.72	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-4.34	[redacted]	[redacted]	-	-		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B2. Can you please confirm that the cost effectiveness results reported in Tables 72, 75 and 76 of the CS include the PAS discount for olipudase alfa?

This is correct – the company can confirm that the data shown in Tables 72, 75 and 76 of the submission includes the PAS discount for olipudase alfa.

B3. Please provide additional justification for your decision to conduct a subgroup analysis in the severe population.

Patients with severe disease have the poorest prognosis and are likely to benefit most from treatment with olipudase alfa. They would therefore be expected to have differential cost-effectiveness.

B4. PRIORITY QUESTION. For the severe subgroup, it would be helpful if you could outline what clinical data were used to inform transition probabilities for the paediatric and adult populations and provide clarity on how these were derived.

The data sources and derived transition probabilities applied to the severe subgroup are the same as those considered for the overall population, with the exception of the mortality data used. A pragmatic approach to modelling a severe subgroup was taken whereby the distribution of patients across health states at model entry was modified to represent a more severe population. In addition data from McGovern et al 2013 (9) was used to inform mortality as this was thought to better reflect mortality for the most severe patients. As discussed in the CS the use of SPHINGO-100 data likely underestimates the impact of ASMD on mortality. This is in line with the clinical advice received during an advisory board and from subsequent communications with a clinical expert. This is now being further investigated (10), with initial results suggesting higher mortality in ASMD patients than that derived from SPHINGO-100.

B5. PRIORITY QUESTION. In the CS, the time horizon is stated to be lifetime (100 years), however in the economic model the time horizon is set to 20 years. Can you confirm that the base case cost effectiveness results are estimated using a 20-year time horizon?

This is an error in the model provided – the data from the base case were generated using a lifetime horizon. A corrected version of the model has been provided.

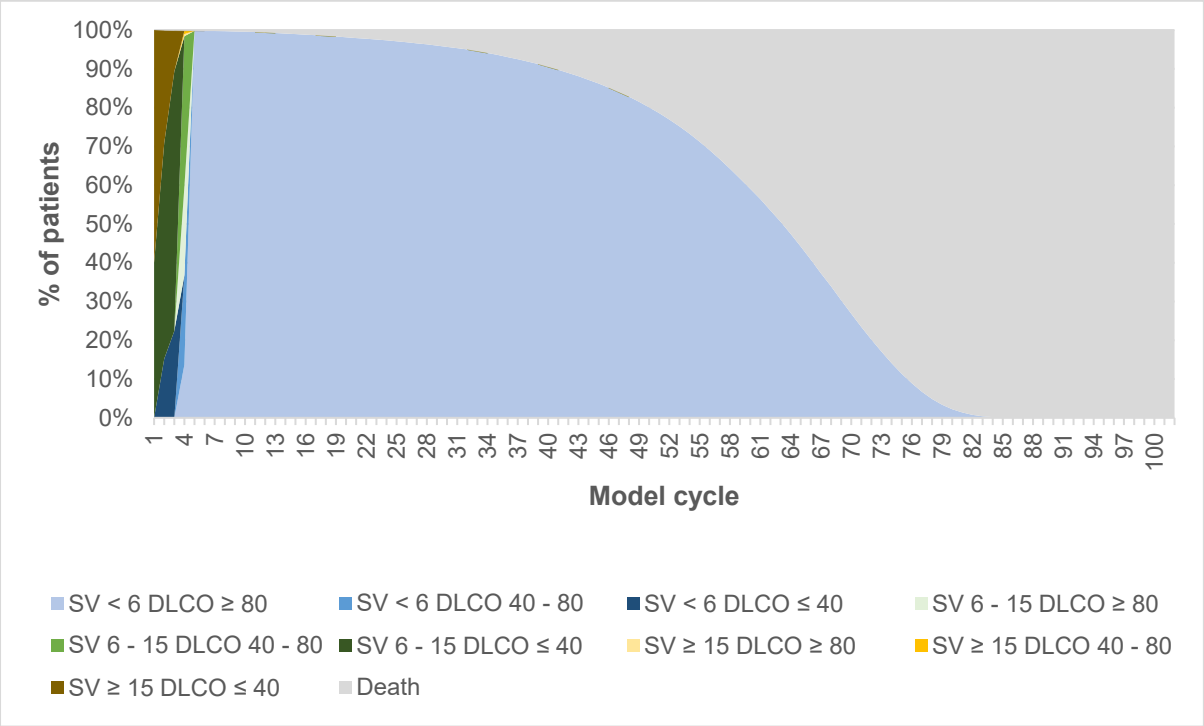
B6. PRIORITY QUESTION. Please provide additional justification for the model assumption for the clinical efficacy of olipudase alfa after year 2, i.e. that patients receiving olipudase alfa only transition to a new health state for up to 2 years, after which they transition to the SV <6 / DLCO >80 state until the end of the time horizon or death.

In the olipudase arm for the first two years patients transition between health states in line with the clinical trial data (11, 12); beyond two years an assumption is made. The assumption that patients transition to the SV <6 /DL_{CO} >80 state is made on the basis that longer term data indicate that patients continue to improve on olipudase alfa and that this is in line with clinical opinion that there would be continued improvement (13).

B7. PRIORITY QUESTION. Please provide additional granularity with respect to the incremental QALY gain (and cost) associated with olipudase alfa, i.e., for the paediatric, adult and overall populations it would be helpful to see a QALY and cost breakdown by health state. Additionally, for each patient population please provide a graphical chart outlining cohort distribution by health state.

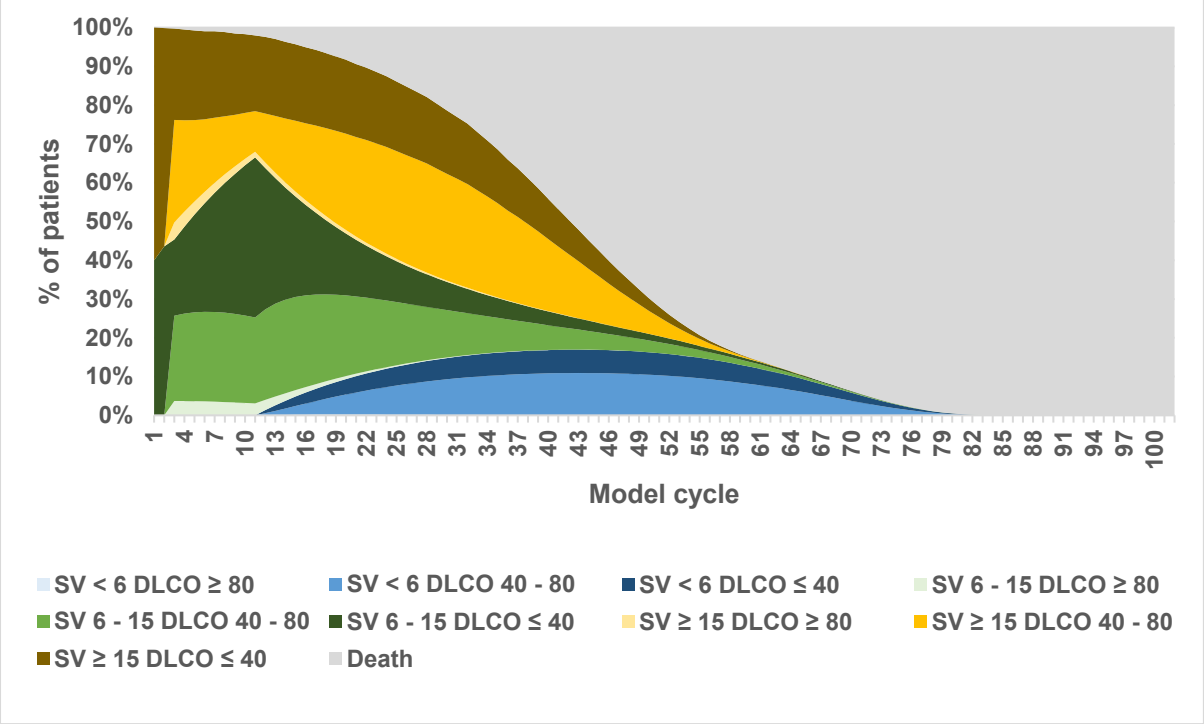
The disaggregated model outputs requested can be found in Tables 93 to Table 96 in Appendix J. Graphical charts outlining the cohort distribution by health state are provided for patients receiving olipudase alfa and BSC in Figure 2 and Figure 3, respectively.

Figure 2: State occupancy in patients receiving olipudase alfa



Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide; SV, spleen volume

Figure 3: State occupancy in patients receiving BSC alone



Abbreviations: DLCO, diffusing capacity for carbon monoxide; SV, spleen volume

B8. In the CS, results for only six scenario analyses were presented (see p.224). Please clearly list all the scenario analyses that were undertaken and provide a rationale for the decision not to report the findings of other analyses in the CS.

All scenarios that were run have been presented in the submission, with no exclusion of scenarios; the model contains additional functionality that was not needed to run these scenarios.

B9. PRIORITY QUESTION. It would be helpful if you could clarify what is meant by 'compliance' in the model (p.210). Is this analogous to relative dose intensity? For instance, does 90% compliance mean that the drug cost for olipudase alfa is based on 90% of the total annual dose.

Compliance is used as a universal term that encompasses missed doses/administrations, alternate doses and so forth – so it is not exactly analogous to dose intensity and instead represents the likely real-world scenario where a proportion less than 100% of the prescribed and scheduled doses are administered.

We confirm the interpretation provided is correct - the compliance percentage is applied to the number of doses received (and thus proportionally to the acquisition and administration costs).

B10. Please provide additional justification for opting to define health states via a combination of spleen volume and lung diffusion of carbon dioxide. Why were other clinical outcomes, particularly those pertaining to the liver, not considered?

In a study designed to identify efficacy endpoints for clinical trials of enzyme replacement therapy, it was observed that SV is correlated with most aspects of disease progression (14). In particular, SV was significantly and strongly correlated with liver volume and negatively correlated with HDL, height z-scores, hemoglobin, and white blood cell count. Nonetheless, SV was weakly correlated with various pulmonary measures, including HRCT ILD score and percentage of predicted DLco. Therefore, defining health states via SV and DLco allows the model to encompass most aspects of disease progression. SV and DLco were the primary endpoints in the ASCEND trial.

Liver outcomes are considered in the model in two ways:

1. By capturing the benefit of olipudase alfa on liver complications through the FIB-4 scores derived from ASCEND liver function tests results

2. By capturing the HRQoL impact of organomegaly (liver volume and spleen volume) within the elicitation of utilities carried out in the ASMD vignette study.

B11. Mortality (standardised mortality ratios), were modelled based the presence or absence of severe splenomegaly. Please outline why severe splenomegaly was selected as the key determinant of mortality in the model.

The only available longitudinal study presenting both survival and clinical endpoint data was the prospective natural history study SPHINGO-100. All available clinical parameters were tested as potential predictors of survival, defined as the time from the date of birth to the date of last visit or death. The only parameter that presented a statistically significantly association with survival was severe splenomegaly as defined using the published threshold of 15 multiples of normal (15).

Clinical experts within an advisory board validated this parameter as indicative of ASMD severity and thus used as is in the model (6).

B12. Please provide justification for the weight applied to the QALYs for the base case analyses for the paediatric, adult and combined populations, referring to sections 6.2.23 to 6.2.25 of NICE health technology evaluations: the manual (2022).

The weighting applied to the QALYs for the base case analyses is in line with the Guidance provided by NICE– in that undiscounted QALY gains between 11 and 30 are multiplied by a proportional weighting between 1 and 3, and QALY gains above 30 are multiplied by a capped weighting of 3. There is compelling evidence that olipudase alfa offers significant QALY gains, with discounted QALY gains of 24.95 in paediatric patients and 16.44 in adult patients despite likely conservative assumptions regarding mortality and patient and family/carer utilities.

Economic model

B13. PRIORITY QUESTION. Please can you clarify the compliance rate used in the model for both the paediatric and adult populations? On p.210 of the CS it

is stated that a compliance rate of 90% is used, however in the 'Treatment costs' tab in the model, it appears that a 95% compliance rate has been used for paediatric patients and 90% has been used for adults.

There is an error in the model provided – the data from the base case were generated using a compliance rate of 90%. A corrected version of the model has been provided.

B14. Can you please confirm that zero drug wastage is assumed in the economic analysis, i.e. that clinicians will be expected to share vials between patients?

According to clinical experts from three different centres (personal communication: [redacted], enzyme replacement therapy doses are routinely rounded up or down to the nearest vial. The same practice was seen in a survey carried out for Pompe disease across all treatment centres and accepted as an appropriate input for the economic analysis in TA821. Vial rounding is therefore expected to be the routine practice in England. As the economic analysis is based on a cohort model, variation in patients' weight, and therefore the number of vials required, is not captured and when the number of vials can be rounded up or down an average number of vials is more appropriate.

B15. Could you please explain why there is a discrepancy between the ICERs reported for the paediatric and combined patient populations on p.213 of the CS, and the ICERs reported in the 'Base case results' tab of the model (see cells J:77 AND I:77).

This is an error in the model, the base case analysis had not been fully run before provision. A corrected version has been provided.

B16. In the 'Base case results' tab of the Base case CEM, please outline which population the ICER in cell F:77 refers to.

The model must be run for adults and children separately – as such the model is run for each in sequence and results/outputs stored in the tables on the right of the worksheet to calculate the weighted average. The values in F77 (and others in that

column) are those representing the last analysis run (adults or children, and by subgroup).

B17. In the 'Scenarios' tab of the Base case CEM, parameter inputs are not appropriately labelled and results have not been provided (for either the adult or the paediatric population). Please amend as appropriate and provide results for all scenarios for both the adult and paediatric populations. Furthermore, for each scenario analysis please provide incremental results.

Given the nature of the model (running child and adult populations separately) the scenarios were run manually rather than via this worksheet/table (as such the table is not informative). The relevant granular results for scenarios are provided in Table 15.

Table 15: Scenario analysis results by patient population

Scenario	Population	Incremental (olipudase alfa vs BSC)			ICER per QALY (£) versus BSC (unweighted)	ICER per QALY (£) versus BSC (weighted)
		Costs (£)	LYG	QALYs		
1.5% discount rate for costs in paediatric cohort	Combined	[redacted]	[redacted]	20.69	[redacted]	[redacted]
	Adult	[redacted]	[redacted]	16.44	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]	24.95	[redacted]	[redacted]
1.5% discount rate for costs in adult cohort	Combined	[redacted]	[redacted]	20.69	[redacted]	[redacted]
	Adult	[redacted]	[redacted]	16.44	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]	24.95	[redacted]	[redacted]
1.5% discount rate for costs in paediatric and adult cohort	Combined	[redacted]	[redacted]	20.69	[redacted]	[redacted]
	Adult	[redacted]	[redacted]	16.44	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]	24.95	[redacted]	[redacted]
Mortality modelled through parametric fit of data from McGovern et al. (2013) (9)	Combined	[redacted]	[redacted]	29.33	[redacted]	[redacted]
	Adult	[redacted]	[redacted]	16.51	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]	42.15	[redacted]	[redacted]
Discontinuation at 80 weeks of 5.56% (zero thereafter)	Combined	[redacted]	[redacted]	15.89	[redacted]	[redacted]
	Adult	[redacted]	[redacted]	12.92	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]	18.86	[redacted]	[redacted]
Patient compliance increased to 95%	Combined	[redacted]	[redacted]	20.69	[redacted]	[redacted]
	Adult	[redacted]	[redacted]	16.44	[redacted]	[redacted]
	Paediatric	[redacted]	[redacted]	24.95	[redacted]	[redacted]

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

Section C: Textual clarification and additional points

C1. Please provide a reference list for the Appendices document.

The references for the appendices document have now been updated and a new version provided which includes the reference list. Reference documents have been previously provided in the original reference pack as part of the company submission.

C2. Table 83 in Appendix M is confusing as several columns do not align with the column headers. Can you please re-submit this table with correct formatting so that the selection criteria for each of the SLR aims is clear?

The selection criteria for each of the SLR aims is provided in Table 84 in Appendix D as opposed to Appendix M. Please find the amended Table 84 below as provided in the company submission.

Table 16: Study selection criteria

Domain	SLR 1. Clinical	SLR 2. Economic Evaluations	SLR 3. Economic Burden	SLR 4. Humanistic Burden	SLR 5. Natural History and Prevalence	SLR 6. Treatment Patterns
Population	Adults and children with a diagnosis of chronic forms of ASMD (i.e., chronic visceral / NPD type B or chronic neurovisceral NPD type A/B); Studies of mixed population of which 80% are of interest					
	Exclude: Non-human subjects, studies on other indications (e.g., infantile neurovisceral ASMD / NPD type A, and NPD type C); mixed populations for which the proportion of patients with chronic forms of ASMD cannot be ascertained.					
Interventions/ Comparators*	Any medical intervention treating the disease or symptoms of chronic forms of ASMD		Any medical intervention treating the disease or symptoms of chronic forms of ASMD, or studies not evaluating specific interventions		Studies not evaluating specific interventions	Any medical interventions treating the disease or symptoms of chronic forms of ASMD
	Exclude: Non-medical interventions, studies not evaluating specific interventions		Exclude: Non-medical interventions		Exclude: Studies evaluating specific interventions	Exclude: Non-medical interventions, studies not evaluating specific interventions

Domain	SLR 1. Clinical	SLR 2. Economic Evaluations	SLR 3. Economic Burden	SLR 4. Humanistic Burden	SLR 5. Natural History and Prevalence	SLR 6. Treatment Patterns
Outcomes	Efficacy: Changes in liver volume Platelet count Spleen volume DL_{CO} Pulmonary function tests Lipid values Safety: AEs Discontinuation rates Deaths	Cost-effectiveness measures: Cost per QALY ICERs Budget impact	Resource use Direct costs Indirect costs (including productivity impacts on patients and caregivers) Resource-specific costs	Validated QoL measures for patients and caregivers, including but not limited to: EQ-5D SF-36 BPI BFI FACIT-dyspnea Utility and disutility values	Mortality Drivers of mortality Complications: Respiratory Splenic Hepatic CVD Major bleeding Breathlessness Fatigue Joint pain Abdominal pain Neurological symptoms Haemoglobin level Liver biochemistry Comorbidities Lipid values Bone mineral density Impact on paediatric growth Prevalence	Current treatment pathways Drivers of treatment choice
Study Design**	Clinical trials, longitudinal studies	Economic evaluations and budget impact models	Clinical trials, observational studies		Observational studies	Observational studies, clinical practice guidelines

Domain	SLR 1. Clinical	SLR 2. Economic Evaluations	SLR 3. Economic Burden	SLR 4. Humanistic Burden	SLR 5. Natural History and Prevalence	SLR 6. Treatment Patterns
	Exclude: Case reports, preclinical studies, non-systematic reviews, commentary, and letters				Exclude: Clinical trials, case reports, preclinical studies, non-systematic reviews, commentary, and letters	
Sample Size	At least 5 patients with chronic forms of ASMD					
Other	English-language					

* “Medical interventions” may include enzyme replacement therapy, surgery, transplantation, pharmacologic treatments, oxygen supplementation; “Non-medical interventions" include approaches such as lifestyle modification, vitamin supplementation, physical exercise, educational progammes.
** “Clinical trials” include both randomized and single-arm designs; “Observational studies” include prospective, retrospective, and cross-sectional designs, such as claims database analyses, medical record reviews, surveys, registry analyses, and case series; “Economic evaluations” include cost-utility models, cost-benefit analyses, and other cost-effectiveness analyses.
▪ Sample size criteria will not apply to prevalence studies.
Abbreviations: AE, adverse event; ASMD, acid sphingomyelinase deficiency; BFI, Brief Fatigue Inventory; BPI, Brief Pain Inventory; CVD, cardiovascular disease; DL_{CO}, lung diffusion of carbon monoxide; EQ-5D(-5L), EuroQoL Five Dimensions (Five Levels); FACIT, Functional Assessment of the Chronic Illness Therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life; SF-36, 36-item Short Form health survey; SLR, systematic literature review

C3. PRIORITY QUESTION. Tables containing efficacy data from the trial CSRs have not been provided in the reference pack. Can you please provide all CSR appendices?

Efficacy data from trial CSRs, as listed below, have now been added to the updated reference pack provided.

- DFI12712 (ASCEND). CSR. 16.2.6. efficacy response data (16)
- DFI13803 (ASCEND-Peds) CSR. 16.2.6. efficacy response data (17)
- DFI13412. CSR. 16.2.6. efficacy response data (18)
- LTS13632. CSR. 16.2.6. efficacy response data (19)

References

1. Sanofi. CSR: NCT00410566. A Phase 1, single-center, single-dose, dose escalation study of recombinant human acid sphingomyelinase (rhASM) in adults with acid sphingoymelinase deficiency (ASMD). Data on file. 2010.
2. McGovern MM, Wasserstein MP, Kirmse B, Duvall WL, Schiano T, Thurberg BL, et al. Novel first-dose adverse drug reactions during a phase I trial of olipudase alfa (recombinant human acid sphingomyelinase) in adults with Niemann-Pick disease type B (acid sphingomyelinase deficiency). Genet Med. 2016 Jan;18(1):34-40.
3. Sanofi. Data on file. Critical appraisal ratings for Cochrane AROB and ROBINS assessment. 2022.
4. McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. Neurology. 2006 Jan 24;66(2):228-32.
5. Wasserstein MP, Aron A, Brodie SE, Simonaro C, Desnick RJ, McGovern MM. Acid sphingomyelinase deficiency: prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. J Pediatr. 2006 Oct;149(4):554-9.
6. Sanofi. ASMD Advisory Board, March 2022. Data on file. .
7. MHRA. SPC olipudase alfa. Available fro: https://mhraproducts4853.blob.core.windows.net/docs/m1000013. Last accessed September 2022. .
8. Villarrubia J, Wasserstein M, Barbato A, Gallagher RC, Giugliani R, Guelbert NB, et al. Pb2314: Olipudase Alfa for Adults with Acid Sphingomyelinase Deficiency: Improvements in Crossover Placebo Patients and Further Improvements in Original Olipudase Alfa Patients after 2 Years in Ascend Trial. Hemasphere. 2022 Jun 23;6(Suppl):2183-2184. doi: 10.1097/01.HS9.0000852080.43506.a5. eCollection 2022 Jun.

9. McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann-Pick disease. Genet Med. 2013 Aug;15(8):618-23.
10. F. Laredo, M.V. Munoz-Rojas, G. Gusto, A. Chandak, A. Khachatryan, T. Banon, et al. Survival of Patients with Acid Sphingomyelinase Deficiency (ASMD) in the United States (US): A Retrospective Real-world Study. Sanofi data on file. . 2022.
11. Sanofi. CSR: DFI13803 (ASCEND-Peds). A Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency. Data on file. 2020.
12. Sanofi. CSR: DFI12712 (ASCEND). A Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, repeat dose study to evaulate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency. Data on file. 2021.
13. Sanofi. CSR: LTS13632. A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency. Data on file. 2021.
14. McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics. 2008 Aug;122(2):e341-9.
15. Sanofi. CSR: MSC12840 (SPHINGO-001-00). A prospective, cross-sectional survey study to collect natural history data in patients with Niemann-Pick B disease. Data on file. 2015.
16. Sanofi. DFI12712 (ASCEND). CSR. 16.2.6. efficacy response data. Data on file. 2021.
17. Sanofi. DFI13803 (ASCEND-Peds). CSR. 16.2.6. efficacy response data. Data on file. 2020.
18. Sanofi. DFI13412. CSR. 16.2.6. efficacy response data. Data on file. 2014.
19. Sanofi. LTS13632. CSR. 16.2.6. efficacy response data. Data on file. 2021.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

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

Clarification questions for the addendum to the original company submission

July 2023

File name	Version	Contains confidential information	Date
ID3913 Company response to EAG clarification questions to CS addendum.docx	1	Yes	28/07/2023

Section A: Clarification on additional data provided in the addendum

A1. Can you please confirm that the only change to the model in this addendum has been to the modelling approach for mortality; that is, overall survival has been estimated using a parametric modelling approach for BSC (using the pooled data analysis provided in the addendum) and a hazard ratio of 0.1 has been used for patients receiving olipudase alfa?

The company can confirm that there were no changes other than to the OS modelling approach for BSC and application of a hazard ratio to model the effects of olipudase alfa on OS.

A2. Could you please clarify where the 0.10 mortality hazard ratio for olipudase alfa was taken from?

In the original submission, the overall survival was modelled using data from the SPHINGO-100 observational, natural history study. In this study, the hazard ratio (HR) for OS comparing patients with spleen volume ≥15 MN (patients with severe splenomegaly) and <15 MN (without severe splenomegaly) was 9.99 (95% CI: 1.03; 97.14) (1). As olipudase alfa decreases spleen volume in patients with ASMD, the relationship between patients with and without severe splenomegaly was used to inform the mortality HR in the parametric modelling approach in the addendum.

A3. In the original company submission (CS), mortality was modelled using standardised mortality ratios (SMRs). Please provide additional rationale for adopting a parametric survival modelling approach in this addendum.

Clinical opinion was sought after the initial submission on the alternative approaches to modelling OS. The parametric fit approach was indicated as being more suitable compared with the SMR approach based on the fact that it followed the observed Kaplan-Meier survival data more closely. This was due to a high level of mortality being observed before the age of approximately 20 years; this would account for patients with the most severe disease. A plateau was observed until approximately 50 years of age followed by a high level of mortality which would account for patients with mild-moderate disease. Additionally, the high level of mortality before the age of approximately 20 years is not observed in the survival curves generated using the SMR approach. Consultants indicated that the parametric fit is easier to understand in the context of known ASMD disease progression. The overall opinion of the consultants was that the parametric fit was the more plausible approach.

A4. Do you have data to support the generalisability of the pooled data analysis to the UK population, given that no patients from the UK were included?

Clinical opinion was sought on the generalisability of the pooled data analysis to the UK. The clinical opinion indicated that the patient sample group and baseline characteristics appeared suitable. More specifically, consultants in inherited metabolic disease indicated that due to only supportive care options being available, there was no reason to expect the UK to have a substantially different patient

population to the rest of the world.

A5. In the NICE Sanofi HST Addendum (Table 1), AIC/BIC statistics appear to be presented for parametric models in the adult population. Please provide AIC/BIC statistics for parametric models in the paediatric population.
All analyses were carried out using the full dataset (for both adult and paediatric patients) and therefore there are no separate AIC/BIC statistics for the paediatric population. The only difference in the economic model is the starting age of the patients.

A6. Can you confirm that Figure 2 in the NICE Sanofi HST Addendum provides KM and parametric survival curves for the adult population?

Yes, Figure 2 in the NICE Sanofi HST addendum includes the Kaplan-Meier curve with the parametric fit curves superimposed.

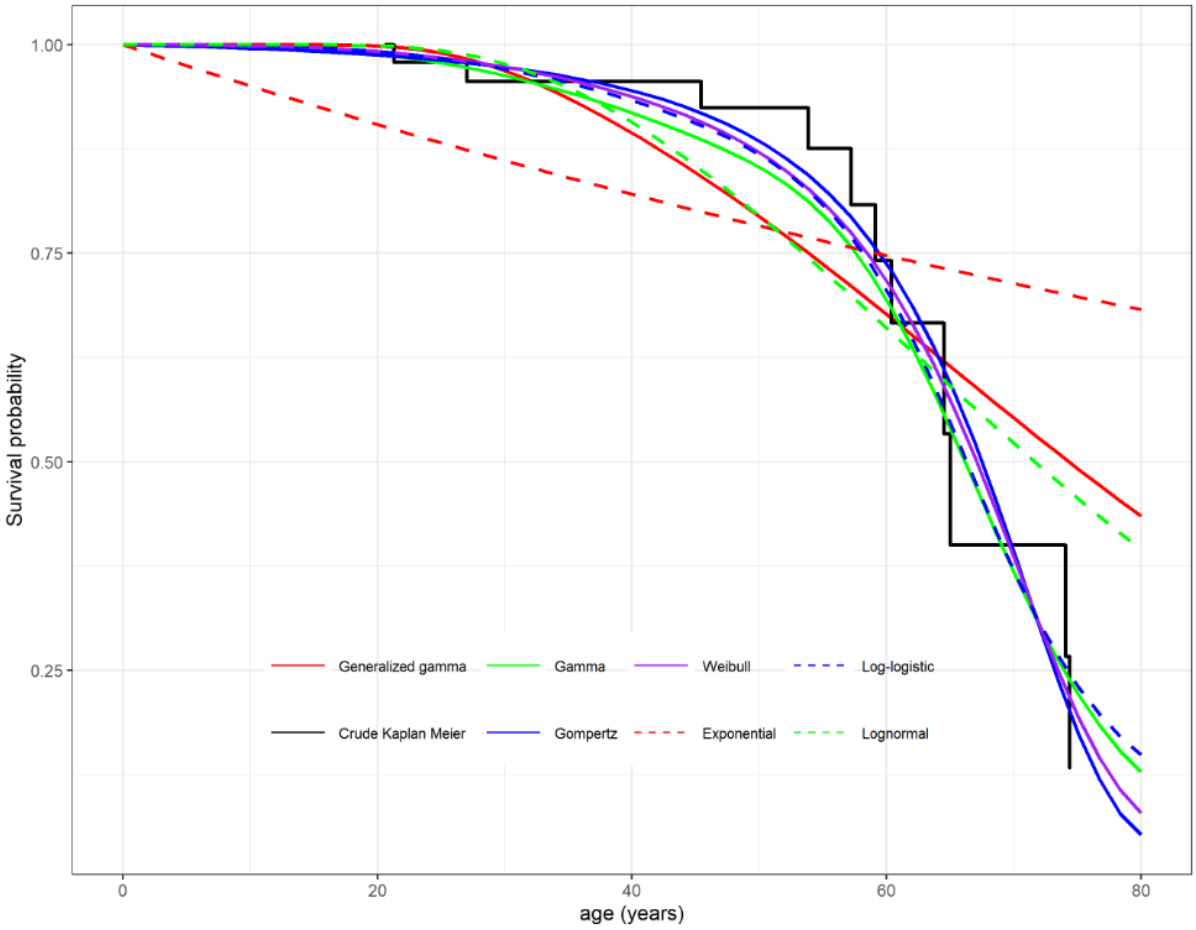
A7. For adults, overall survival was estimated via a piecewise approach whereby a Gompertz distribution was used before 40 years and a Weibull distribution after 40 years. Please provide rationale for selecting 40 years as the cut-point at which a Weibull model was applied

The decision to use 40 years as the cut-off point which separated the Gompertz and Weibull distribution was based on the fact that the survival curve plateaued at approximately 40 years. The plateau in the survival curve from approximately 30 years to 50 years was observed after the high level of mortality associated with patients with the most severe disease and before the high level of mortality associated with patients with mild-moderate disease. Splitting the curve allowed the model to achieve a good fit both before and after the cut-off point.

A8. In the supplied survival analysis report (Fig 20.c), the Weibull distribution was not presented. Please can you resubmit this figure to include the Weibull distribution?

The updated figure with the Weibull distribution included is presented in Figure 1.

Figure 1: Survival curves



A9. For paediatric patients, a one-piece Weibull distribution was used to estimate overall survival for BSC patients. However, based on fig 20.b in the supplied survival analysis report, the Weibull resulted in one of the lowest survival probabilities and did not appear to fit the KM data in the long term. Please therefore can you please provide justification for selecting the Weibull?

The Weibull distribution was selected as it was considered it reflected the more severe presentation of ASMD in paediatric-onset patients compared to adults.

A10. Updated base case and scenario analyses results (Tables 2-4 in the NICE Sanofi HST Addendum) were only presented using weighted QALYs. Please can you provide these results using un-weighted QALYs?

The updated result tables with both weighted and un-weighted QALYs included are provided in Table 1, Table 2 and Table 3 below.

Table 1: Base-case results

Technologies		Total			Incremental (olipudase alfa vs BSC)				Unweighted ICER (£/QALY)	Weighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	QALYs (weighted)		
Children	Olipudase alfa	[redacted]	[redacted]	25.13	[redacted]	[redacted]	36.28	108.87	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-11.15	–	–	–	–		
Adult	Olipudase alfa	[redacted]	[redacted]	16.55	[redacted]	[redacted]	20.85	62.55	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-4.30	–	–	–	–		
Combined	Olipudase alfa	[redacted]	[redacted]	20.84	[redacted]	[redacted]	28.57	85.71	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-7.73	–	–	–	–		

Abbreviations: BSC, best supportive care; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 2: Summary of scenario analyses (paediatric population)

Scenario	Incremental (olipudase alfa vs BSC)				Unweighted ICER (cost/QALY) versus BSC	Weighted ICER (cost/QALY) versus BSC
	Costs (£)	LYG	QALYs (unweighted)	QALYs (weighted)		
Piecewise: Gompertz-Gompertz	[redacted]	[redacted]	29.99	89.97	[redacted]	[redacted]
Piecewise: Gompertz-Weibull	[redacted]	[redacted]	31.00	93.00	[redacted]	[redacted]
One-piece fit: Gompertz	[redacted]	[redacted]	22.43	67.28	[redacted]	[redacted]
One-piece fit: Weibull	[redacted]	[redacted]	36.29	108.87	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 3: Summary of scenario analyses (adult population)

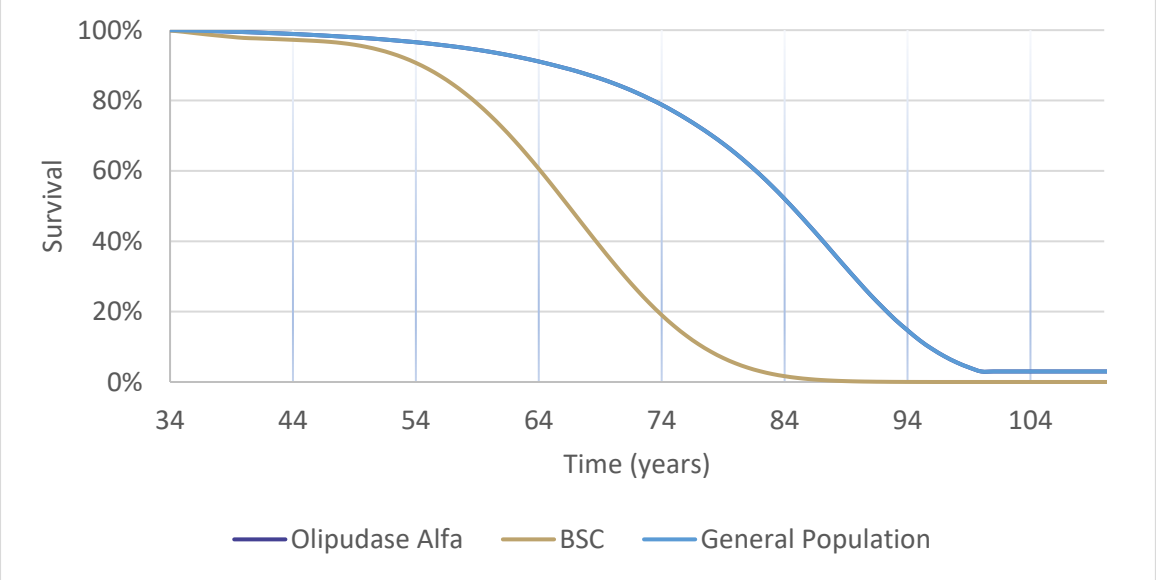
Scenario	Incremental (olipudase alfa vs BSC)				Unweighted ICER (cost/QALY) versus BSC	ICER (cost/QALY) versus BSC
	Costs (£)	LYG	QALYs (unweighted)	QALYs (weighted)		
Gompertz-Gompertz	[redacted]	[redacted]	19.20	56.14	[redacted]	[redacted]
Gompertz-Weibull	[redacted]	[redacted]	20.85	62.55	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year.

A11. Based on Figure 4 in the NICE Sanofi HST Addendum, there was no difference in modelled overall survival between BSC and olipudase alfa in the adult population. However, as per Table 2, olipudase alfa resulted in an incremental LYG versus BSC. Please can you clarify the reason for this discrepancy?

Upon review of Figure 4 in the NICE Sanofi HST Addendum, it was found that the footnote text is incorrect. The footnote label should have been '* olipudase alfa curve is not visible as it overlaps with the general population curve'. The revised figure is included in Figure 2 below.

Figure 2: Model projections of survival for adults treated with olipudase alfa, BSC, and the general population



Abbreviations: BSC, best supportive care.

* olipudase alfa curve is not visible as it overlaps with the general population curve.

References

1. Kapetanakis V, Shukla P, Fournier M, Folse H, Pulikottil-Jacob R. Analysis of overall survival in patients with acid sphingomyelinase deficiency type B using the standardized mortality ratio method. Poster presentation presented at the 18th Annual WORLDSymposium, February 7–11, 2022, San Diego, CA, USA. 2022.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	Elaine Murphy
2. Name of organisation	British Inherited Metabolic Disease Group. Also representing University College London Hospitals NHS Trust.
3. Job title or position	Consultant adult inherited metabolic disease – Charles Dent Metabolic Unit, UCLH.
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes – as above. A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Inherited Metabolic Disease Group – a charity with the aim of advancing the education of individuals (doctors, nurses, dietitians, psychologists, clinical scientists and pharmacists) involved in the diagnosis, care and treatment of people with inherited metabolic disease, and promoting research in the field. Funded by membership subscriptions.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	BIMDG has received sponsorship for its annual conference from the manufacturer. The Charles Dent Unit has participated in clinical trials of olipudase alfa in adults.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. To improve hepatosplenomegaly and associated complications. 2. To improve respiratory disease / interstitial lung disease. 3. To improve haematological disease. 4. To improve bone disease and associate complications. 5. To prevent significant morbidity and premature death from pulmonary and liver disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Studies have shown clear (clinically significant) improvements in: • Liver volume (can reach normal volume with treatment) • Spleen volume (can reach normal volume with treatment) • DL_{CO} of the lung (can reach normal values with treatment) • Forced vital capacity (can reach normal values with treatment) • Interstitial lung disease (significant improvements in most individuals; stability in some) • Bone mineral density (increase from osteopenia to normal BMD) • Reductions in biomarkers (lyso-sphingomyelin and chitotriosidase) to normal / close to normal ranges. • Lipid profiles (reductions in HDL-cholesterol can reach normal values)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – this is the only disease specific treatment available for NP A/B that can address all non-neurological aspects of the condition. It is life-transforming.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Supportive measures. • Nutritional support (+/- feeding tubes) • Respiratory support (including supplemental oxygen and treatment of infections) • Support for liver disease (including consideration of liver transplant on occasion) • Blood products if required. • Treatment for low bone mineral density eg. calcium, vitamin D.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Wasserstein M, Dionisi-Vici C, Giugliani R, Hwu WL, Lidove O, Lukacs Z, Mengel E, Mistry PK, Schuchman EH, McGovern M.Mol Genet Metab. 2019 Feb;126(2):98-105. doi: 10.1016/j.ymgme.2018.11.014. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, Eugen Mengel K, Mistry PK, Schuchman EH, Wasserstein MP.Genet Med. 2017 Sep;19(9):967-974. doi: 10.1038/gim.2017.7.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Patients should be referred to one of the paediatric or adult LSD specialist services. It would be expected that all diagnosed patients are known to a specialist centre.

9c. What impact would the technology have on the current pathway of care?	Patients would continue to be reviewed at specialist LSD centres. Once biochemical and clinical parameters had improved / normalised then supportive treatment measures could be reduced and patients would enter a surveillance programme, with minimal need for treatment other than ongoing enzyme replacement therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Similar to ERT for other LSDs eg. Gaucher disease.
10a. How does healthcare resource use differ between the technology and current care?	As for questions 9c and 10.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Diagnosis, initiation of treatment and surveillance via LSD specialist services. It is likely that dose escalation will take place in the specialist LSD centre (hospital environment). Ongoing treatment (regular intravenous infusions of olipudase alfa) could be moved to homecare once patients are stable.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As for questions 9c and 10. Dose escalation is likely to be done in a hospital setting.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – see above.
11a. Do you expect the technology to increase length of life more than current care?	Yes – see above.

11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – see above.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Olipudase alfa is not expected to directly impact on neurological disease in those patients who have neurovisceral disease (although it will still improve the visceral component of their condition).

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As above. Regular intravenous ERT is widely accepted among many different patient groups.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	

include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes – as above. See question 7.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – as above. See questions 7 and 8.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Infusion associated reactions are possible. Dose escalation is required in order to avoid the possibility of rapid release of active sphingomyelin metabolites. The specialist LSD centres are experienced in managing the above.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Patients who participated in clinical trials are now able to receive treatment at home.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s)	No.

since the publication of NICE HST guidance [HSTXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	In our experience (we have had a number of adult patients participate in the clinical trials and subsequent extension treatments), the benefits as listed above have continued and been sustained. No patient has relapsed.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Olipudase alfa is effective in improving clinical parameters (liver and spleen volumes, lung function, bone mineral density) • Olipudase alfa is effective in improving biochemical parameters (lipid profile, chitotriosidase, lyso-sphingomyelin) • Olipudase alfa is well-tolerated • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	Toni Mathieson
2. Name of organisation	Niemann-Pick UK (NPUK)
3. Job title or position	CEO
4a. Brief description of the organisation (including who funds it). How many members does it have?	Niemann-Pick UK was established in 1991. We are the only patient organisation providing information, support and advocacy services to patients affected by ASMD Niemann-Pick disease and Niemann-Pick disease type C, plus their families and the professionals involved in their care. Our charitable objectives are to relieve sickness and any distress which may arise there from, and to advance the education and awareness of families, professionals and the general public in all matters concerning the disease. Our vision is a world where the burden of Niemann-Pick disease is minimised, those affected have access to effective therapies, can meaningfully participate in society, reach their full potential and achieve the best quality of life possible. Our organisation has the widest experience of supporting Niemann-Pick patients and their families in the UK, developed over 31 years. We aim to make a positive difference to the lives of those affected, from diagnosis to bereavement and beyond, through the provision of individualised support and advocacy services, delivered by our expert team. Since 1999, we have funded the post of a full time Clinical Nurse Specialist (CNS), currently based at Salford Royal Hospital, and working in conjunction with the designated NHS specialist centres in England to provide expert care and practical advice in clinic and at home. We also provide non-clinical advice and advocacy, mental health and wellbeing support via a 24-hour helpline, website and social media activities, plus a range of educational resources and mutual support opportunities. We collaborate nationally and internationally with other patient organisations and relevant institutions. International links are vital in providing support and information to patients and families affected by ultra-rare conditions such as ours. In 2009, we cofounded the International Niemann-Pick-Disease Alliance, a network of 24 patient organisations working to support those affected by NPD across 17 countries. In 2012, we played a leading role in the development of the International Niemann-Pick Disease Registry (INPDR). This disease-specific registry collects clinical and patient-reported data, documenting the patient experience and supporting clinical and epidemiological research. Currently, we support approx. 90% of known UK patients (149) affected by Niemann-Pick diseases, both ASMD Niemann-Pick disease (37) and Niemann-Pick disease type C (112). In addition, we support immediate and extended family members, families that have been bereaved, and we offer information for health, social care and research professionals. For example, “A Guide to ASMD Niemann-Pick Disease Types A and B for Healthcare Professionals” is included as part

	this submission. We share our newsletter and disease updates to more than a thousand people worldwide and we do not charge a membership fee. We are entirely supported by grants, voluntary donations and fundraising. Currently, our work is funded by the Charities Aid Foundation (CAF), the Pears Foundation, the Joan Ainslie Charitable Trust, BBC Children in Need, the Hollie Foundation, the Tesco Community Foundation and unrestricted educational grants from industry.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the evaluation stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	In the last 12 months, we have not received funding from the company bringing the treatment to NICE for evaluation and there are no comparator treatment companies. We have received unrestricted educational grants from two companies working in the Niemann-Pick type C field, amounting to £60k and equivalent to 25% of our total grant funding income.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have very strong links with the community we serve. This is built upon the quality of services that we provide, and how we are viewed by those we support: honest, trustworthy and working with integrity. The work of our Care and Support team enables direct and regular communication and conversation about the needs of those within our community and how they change over time. These strong relationships ensure we can reach all relevant patients and carers and to ensure they have equal opportunity to share their thoughts and experiences with us. We recognise the value of the patient voice and experience in shaping the services we provide. Therefore, patient experience data is gathered throughout the year, not just for specific purposes. We employ different methods to capture

	this experience, including hosting focus groups and workshops, providing one to one interview sessions (in person and virtually), direct feedback to staff team members and the use of self-completion surveys. Utilising the strength of two national patient organisations and our own registry (Niemann-Pick UK, the National Niemann-Pick Disease Foundation (NNPDF) and the International Niemann-Pick Disease Registry (INPDR)), we commissioned an organisation called Rare Disease Research Partners (RDRP) to conduct a survey *"The impacts of olipudase alfa on paediatric patients with ASMD and their families"* to highlight the patient experience and perspective regarding the burden of disease, burden of therapy, benefits of therapy, risks, and tolerance of risk. The study aims were to: (1) increase the understanding of the impacts of ASMD on paediatric patients and their families, (2) explore the effects of olipudase alfa on paediatric patients and their families and (3) gain insights from patients and their families into the unmet need for treatment of ASMD. We engaged with RDRP as a professional third-party research organisation to reduce bias and maintain scientific rigor. The purpose of this study was to collect additional evidence, from the patient and caregiver perspective, on the impact of olipudase alfa therapy on paediatric patients with acid sphingomyelinase deficiency (ASMD). This supplements clinical trial results and provides additional information to support our submissions to regulatory agencies. The final survey report is included as an appendix to this form. Patients and carers have also contributed to the development of informative publications, including "Acid Sphingomyelinase Deficiency Niemann-Pick disease type B: A practical guide for individuals, parents and carers", a copy of which has been included with this submission. First produced in 2011, this publication is currently being updated with the support of the ASMD patient community with the revised version available in print later this year

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	ASMD is a progressive and life-limiting disease which significantly reduces life expectancy. Clinical features of the disease result in significantly debilitating symptoms and multiple long-term healthcare needs, resulting in significant health service input involving frequent hospital appointments with multiple clinical specialties, and frequent monitoring tests and investigations. Natural history studies have shown that patients die of lung and or liver disease at an early age, this is reflected by our experience during the past 30 years of supporting those affected. The severity of symptoms often prevents patients from fully participating in daily activities, affecting their ability to attend school, to work and take part in activities they wish. This places great psychological and financial strain on patients and their families. Being an ultra-rare condition, with knowledge and understanding limited to a handful of expert centres, patients can feel bewildered and isolated due to conflicting advice or a lack of information specific to their condition. The psychosocial impact of ASMD for both patients (body image, bullying, unable to socialise, standing out as being different) and their carers (anxiety, guilt, relationship breakdown, loss of earnings, genetic implications for family planning) is significant. Patients describe reaching a point 'of no return' in their disease progression, where the disease 'creeps up' without early indicators, suddenly taking over. Patients often don't realise how clinically unwell they are, as feeling unwell is their 'normal'. This was highlighted during the clinical trial of this technology, with those participating reporting significant changes in their energy and wellbeing, with the realisation of how limiting their condition was on daily life prior to the trial. Patients and carers have reported the following disease manifestations and impacts of living with ASMD: increased and significant fatigue, shortness of breath, enlarged organs and increased abdominal girth, early satiety, risk of spleen rupture, liver disease and cardiac issues. In addition, the psychosocial impact for patients is a major factor and includes negative body image, a sense of 'feeling different', a consequent of the abdominal swelling, due to significantly enlarged abdominal organs. <u>Bone issues</u> ASMD affects bones, with patients more likely to be affected by bone thinning (osteopenia/osteoporosis). Patients report bone pain, muscular pains, back pain (due to the weight and size of the enlarged spleen / liver), and due to bone thinning, an increased risk of fracture. <u>Enlarged organs</u> An enlarged spleen and/or liver is common in ASMD patients, causing considerable discomfort and pain. Furthermore, the enlarged organs restrict lung capacity, causing breathing problems, puts pressure on the stomach, affecting one's ability to eat usual sized meals, impacting digestion, causing nausea and frequent vomiting. An enlarged spleen is susceptible to injury, consequently patients are prevented from usual play / sports activities due to this risk, reducing social opportunities and reinforcing the sense they are different. A further consequence of the enlarged spleen is hypersplenism, with associated anaemia, thrombocytopenia, and risk of bruising or bleeding, and a low white blood cell count, with an increased risk of infection.

	"I was diagnosed when I was three years old, and from an early age I knew that I was different, that I was special. Unlike the other kids I was always going into hospital for tests. I had to have blood tests, flu jabs, x-rays, overnight stays at the hospital for monitoring. But the biggest hint was my large tummy that was noticeable from being a toddler." "As I progressed into my teens, that's when I started to take more notice of what was wrong with me. I was and still am noticeably shorter than the other boys and due to my over-sized, liver and spleen I had to sit out of PE lessons whenever we did full contact sports such as rugby. I had to quit playing football in my team as I was in danger of getting hurt as the other teams didn't know what was wrong and I was an easy target due to my size." "He is still a very happy boy, but no child wants to be throwing up five times a day. And he'd wake up first thing in the morning throwing up, and it was just uncomfortable for him to sit for really short periods of time. You could just tell it was uncomfortable in his belly. So, it affected really all areas of his development." (Interview, before treatment, started treatment at 2 years of age) <u>Bruising and Nosebleeds</u> ASMD patients can experience frequent nosebleeds, which can be challenging to manage and, in some cases, requires medical intervention. Many also report difficulties in stopping bleeding, if injured. Bruising easily and frequently is also reported "And then really hard to stop his bleeding, he didn't have nosebleeds, but if he got a cut or a scrape… You could see the effect of the disease on the spleen, like that part was hard, it was very to get his bleeding to stop, although he never really had nosebleeds, which was interesting with him." "Bruising was very noticeable at a very early stage, I dreaded putting our son in short trousers as he looked as though he had been beaten, his legs and arms pickled with bruises from normal play, On one occasion after surgery to remove a cyst from his cheek, on returning to the hospital to have his stitches removed, he was whisked off and my husband and I questioned, as they really could not believe that the amount of bruising he had on his face was a result of the surgery, eventually a call to our consultant confirmed that bruising due to low platelets does take place. The nosebleeds happened a lot later, probably when he was 13, alarming at first but we all soon learnt how to cope with them, he had his nose cauterised a couple of times, again though this was due to his low platelets, as a side effect of his enlarged spleen" <u>Slow growth and delayed puberty</u> Delayed growth and puberty due to ASMD is a source of significant anxiety and distress for patients. Children feel 'different' and this often leads to increased insecurity and negative body image, as they watch their peers 'growing up' whilst they remain 'a child'. In some cases, puberty does not happen until late twenties, with patients remaining shorter in stature "At 23 my son is still showing very few signs of puberty, his voice is slightly deeper, and he gets an occasional spot, but he had no body hair, so appearance wise looks about 15. We have been told he may not reach puberty until his late twenties. The effects of this are that he has friends who are girls, but no girlfriend; he is constantly being evicted from pubs, as they think he is underage, although his driving licence now helps, shops refuse to sell him certain items, and when starting his own business no one took him seriously."

	Body image Patients experiencing delayed growth and puberty, plus enlarged organs resulting in a swollen stomach often leads them to feel self-conscious and 'different'. This changes the way they see themselves, especially when they compare themselves to their peers. This results in a negative body image and low self-esteem and with slow growth and delayed puberty, with feelings developing into psychological issues and often continuing into adulthood. "I remember that sometimes she cried, and when I tried to explain that her belly was somewhat different from the belly of other children, and that we had to be careful with it, sometimes she really started to cry and she was very sad. Sometimes she really got sad, and she said, I don't want to have another belly than other children." Tiredness & Fatigue Tiredness and fatigue is a common symptom for people living with ASMD and results in patients having to make adjustments in their daily work/school and social lives to compensate. As patients have an enlarged spleen, this affects the level of red blood cells, leading to anaemia and less oxygen being transported around the body, causing fatigue. An enlarged spleen uses up a lot of energy from calories consumed and patients find it difficult to take in additional calories due to pressure this causes on the stomach, limiting intake of food and requiring patients to eat little and often. "Tiredness and fatigue is the most noticeable effect of the disease. My endurance is quite limited and my concentration has suffered as a result, though careful planning helps to counteract this. I began noticing the tiredness much more after a serious stay in hospital when I was 17. It was quite jarring to suddenly have to be carted about by my parents in the car all the time at that age.", "…And as time passed by, we noticed that her energy level decreased, and when she got home from school, she asked us to go to bed.[…] And we also noticed that if she had to walk a certain distance, that it was difficult for her to catch up with the other children because she was always tired." Shortness of breath ASMD patients can experience breathing difficulties and shortness of breath in completing everyday tasks such as climbing stairs, getting dressed or walking short distances. Patients report an extremely unpleasant feeling of finding it more difficult or uncomfortable to breathe, to a greater degree than you would normally expect during exercise. Storage in the lungs reduces the flow of oxygen to the body's cells, with most ASMD patients showing evidence of interstitial lung disease. And being more prone to respiratory infections. "It was her favourite thing to do is play tag. […] And when she'd run and she'd be holding her stomach to get away, she'd get to the safe spot, and you could see her just always out of breath." Disruption to family and social life Multiple medical appointments and screening tests often limit a patient and carers ability to go about their daily lives, with time away from school or work impacting on their ability to achieve educational goals or financial stability. This impacts heavily on family life and disrupts routines for the patient and other members of the family. For patients, extreme fatigue is also a factor that prevents full participation in usual daily and social activities. Adaptations to the home, or supportive measures at school or work may also be required.

	"Our son was diagnosed prior to starting Primary School, so before he started, I met with the Headmaster and explained my fears about his safety. Being so rare, ASMD doesn't fit into any of the 'tick boxes' or follow any standard procedures. By getting the school on side by communicating on a personal level; working with the school nurse on a care plan; giving a little informal talk to all the teachers and by sharing my fears and emotions with his main teacher each year; my son's care at school has been absolutely excellent. From little things like making sure he is always at the front of a queue so his spleen and liver won't get knocked, to putting in a lower urinal because he was shorter than the other boys and couldn't reach!" Bullying In ASMD, bullying is reported all too often, due to a lack of understanding the condition or the fact that patients may be regarded as 'different' due to their physical appearance, for example if they have a shorter than average stature or an enlarged spleen. It can also happen if they are seen to be receiving special allowances or additional support at school, or they get to sit down whilst their peers must stand. Bullying can make the difference between a child's life being tolerable or miserable. Research suggests that children with disabilities or long-term conditions are three times more likely to be bullied than their peers. "Everyone was taller than our son; this caused him problems at school with name-calling, bullying and lack of female interest. Although it sounds unkind we would light heartedly tease him, long before he went to school, he got used to being teased, so when the children at school started it didn't seem to hurt so much. He picked big friends, who were really great and protected him." "When I first started my new school people made up a rumour that I was pregnant because of the size of my belly; but no-one says it now because everyone knows me." Mental Health – Patients Living with ASMD is challenging and results in numerous psychological stresses including extensive medical testing and uncertainty of disease course, coping daily with the effects of a chronic illness, and grief and bereavement surrounding this progressively debilitating, and ultimately, fatal disease. Patients develop a different perspective on life to their peers. Five major findings emerged from a study conducted by the University of California: (1) limited physical activity, social isolation, and peer rejection were identified as significant stressors; (2) stressors had a specific impact during the age span of 10–16 years; (3) parents and adult patients expressed frustration regarding the lack of available information and treatment; (4) patients described close family relationships as a way of coping with illness; and (5) adult patients identified early medical experiences as having a considerable psychological impact. "And it was very obvious through her leotard that her stomach was somewhat extended for a certain reason. Kids would ask her why is your stomach so big, blah, blah. So, it was noticeable, not to us, but just to other people, as well. […] I think she was just a little bit distracted, to a degree, and thinking about other issues within her body that were uncomfortable. […] I think it was more of a psychological impact, possibly, because she was so much smaller than everyone, and her stomach was bigger."

	"Every day she told us that she was having pain in the belly, and of course, yes, she didn't like it. So, from that point of view, it had an impact on her wellbeing, of course." Effects on Parents/caregivers Parents and carers reported feelings of anxiety, stress and depression. These feelings were linked to their thoughts about: keeping their child safe, the child's health, guilt and feelings of being 'at fault' (for passing on a genetic disease, not spending enough time with siblings, their child's quality of life, what their child is missing out on: "It was dark times. We questioned and felt a lot of guilt and questioned did we do the right thing looking to have kids? Should we have done more genetic testing? Were we selfish to think that we thought we didn't have these mutated genes in our cells? There was a lot of stress for us as parents just knowing that we brought kids into this world who were going to have an uphill battle." These are exacerbated by a lack of sleep and constant fatigue from the child waking up at night, and isolation associated with being a caregiver. Sadness was also an issue for parents/caregivers who saw their child not being able to do what they wanted to do. A recurring theme was being under extreme stress not knowing how the disease was going to progress and waiting for the child to die knowing that this was the outcome if the disease was left untreated. Parents and carers also reported impacts on their work and social life, with many having to give up work entirely or go part time, to care for their child and attend medical appointments, often with severe consequences on family finances. "It is heart-breaking to watch your child go through everything that he's been going through. Really, it puts a lot of stress on us as parents, but also me and my husband's relationship, and it affects all aspects of our lives. Before his infusions and stuff, he required so much care." "I think you think of them every day and you think of them every night. You wake up thinking about it. That takes over your life, how am I going to normalize my child's life? How is she going to be able to live normal and not be constantly sick and in the hospital?" "Extreme anxiety, extreme depression on my end, a lot of frustration. My husband and I, you go from living this typical life essentially to being thrown with a potentially life-threatening diagnosis of your child." "In terms of stress. There were times when my wife would go in her bedroom and cry." Effect on siblings Parents and carers often have little time to spend with healthy siblings and find it difficult to answer questions and give information about ASMD. Other siblings don't understand why their affected sibling receives more attention and the children of affected adults, who are often 'young carers' experience a range of practical, emotional and psychological issues, which can lead to problems at school, social isolation, feeling neglected and being bullied. Teenage siblings have more complex needs; they cannot explain what is wrong with their affected sibling and can feel embarrassed about bringing friends into their home. They have questions about ASMD inheritance and relationships that they feel can't be discussed with their

	parents – leading to a breakdown in communication. They worry about death and dying and what will happen to their siblings as ASMD progresses. Sibling speakers at our 2019 Family Conference spoke with great emotion about how they felt growing up -with feelings of guilt (not being affected, not having health issues), how they felt left out, isolated, not knowing what was going on, how they could at times be resentful of the attention that their affected sibling was receiving and their embarrassment when friends came to their homes. They also talked of bullying and anxiety for their affected sibling.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers reported dissatisfaction with their diagnostic journey, which in some cases is stretched over many years, leading to delays in accessing expert care, practical support, and symptomatic treatments, as well as impacting family planning decisions. Most patients in England receive care at one of the eight designated NHS Specialist Centres providing Highly Specialised Services for patients affected by Lysosomal Storage Disorders. Patients and carers report difficulties in travelling to specialist centres, which are often located far from their home. This is especially so when the disease is more progressed and their burden of disease greater, or when there are family and/or financial constraints. Despite this, patients and their carers report high levels of satisfaction with the care they receive, feeling confident and supported by their clinical teams' knowledge and expertise in this rare condition. However, there are currently no treatment options for ASMD except supportive care. Best supportive care is complex and costly, due to the progressive and multisystemic nature of ASMD and involvement of many different specialities. Treatments, involve symptomatic relief of the disease, including pain relief for musculoskeletal pain, the management of the complications of the disease, (e.g., blood transfusion following bleeding episodes, significantly elevated cholesterol levels and the consequential cardiovascular disease, dietary /digestive aids and invasive surgeries). For patients, this means years of frequent and multiple medical appointments, with regular monitoring and often invasive tests through involving several different clinical teams, including: Cardio/respiratory, Endocrinology, Haematology, Hepatology, Physiotherapy, Dietetics. With these clinical teams often located in different locations around the country, the coordination of these appointments can be challenging. In addition, appointments with highly specialised teams are limited, usually twice per year, and patients and carers report much lower levels of satisfaction with locally based GP and hospital care. This is related to a lack of knowledge and understanding of their condition, the progressive nature of symptoms and their inability to access suitable symptomatic treatments, supportive aids and/or adaptations in a timely manner.
8. Is there an unmet need for patients with this condition?	There is a significant unmet need for patients and family living with ASMD. The scale of issues is enormous, with patients experiencing substantial challenges in both their emotional and physical health. They experience difficulties in attending school/work, participating in recreational activities, and in their social and economic wellbeing. The emotional burden of a complex and debilitating disease with symptoms that are constantly changing but always progressing is huge. As the disease relentlessly progresses patients need for multi-specialist clinical care and interventions increases. Their health and care needs also increase, with a greater impact on the wider family, including parents carers/ siblings and the children of affected adults. The impact of not funding this treatment includes early death, irreversible damage and disability, families taking drastic action to access treatment outside of the UK, an increasing burden on the public purse, plus long-term mental health issues within affected families. Despite the overwhelming benefits of olipudase alfa, there remains unmet need in managing the neurological manifestations of ASMD, particularly associated with classical type A homozygous mutations, and this remains a high priority for many patients and families.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Olipudase alfa is the only disease modifying treatment option for ASMD patients and has the potential to make a significant impact on their health outcomes. Patients and families observed life-changing effects with olipudase alfa, based on their experience. They consistently reported the view that all patients with ASMD should have access to olipudase alfa. Olipudase alfa not only appears to halt progression but reverses many aspects of this debilitating and life limiting disease. With early treatment that prevents irreversible disease, patients are no longer exhausted, can attend school /work for a full day, eat normal size meals, walk greater distances without breathlessness, contribute to society and have the energy to enjoy family or social life. Furthermore, they should expect to have a far greater life expectancy, with less dependence on healthcare and clinical interventions. When surveyed, participants reported the advantages of the technology as significant improvements in many symptoms, leading to improved quality of life: "Also, the energy, she is really full of energy now. It's amazing. She's very active and she likes to do sports, […] Now she's really an early bird, she's awake very early, and it's not a problem for her to handle these long schooldays anymore." They reported the benefits of this treatment being so obvious and life changing that in some cases there were no symptoms or signs of ASMD at all, they felt that treatment must continue and be accessible to everyone with ASMD. "The drug has drastically improved our son's life. He looks and acts like any other kid his age. He is much more confident now that his belly is small, and he is similar in size to his peers. […] You would never know that he has ASMD." Although this survey focussed on paediatric patients, similar outcomes have been reported by adult patients: "My abdomen is vastly different. I was recently told by a sonographer that an ultrasound of my abdomen showed that my spleen was now normal size as was my liver. My lungs have continued to improve, so much so, I now cycle to work and back every day, something I could have never have done before. I no longer feel hungry all the time and for the first time in my life have normal bowel habits, it sounds a small detail, but when you have had an upset stomach all your life, it's a huge change." We expect to be able to further demonstrate the experience of adult patients following phase 2 of the survey, which is currently in development.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Disadvantages mentioned in our survey included the treatment not crossing the blood-brain barrier, missing school or work to receive treatment, and the demands and challenges of the clinical trial. In our survey, all parents/caregivers reported that the benefits of the treatment outweighed the risks and disadvantages, with most saying that there were no adverse impacts on their child. Adult patients have also reported no disadvantage: • Benefits outweigh the risks • Side effects were minor issues compared to the effects of ASMD • Any concerns about the treatment were addressed by the clinician and vanished once results were apparent • Patients and families adapted easily to the two weekly infusions, at home or in clinic, with homecare the preferred option

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Clinical data is very strong and shows clearance of storage and reversal of disease. As it is currently not possible to accurately identify where a patient sits on the spectrum of ASMD disease, outside of very small numbers of classical type A homozygous mutations, treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None identified.

Other issues

13. Are there any other issues that you would like the committee to consider?	Early diagnosis and treatment for patients with clinically detectable disease will prevent significant and irreversible burden of disease, reduce comorbidity and mortality. The introduction of this technology requires no new specialised equipment or services, IV infusions can be managed in existing clinical centres through current service specifications, or preferably by a home-based infusion service or if appropriate, self-infusion. Whilst this technology may be viewed as a 'high-cost treatment' there will be a significant and long-term downstream reduction in healthcare and societal costs over the lifetime of a treated patient. For untreated patients, with only symptomatic management, i.e., antibiotics and hospitalisations for respiratory infections, home oxygen needs, medications and treatments to manage bleeding or low platelets, medications to address high cholesterol, portal hypertension and other consequences of a chronic condition, the cost will be much greater. The impact of this technology beyond direct health benefits and the cost saving for health systems, include societal economic benefits such as maintenance of earning potential for the patient and carers. The development of this technology has benefitted from 20plus years of investment from the patient community, including surveys, PROMs, natural history studies, invasive and burdensome trial protocol – nevertheless, patients and their families have been actively engaged, as this presents the only potential option for patients and evidence shows it can make a huge difference to their quality of life with long term implications. It is important to state the small numbers of patients affected by ASMD and therefore potentially eligible for treatment. In our experience over 30 years of working with the ASMD community, the number of patients supported in any given year has not exceeded 40. It must be noted that this is a life-limiting and life-shortening disease, and that patients don't have a normal lifespan, and that there will be some who have milder disease and therefore have not yet been diagnosed or misdiagnosed. NPUK currently support 37 ASMD patients 34 with ASMD Niemann-Pick disease type B (16 Children, 18 Adults) and 3 with ASMD Niemann-Pick disease type A. For newly diagnosed patients, Genetic counselling should be provided prior to and following diagnosis to assist patient and family understanding and enable informed decisions regarding family planning, including carrier status and potential impact on future offspring and siblings. This should be included within the service provision and provided in a timely manner. Currently there is no routine screening for ASMD as part of the UK's newborn screening programme. Whilst we understand the Committee or any decision they make will not influence or change this, it must be noted that to enable the full benefit of this treatment, inclusion in the NBS programme is highly recommended. In addition, we ask the Committee to give appropriate and careful consideration to the management of patients currently receiving olipudase alfa post trial and in any period leading up to and post their decision-making process, to avoid additional and unnecessary anxiety and stress.

14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every evaluation.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• ASMD is a systemic disease with a wide array of manifestations causing high physical and psychological burden (for patients, carers and siblings) and significantly impacting quality of life • There are no treatment options for ASMD except best supportive care, which is complex and costly, due to the progressive and multisystemic nature of ASMD and involvement of many different specialities. • There is a high level of unmet medical need in the patient community • Olipudase alfa is the only potential treatment option for patients; evidence has shown significant and long-term impact on quality of life and psychosocial status for patients and their families • Patients and families observed life-changing effects with olipudase alfa based on their experience, consistently reporting the view that all patients with ASMD need access to olipudase alfa

Thank you for your time.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**James Dyson**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Niemann Pick Disease UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	There are so many facets to living with this life limiting disease ASMD Type B that it is difficult to summarise. As a child my development was affected in so many ways, regular abstraction from school to attend hospital appointments, ill health due to infections that were always very difficult to fight off, constant fatigue, upset stomach, hunger and constant fear. Fear from being physically hurt, excluded from everything, fear of being included and not being able to cope, to list just a few. Being susceptible to so many illnesses in a social environment resulted in lots of time in semi or total isolation, which meant I was always trying to catch up and spend a lot of time learning from books, parents, or carers because I missed important lessons. Often, I was prohibited from participating in activities with my friends in case I was hurt. This social isolation at a time of key social development is difficult as a child and has lead to minimal friends as an adult. Regularly being told you are different and that you needed to be treated differently affects your long-term mental health. As a child with ASMD type B, there were so many activities I wanted to do and be apart of but was denied the opportunity due to

	either my health or the risks associated with doing it. Instead, I spent a lot of time in and out of hospital having an array of tests and procedures and getting to know clinicians on first name terms or learning handwriting or playing ping pong on my own because no one knew what to do with me. At the age of 11 I was so badly affected with the condition that I was regularly in discussions with paediatricians about how ill I was and that I needed lifesaving surgery. At this young age, having these discussions with doctors and my parents about my own mortality was terrifying especially given the risks associated with the procedure, (Partial Splenectomy) all of which I didn't truly understand at the time. I was even sent on the trip of a lifetime with Dreamflight to Florida as I think few expected me to survive. In fact as a child I was aware that my life expectancy may only be another 5 or 10 years and I was regularly reminded of this as at this time there was very limited information about the disease. As an adolescent, my physical development was delayed, the small group of friends I did have were going through puberty and showing interests in partners. I was still 4'10" and looked about 11 years old even when I was 16 and 17. At this stage in my life my abdomen was significantly distended and I looked like I was pregnant, however my extremities were tiny and malnourished. I used to get pushed around at school and was prone to bullying because of my size. On several occasions I ended up in A+E being monitored for hours to make sure I hadn't ruptured anything after being assaulted by other students. Desperate to fit in and look my age, I would regularly have growth hormone injections to help induce puberty and allow me to grow. This took years and was slow to see any changes, while my friends seemed to be changing in front of my eyes. I didn't realise how much this phase in my life affected me until I was older and looked back. As the disease develops you become more and more tired. You can eat 10 meals a day and never gain any weight because the storage affects the absorption of food through the gut. Your lungs deteriorate and you become out of breath more easily, as well as developing 4 or more chest infections over the winter, no sooner do you recover from one but develop another. There were more requirements for increasing hospital intervention and because of the rarity of the disease and the fact that I was no longer a child, I had no choice but to travel to either London or Manchester from Devon for my care as there were no local specialists or even doctors that could help me. This meant these regular appointments, which would sometimes take 18 or so hours to complete or often required an overnight stay which sounds simple but for my parents trying to juggle work commitments and trying to pay for these visits was very stressful and expensive.

	After leaving school, I had several jobs before joining the NHS ambulance service as a trainee paramedic. This was something I was extremely passionate about and I felt I had a lot to offer with all my own medical experience. I had to work so hard to achieve this. Training at the gym for 3 hours a day after work to build up my strength. Running and cycling for miles even though I was exhausted. All of which was very difficult when you don't retain nutrients. On a few occasions I was really ill from overdoing it because my body couldn't take anymore, but I was determined that I was not going to be a victim of this disease and I would have a life. After qualifying to be Paramedic at the age of 23 a new set of challenges began. With the demands of shift work, which any normal 23-year-old would have no issues, I used to find myself falling asleep in between jobs, because I was constantly exhausted. Suffering from thrombocytopenia I was always covered in bruises and my weakened immune system meant I was always ill as I worked around poorly people, but I loved my job and refused to be defeated by my disease. I struggled with relationships as a young adult because I lacked complete confidence in this area, and I dreaded having to tell people about my condition and would be regularly reminded at home that I buried my head in the sand. I met [redacted], my wife around the time I joined the ambulance service. A time that was full of excitement and firsts but also clouded by the thought of having difficult discussions surrounding my health, my reduced life expectancy and what the disease involved and what the future looked like. [redacted] was fantastic about all of this and continues to be a huge support to me. I have [redacted] who we have also had to discuss these topics with. They received the information well but [redacted] who was only [redacted] at the time did not fully understand the extent of the disease. As she has grown and understood my condition fully, she has spent many hours on the internet looking up how to check organ compatibility in case I needed a transplant in the near future. Physically there are many well-known effects this condition has on your body, but there is less emphasis on the long-term effects on your mental health and that of those around you. Prior to treatment my close friends and family were constantly worried about my health and what the future would if any, look like. All year long I would develop one illness after another, every hospital visit showed a further decline in my health and my family were aware that many people with my condition don't survive beyond middle age if they are "lucky". In my adult life I never committed to anything that didn't help or add fulfilment to my personal wellbeing because I refused to waste precious time on it, as my life was limited. I have never planned for the long-

	term future, I never knew how to. Even now I struggle with this, because it has been drummed into me all my life that I might not be around to enjoy it, a privilege many take for granted. I have worked extremely hard to prove to others that I can do something even at my own detriment because I will not be told that I'm not capable. I have been fighting all of my life for a chance of 'a life'. The ERT has given me that life. It has changed my world completely. Medically it has reversed all the damage the disease has done to my body. I no longer feel weak, tired, hungry, sick, constant pain in some form, but most of all I haven't been frightened. Medically it has achieved much more than we all hoped for in the very beginning of the trial 10yrs ago. With this treatment for the first time in my life I have the chance of a future.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There are no treatments for this condition, except the ERT. Treatment or care only limits the effects of the disease or buying the effected individual more time. I was extremely fortunate within my lifetime to have experienced some groundbreaking procedures executed by some extremely clever and pioneering individuals and their care brought me time I wouldn't have had otherwise. I have tried many medications and procedures to varying effects, but none have ever improved my health, but merely slowed my deterioration. The last conversation I had with my consultant before starting the trial was that we needed to discuss the possibility of a liver transplant as there were few other options available to me, certainly nothing less than more lifesaving surgery.
10. Is there an unmet need for patients with this condition?	Yes, absolutely, prior to the development of this enzyme replacement therapy, there was a total unmet need for patients with this condition. In my lifetime, I have lost several friends to this disease who despite all the best attempts to save them including, liver transplants have died. There is nothing the NHS currently offers that even successfully slows down the disease let alone reverses the existing damage.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This drug has changed my life in an unquantifiable way. It has given me excellent health! Not just slightly improved but a life changing difference. For the first time I have a future with my family and loved one's. Since starting the treatment 10 years ago I have only been ill a few times with minor winter colds. I have had COVID 19 three times but on all of these occasions have had very minor or no symptoms and have recovered quicker than healthier people I know. Before the enzyme I would have surely died catching COVID19. I eat less, as all food stays in my system long enough now to be absorbed and my health and strength improve accordingly. I am no longer tired all the time, I noticed this significant change after approximately 10 months on the trial, resulting, with being able to easily work full time while simultaneously attending college part time in the evenings for 3 years to achieve a diploma in engineering and still travelling to London every 2 weeks for the enzyme. [476-mile round trip]. My health has continued to improve so much year on year that 12 months ago I ran a half marathon one Sunday with no training just because I wanted to see how far I could run in one morning. I now have a hugely responsible job, overseeing and managing the Southwest of England's ambulance fleet of NHS emergency vehicles. I regularly experience huge levels of stress and work 65 – 70 hours a week, yet I am never poorly and continue to have brilliant health. My abdomen is no longer painful and does not wake me three or more times a night, and I rarely bruise. My hospital attendances are now solely due to check ups and never last long as everything is either continuing to improve or is as 'normal'. I no longer make rushed decisions in the fear that I am wasting my life and instead look forward to what the future may hold. My liver function is now normal, and I don't have to face another life-threatening surgery. All the medications I took regularly have now stopped with the exception of calcium. I love my life now and make the most of everyday as this treatment has given me the ability to live it and not just exist. I see a future that doesn't involve hospital operations and premature death and the only thing that terrifies me now is the thought that this treatment will stop. Something that everyone who cares for me also shares.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	There are no disadvantages to this technology, only huge gains.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No, because the gains are subjective. A young person affected will see a less dramatic improvement in their health due to reduced amount of time they have been exposed to the disease, but indirectly will benefit massively from the lack of mental health associated with the disease. Similarly, the severely affected patient will see huge changes in their physical health but slower changes in their mental health due to trauma they have already experienced. In my opinion any ASMD Type B patient who is given this technology will experience a vast improvement in their health in one form or another.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that I can think of.

Other issues	
15. Are there any other issues that you would like the committee to consider?	I would like them to look at the not only the overwhelming physical data but the also the psychoemotional effect associated with the huge changes in someone's health. This treatment hasn't suspended deterioration or showed minor to moderate improvement in the quality of someone's life, but reversed decades of increasing ill health and improved my health from imminent liver transplant to 25% healthier than the average male of my age. My mental health and that of those around me has also improved with the hope of a positive future.

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- This treatment has reversed decades of extreme ill health.
- Changed my life from, life limited to a normal prognosis.
- Prevention from imminent liver transplant to 25% healthier than the average male of my age in the time I have been on the treatment.
- Improvement of my mental health and that of my families, with the hope of a positive future.
- This treatment has worked so well it has removed the lifelong fear I have always had to live with.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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

A Highly Specialised Technology Appraisal

Produced by

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Author Contributions:

Brian O'Toole	Lead for the EAG's appraisal of the economic evidence, drafted economic sections of the report, writing and editorial input
Caroline Farmer	Lead for the EAG's appraisal of the clinical evidence, project management, writing and editorial input
Elham Nikram	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out further scenario analyses, and drafted economic sections of the report
Helen Coelho	Critical appraisal of the clinical evidence and drafted sections of the report
Naomi Shaw	Critical appraisal of the literature search strategies
Paul Gissen	Clinical advice and review of draft report
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Frances Platt	Expert advice and review of draft report
Rebecca Whiteley	Clinical advice and review of draft report
Dawn Lee	Quality appraisal of the company's economic model and senior guidance on economic analyses
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
Edward Wilson	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report. Guarantor of the report

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Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ASMD	Acid sphingomyelinase deficiency
AST	aspartate aminotransferase
BSC	best supportive care
CCL18	Cc chemokine ligand 18
CI	confidence interval
CS	company submission
CV	cardiovascular
EAG	External assessment group
EED	Economic Evaluation Database
EMA	European Medicines Agency
ERT	enzyme-replacement therapy
FDA	Food and Drug Administration
FEV1	forced expiratory volume
FVC	forced vital capacity
HDL	high-density lipoprotein
HRQoL	health-related quality of life
HS	health state
HST	highly specialised technology
ICER	incremental cost-effectiveness ratio
IAR	infusion associated reaction
ITT	intention to treat
LDL	low-density lipoprotein
LY	life-year
MeSH	medical subject heading
mITT	modified intention to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPD	Niemann-Pick Disease
NR	not reported
O^2	oxygen
ONS	Office for National Statistics
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PSA	probabilistic sensitivity analysis
PSS	personal social services
QALY	quality-adjusted life year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation

AE	adverse event
SE	standard error
SLR	systematic literature review
SMR	standardised mortality ratio
SoC	standard of care
SRS	Splenomegaly related score
TDABC	time driven activity-based costing approach
TEAE	treatment emergent adverse event
TP	transition probability
TTO	time-trade-off
VN	voretigene neparvovec

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3 to 1.6.

Table 1: Summary of key issues

Key issue	Summary of issue	Report sections
Discounting	The company used differential discounting, which is not consistent with the NICE reference case	4.2.5
Olipudase alfa treatment efficacy	The company's long-term efficacy assumption was not supported by robust clinical data.	4.2.6
Carer HRQoL	The EAG disagreed with several of the company's assumptions used to model carer HRQoL	4.2.9.1
Mortality	There was uncertainty surrounding the company's approach to modelling mortality	4.2.8
Modelled patient weight	Where was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	4.2.3
Uncertainty surrounding the company's economic analyses in those with severe disease	The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations.	4.2.3.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Discounting	Discounted costs at 3.5% and benefits at 1.5%	Discounted both costs and benefits at 3.5%	4.2.5
Treatment efficacy	From 2-years onwards all patients on olipudase alfa transitioned into the least severe health states (based on spleen volume and DLco)	To freeze TPs in the olipudase alfa arm at 2-years	4.2.6
Carer HRQoL	• The company applied carer disutility to health states in the BSC arm only i.e. carers of patients receiving olipudase alfa did not experience a negative impact on HRQoL • The company assumed carer disutility did not differ according to health state severity i.e. a carer disutility of -0.15 is applied to both the least severe and most severe modelled health states • The source of carer disutility was a published study in people with Pompe disease, (estimated to be -0.15) [1] • The company assumed 1.78 carers for children and 1 carer for adults, based on a prior NICE HST appraisal (HST11: voretigene neparvovec for inherited retinal dystrophies caused by RPE65 gene mutations) [2] • The company applied a carer disutility associated with patient death (assumed to be -0.5, applied for the entire duration of the modelled time horizon	• Application of carer disutility to model health states (irrespective of treatment) • A dynamic disutility approach i.e. applied higher disutility to severe states and lower disutility for other states. Differential carer disutilities were used for adult and paediatric populations • The EAG used alternative published literature sources for carer disutility • One carer was assumed for all health states in both adults and children • Carer disutility associated with death was removed	4.2.9.1
Mortality	The company model included disease-specific mortality for the paediatric population.	Based on UK clinical opinion to the EAG, disease-related mortality was not apparent in paediatric patients. For the paediatric population,	4.2.8

		disease-related mortality was removed and patients were assumed to follow background mortality until they reached adulthood.	
Modelled patient weight	Weight was not based on the mean weight of UK patients.	The EAG preferred to use the mean UK population weight (based on Health Survey England data), and use the z-score for 18-year olds (as estimated by the company) to account for reduced weight due to ASMD	4.2.3

Abbreviations: ASMD, acid sphingomyelinase deficiency; BSC, best supportive care; HRQoL, health-related quality of life; HST, highly specialised technology; TP, transition probability; UK, United Kingdom

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- **Improved treatment efficacy**. The incremental QALY gain associated with olipudase alfa was primarily driven by the company's long-term efficacy assumption i.e. from two years onwards all patients on olipudase alfa transition into the least severe health states (spleen volume SV<6MN and DLco>80), where they experience a relatively high utility value and remain until death (see Section 4.2.6). For the adult and paediatric populations respectively, approximately [redacted] and [redacted] of the incremental gain stems from patients remaining in this health state.
- **Reducing mortality**. The company modelled disease mortality based on the presence or absence of 'severe splenomegaly' using data from the observational study SPHINGO-100 (see Section 4.2.8). Due to the modelled efficacy associated with olipudase alfa, fewer patients died relative to those on best supportive care (BSC), resulting in an increase in life-years gained and QALYs.
- **Reducing the HRQoL burden on carers**. Due to the company's assumptions surrounding carer health-related quality of life (HRQoL; see Section 4.2.9.1), fewer caregiver QALYs are modelled to be lost in the olipudase alfa arm.
- **Discounting benefits at 1.5%.** The company applied differential discounting in their base case i.e. used 3.5% for costs and 1.5% for benefits. The lower discount rate

applied to benefits had a substantial impact on QALYs accrued (see Section 4.2.5 and 6.2.9).

Overall, the technology is modelled to affect costs by:

- Increasing treatment-related costs. Drug acquisition costs were the primary driver of olipudase alfa incremental costs (accounting for [redacted] of total costs). Annual drug costs were estimated based on patient weight and their compliance with the treatment.

The modelling assumptions that have the greatest effect on the ICER are:

- The company conducted one-way sensitivity analyses varying parameters arbitrarily by +/- 20%. The parameters/assumptions with the largest impact on the ICER were patient weight, drug unit costs, compliance and starting age. Discounting costs at 1.5% also had a high upward impact on the ICER in both populations, as well as the inclusion of a discontinuation rate at week 80 and a higher compliance rate of 95%. Based on the EAG scenario analyses, the ICER was most sensitive to alternative long-term effectiveness assumptions for olipudase alfa, the application of carer disutility to model health states (irrespective of treatment), the removal of carer disutility associated with death, and the use of reference case discounting.

1.3. The decision problem: summary of the EAG's key issues

The EAG did not identify any key issues related to the decision problem.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

There are limitations in the clinical evidence base for olipudase alfa, which may be expected given the rare nature of the condition. However, the EAG did not identify any key issues with the clinical effectiveness evidence.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The EAG identified six key issues with the cost effectiveness evidence for olipudase alfa.

Key Issue 1: Non-reference case discounting may not be appropriate

Report sections	Section 4.2.5 and Section 6.2
Description of issue and why the EAG has identified it as important	In the company's base case analysis, costs were discounted at 3.5% and benefits were discounted at 1.5%.

	The EAG did not consider the application of non-reference case discounting to be appropriate.
What alternative approach has the EAG suggested?	The EAG conducted a scenario analysis whereby both costs and benefits were both discounted at 3.5%. This was included in the EAG's preferred base case analysis.
What is the expected effect on the cost-effectiveness estimates?	The ICER was highly sensitive to this analysis.
What additional evidence or analyses might help to resolve this key issue?	This issue was resolved.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio

Key Issue 2: Uncertainty surrounding olipudase alfa long-term treatment effect

Report sections	Section 4.2.6 and Section 6.2
Description of issue and why the EAG has identified it as important	In the company's base case analysis, 100% of patients who receive olipudase alfa were assumed to transition to the least severe health states (SV<6MN and DLco≥80%) and remain there for the duration of the modelled time horizon (subject to mortality). In contrast, patients in the BSC arm were assumed to transition in every cycle until the end of the time horizon or death. Clinical experts advised the EAG that the long-term efficacy assumption for olipudase alfa may be plausible (see Section 4.2.6). However, due to the lack of long-term treatment effectiveness data and the potential for the assumption to overestimate the incremental QALY gain associated with olipudase alfa, the EAG considered there to be a high degree of uncertainty surrounding this assumption.
What alternative approach has the EAG suggested?	The EAG conducted several scenario analyses to test uncertainty surrounding the long-term treatment effect associated with olipudase alfa. These included the following: • observed benefit is frozen at 2 years • observed benefit is maintained (transition probabilities in year 2+ are replayed) • treatment effect waning (from 2 years, assume that all olipudase alfa patients follow BSC transitions)
What is the expected effect on the cost-effectiveness estimates?	All three scenarios resulted in an upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Long-term clinical effectiveness data would help to reduce modelled uncertainty. These data are not currently available, therefore uncertainty surrounding long term treatment effect remains.

Abbreviations: DLco, diffusing capacity for carbon monoxide; EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; SV, spleen volume

Key Issue 3: Uncertainty surrounding modelled carer disutility

Report sections	Section 4.2.9.1 and Section 6.2
Description of issue and why the EAG has identified it as important	The EAG disagreed with the following assumptions regarding carer disutility that were included in the company base case: • The company applied carer disutility to health states in the BSC arm only i.e. carers of patients receiving olipudase alfa did not experience a negative impact on HRQoL. The EAG did not consider that the company justified this approach, and considered it more plausible to associate carer disutility with the health state of the patient, regardless of treatment arm • The company assumed that carer disutility did not differ according to health state severity i.e. a carer disutility of -0.15 was applied to both the least and most severe modelled health states. The EAG did not consider this to be plausible, as carer disutility would be expected to be greater for patients in more severe health states • Data on carer disutility in people with ASMD types B and A/B were not available. The source of carer disutility used by the company was based on a population with Pompe disease (estimated to be -0.15). [1] Clinical advice to the EAG was that Pompe disease is not sufficiently similar to ASMD types B and A/B, and it would be expected to have overall greater carer burden. • The company assumed 1.78 carers for children and 1 carer for adults. The EAG did not consider that the company had provided sufficient justification for the number of carers in the paediatric population, and clinical advice suggested that this may be an overestimation. • The company applied a carer disutility associated with patient death (assumed to be -0.5 and applied for the entire duration of the modelled time horizon). The EAG did not consider that the company had provided justification for this approach.
What alternative approach has the EAG suggested?	Based on clinical expert opinion to the EAG and a review of published literature, several scenario analyses were conducted, including the following: • Carer disutility was applied to model health states (irrespective of treatment) • A dynamic disutility approach was used i.e. higher disutility was applied to severe states and lower disutility for other states. Differential carer disutilities were applied for adults and paediatric populations

	• Alternative published literature sources were used for carer disutility (see Section 4.2.9.1 for alternative values used) • One carer was used for all health states in adult and paediatric populations • carer disutility associated with death was removed
What is the expected effect on the cost-effectiveness estimates?	All scenario analyses had an upward impact on the ICER (in both populations). Results were most sensitive to the application of carer disutility to health states (irrespective of treatment) and the removal of carer disutility associated with death. See Section 6.2 for results.
What additional evidence or analyses might help to resolve this key issue?	The EAG explored alternative carer disutility assumptions to assess uncertainty surrounding this modelled assumption. Collection of HRQoL data in carers of people with ASMD types B and A/B would help to reduce uncertainty.

Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio

Key Issue 4: Uncertainty surrounding modelled mortality rates

Report sections	Section 4.2.8 and Section 6.2
Description of issue and why the EAG has identified it as important	In the company's base case analysis, mortality was modelled according to whether patients did or did not have severe splenomegaly. The company estimated SMRs using data from the SPHINGO-100 observational study. [3] The EAG identified the following key uncertainties surrounding the company's handling of mortality in the model: • SPHINGO-100 is an older study that included a small sample and reported few deaths (n=9), and therefore is not a robust source for mortality risk. • The company's model included disease-specific mortality for the paediatric population, however clinical advice to the UK is that disease-related mortality was not apparent in the paediatric ASMD population.
What alternative approach has the EAG suggested?	The EAG conducted the following scenario analyses to determine whether results were sensitive to a change in mortality assumptions: • the SMR associated with severe splenomegaly was reduced by 50% • disease-related mortality in the paediatric population was removed and patients were assumed to follow background mortality until they reached adulthood.
What is the expected effect on the cost-effectiveness estimates?	Reducing the SMR by 50% had a relatively minor upward impact on the ICER in both patient populations. Removing

	paediatric mortality had a minor downward impact on the ICER for the paediatric population.
What additional evidence or analyses might help to resolve this key issue?	The EAG requested additional mortality data from the International Niemann-Pick Alliance (INDPA). These data may become available at a later stage during the NICE appraisal.

Abbreviations: ASMD, acid sphingomyelinase deficiency; EAG, External Assessment Group; SMR, standardised mortality ratios

Key Issue 5: There is some uncertainty surrounding the company's approach to modelling patient weight

Report sections	4.2.3 and 6.2
Description of issue and why the EAG has identified it as important	The EAG noted some uncertainty surrounding the company's estimation of patient weight in the model. Paediatric population • The company derived the z-score function based on data from the SPHINGO-100 trial. The z-score function (which estimates the change in paediatric weight over time) was applied to weight from UK growth charts. The EAG noted that weights from the UK growth chart appeared low compared to weight data from Health Survey for England (2019). Adult population • Patient weight for adults appeared low (64.5kg) relative to the average UK adult weight, and the mean weight estimated by the company for patients aged 18-years (62kg). Given that olipudase alfa dosing is weight based, an increase in the starting weight of patients results in higher drug costs for olipudase alfa. If drug costs are underestimated in the CS, the ICER will likewise be underestimated.
What alternative approach has the EAG suggested?	The EAG undertook the following scenario analyses: • For children, patient weights based on UK growth charts were replaced with weight data from general population norms in the Health Survey for England report (2019). [4] • For adults, two scenario analyses were conducted a) the UK mean weight was used (estimated from the male/female split from ASCEND) b) the UK mean weight was used and the z-score for 18-year olds (as estimated by the company) was applied. This was to account for patients potentially having a lower weight than the

	general population as a result of ASMD. The EAG incorporated this scenario into their preferred base case
What is the expected effect on the cost-effectiveness estimates?	The ICER was sensitive to assumptions about patient weight. The EAG scenario analyses had an upward impact on the ICER due to a corresponding increase in drug costs
What additional evidence or analyses might help to resolve this key issue?	High-quality evidence for the average weight of the target population would allow for drug costs to be more accurately estimated in the model. The EAG was uncertain to what extent patient weight may change following treatment with olipudase alfa; for example, it is plausible that children who respond to treatment may be more likely to meet normal growth milestones over time. Long-term follow-up data for weight in those treated with olipudase alfa would provide clarity.

Abbreviations: EAG, External Assessment Group

Key Issue 6: Uncertainty surrounding the company's economic analysis for those with severe disease

Report sections	Section 4.2.3.1 and 5.3.3
Description of issue and why the EAG has identified it as important	The company provided economic results for a population subgroup in both children and adults with severe disease. There were several uncertainties surrounding the company's approach to modelling the severe population that significantly undermine the validity of the findings: • Clinical effectiveness data used to inform transitions were not derived from trial participants with severe ASMD. Rather, the company assumed 100% of patients began in the severe health state and used transition probabilities from the overall trial population. Based on clinical opinion to the EAG, this assumption may not be appropriate • Instead of using trial data, the company estimated mortality amongst the severe population using a published literature source (McGovern et al).[5] The EAG had concerns about the reliability of these data for estimating mortality, and there was a lack of transparency in the company's approach to estimating survival i.e. for both the adult and paediatric populations the company applied a Weibull distribution to the mortality data, however rationale for this curve selection was not provided, AIC/BIC statistics were not presented and no attempt was made to discuss visual fit of alternative functions. • No sensitivity analysis was presented in the CS for the severe subgroup, increasing uncertainty in the base case results.

What alternative approach has the EAG suggested?	The EAG were unable to resolve this issue with the current evidence base, and no additional analysis was conducted.
What is the expected effect on the cost-effectiveness estimates?	The EAG cannot determine whether transition probabilities used in the company's severe subgroup analysis are representative of the true population. Clinical advice to the EAG was that this may not be the case, and therefore the EAG considered that the subgroup analysis for the severe population was subject to extreme uncertainty and may not be appropriate for decision making.
What additional evidence or analyses might help to resolve this key issue?	The EAG considered that the company had used the best available evidence for the severe subgroup given that very few people in the company trials were considered to have severe disease at baseline. However, as this evidence is limited, robust subgroup data with respect to treatment effect, impact on mortality and HRQoL in both paediatric and adult populations would help to alleviate uncertainty. The EAG also considered that further information from the company regarding their methods for estimating survival in the severe subgroup would help to reduce uncertainty.

Abbreviations: EAG, External Assessment Group

1.6. Other key issues: summary of the EAG's views

The EAG did not identify any further key issues.

1.7. Summary of EAG's preferred assumptions and resulting ICER

The EAG's preferred assumptions and deterministic and probabilistic ICERs for the adult and paediatric populations are summarised in Table 3 to Table 6. The EAG noted that there were differences between the deterministic and probabilistic results in both the adult and paediatric populations. This occurs in non-linear models, and probabilistic analyses provide the expected costs and outcomes in these cases. However, probabilistic sensitivity analysis (PSA) is subject to Monte Carlo error (simulation noise). The PSA was run for 1000 iterations. When the EAG ran the PSA for 10,000 simulations, the ICERs remained stable. The EAG therefore considered that the deterministic results should be interpreted with caution.

Modelling errors identified and corrected by the EAG are described in 6.1. For further details of the exploratory and sensitivity analyses conducted by the EAG, see Section 6.2.

Table 3: EAG's deterministic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.95	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	26.05	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	15.36	[redacted]	[redacted]
Removed carer disutility associated with death of patient	6.2.3	[redacted]	21.62	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	22.57	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	19.22	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.94	[redacted]	[redacted]
• Assume 1 carer in each health state	6.2.3	[redacted]	25.00	[redacted]	[redacted]
Removed disease-related mortality (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	25.86	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	26.05	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.57	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 4: EAG's probabilistic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.07	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	25.06	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	14.90	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.29	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	21.86	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.41	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	20.87	[redacted]	[redacted]
• Assume 1 carer in each health state	6.2.3	[redacted]	24.21	[redacted]	[redacted]
Removed disease-related mortality removed (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	24.81	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	25.20	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.29	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 5: EAG's deterministic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	16.44	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	17.59	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually) 6.2.1					
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	12.25	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.88	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2-years	6.2.1	[redacted]	13.99	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	13.67	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	15.18	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	17.59	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	5.30	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 6: EAG's probabilistic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	15.39	[redacted]	[redacted]

EAG corrected company base case	6.1	[redacted]	16.32	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually)					
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	11.46	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.33	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.36.2.1	[redacted]	13.74	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
• Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	12.48	[redacted]	[redacted]
• Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	13.60	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	16.27	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	4.83	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Sanofi in support of olipudase alfa for treating acid sphingomyelinase deficiency (ASMD) types B and A/B (otherwise known as Niemann-Pick disease types B and A/B).

2.2. Critique of the company's description of the underlying health problem

2.2.1. Epidemiology

The company provided an overview of the literature related to the epidemiology of ASMD (CS B.1.3). The EAG agreed with the company's characterisation of ASMD as a very rare disease: the CS reported that there are approximately 40–50 prevalent children and adults currently in the UK, which was is in line with clinical expert advice to the EAG and with comments from Niemann-Pick UK (NPUK) during scoping for this appraisal (NPUK support 37 UK patients, who make up 90% of the known UK population). The CS also stated that most people in the UK with ASMD have type B or A/B, with the majority being type B. This is likely due, in part, to the higher mortality risk associated with type A compared with type A/B and B. There is also an increased risk of mortality amongst people with ASMD type A/B compared with type B.

The company used data from six studies (based in Australia, Czech Republic, Netherlands, Portugal, United Arab Emirates [UAE] and the United States [US]) to inform rates of ASMD type B and A/B (see CS B.1.3, Table 5). Incidence rates in these studies ranged from 0.1 to 0.25 per 100,000 live births for type B and from 0.33 to 0.9 per 100,000 live births for type A/B. The differences in estimates of type A/B across these studies are likely due to population differences across the studies. Indeed, the EAG agreed that the incidence of ASMD would be expected to vary according to population/country and that there are numerous potential reasons for this including: the genetic, recessive nature of the condition; phenotypic variation amongst those with the same genotype and early mortality amongst those with severe presentation; differing prevalence of populations with specific genetic mutations; and diagnostic screening programmes that are present in some countries and not others (not currently present in the UK). These factors may contribute to the lower incidence of ASMD (and in the case of diagnostic screening programmes, to the possibility of under-diagnosis) in the UK.

The EAG noted that, of the six studies presented in CS B.1.3 Table 5, only two were identified by the company's systematic literature review (SLR; Pinto et al., 2004[6] and Burton et al., 2017[7]). The company's searches did not retrieve the other four studies and it is unclear how these were identified. The EAG also highlighted that one of the studies included in CS B.1.3, Table 5 (Poorthuis et al., 1999[8]) did not clearly provide incidence data for type B or A/B either alone or in combination. The data from this study appeared, therefore, to be outside of the scope of this appraisal. The EAG checked the lists of included and excluded studies from the company's SLR (CS Appendix D Tables 84 and 85) and did not identify any additional studies providing relevant epidemiologic data.

2.3. Critique of the company's overview of current service provision

The CS provided an overview of the current service provision for the diagnosis and management of ASMD types B and A/B. Overall the EAG considered the summary provided by the company to be accurate, though noted the following additions:

- The company correctly stated that there is no diagnostic test to differentiate between subtypes of ASMD, though advice to the EAG was that type A is clearly differentiated from types B and A/B at an early stage, due to the speed of progression and severity of symptoms. The EAG therefore considered that the target population for olipudase alfa would be clearly recognisable to clinicians.

- The company correctly noted that most people with ASMD are diagnosed in childhood. Expert advice to the EAG indicated that diagnosis is frequently earlier in those children with a familial history of ASMD, due to earlier recognition of symptoms and/or diagnostic screening. The EAG were also advised that those without familial history who have mild disease may not be diagnosed until adulthood, but this is infrequent, meaning that the incident population eligible for olipudase alfa will include a small minority of adults.

- The company provided an overview of the background treatments that people with ASMD types B and A/B may receive. These treatments may be medical or non-medical and are targeted to treat the symptoms and health consequences of the condition. Advice to the EAG was that these treatments would be expected to reduce if an effective treatment for ASMD was identified.

2.4. Critique of company's definition of decision problem

The company stated that their submission was consistent with the NICE scope for this appraisal. The EAG appraisal of the company's definition of the decision problem is outlined in Table 7. In general, the EAG agreed with the company assessment though noted that several outcomes specified in the NICE scope were not represented in the company's evidence base. In addition, the EAG were concerned that at clarification the company were unable to confirm that trials of olipudase alfa included participants with ASMD type A/B. The EAG assumed this was the case due to estimates provided in the report of olipudase alfa by the European Medicines Agency (EMA), though these estimates were not provided separately for each arm, and the EAG was unclear where these data were derived from. This issue is discussed further in Sections 3.2.2.2 and 3.2.3.1.

Table 7: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with acid sphingomyelinase deficiency (also known as Niemann-Pick disease type B or type AB)	As per scope	N/A	The CS was consistent with the population described in the NICE scope, although the EAG noted that the company were uncertain about how many participants in the included trials met criteria for a diagnosis of ASMD type A/B. In its assessment, the EMA reported the number of participants in ASCEND and ASECEND-Peds with type A/B, however given the company could not provide this (clarification QA15) the EAG assumed that this was an estimate based on baseline characteristics. On the basis of expert advice, the EAG expected that olipudase alfa was likely to have a similar effect on visceral symptoms of ASMD for each subtype. However, neurological symptoms experienced by people with ASMD type A/B would not be expected to be responsive to treatment with olipudase alfa, and it's feasible that broader outcomes related to functioning and HRQoL may vary between subtypes.
Intervention	Olipudase alfa	As per scope	N/A	No comment
Comparator(s)	Best supportive care (BSC)	As per scope	N/A	There was no alternative treatment for ASMD types B and A/B and the EAG agreed that BSC, consisting of treatments to manage the symptoms and complications of ASMD, was the main comparator to olipudase alfa. In its response to clarification (QA4) the company stated that they did not include evidence for purely non-pharmacological interventions in the CS. The EAG understood that non-pharmacological interventions may be commonly used by people with ASMD, though noted that these would have been permitted during the trials for all participants.

Outcomes	• change in spleen volume • change in lung function • change in liver function and volume • change in physical observations (including observations or measurements from examination of the skin, head, eyes, ears, nose and throat; lymph nodes; heart, vital signs, lungs and abdomen; bone marrow; extremities and joints) • change in weight, height and onset of puberty in children and young people • change in neurological observations (including observations or measurements from examination of coordination; cranial nerves; extrapyramidal features; fundoscopy; gait; motor skills; peripheral nervous system; reflexes; sensory nervous system; strength and mental status) • change in biomarkers (including high sensitivity c-reactive protein; ceramide; iron; cardiac troponin I; ferritin; CCL18 levels; lysophingomyelin, oxysterols, lipid profile)	Partial	None provided	Advice to the EAG was that key outcomes measured by the company trials were highly relevant to understanding the potential efficacy of olipudase alfa for treating ASMD types B and A/B, including change in organomegaly, pulmonary function, liver function, HRQoL and functioning, and AEs. The EAG therefore concluded that the evidence reported was sufficient for judging the key benefits of olipudase alfa, though the absence of some outcomes has limitations for inputs within the company model.

	• Change in fatigue and exercise tolerance • Mortality • Adverse effects of treatment • Health-related quality of life • Carer quality of life			
Economic analysis	Analysis expected to be consistent with the NICE reference case	As per scope	N/A	The company submitted a cost utility analysis, which was appropriate. The EAG noted that the company's base case differed to the NICE reference case regarding discounting (see Section 4.2.5). Furthermore, the company made several assumptions with respect to carer disutility that did not align with NICE guidance (see Section 4.2.9.1).
Subgroups	None specified	N/A	N/A	ASMD types B and A/B are heterogeneous conditions with broad variation in the age of diagnosis, disease severity and symptom profile across the population. These differences are related to the various genetic mutations responsible for the condition, though there is currently no validated marker of disease severity or prognosis. The EAG considered that subgroup analyses that compared the effect of olipudase alfa between meaningful groups, such as according to genetic markers, age of onset, or baseline severity would be of interest to provide more information about the effect of olipudase alfa and how it may be used in practice. However, the EAG accepted that this is a very rare condition, and the company evidence consisted of very little comparative evidence from which to conduct analyses. In response to a request from the FDA, the company conducted subgroup analyses comparing a small number of clinical outcomes in ASCEND according to markers of disease severity at baseline, the results of which are reported in the CS. As expected, these analyses were limited due to the available sample size, and so at this

				time the EAG considered that the current evidence base for olipudase alfa was not sufficient to fully explore potential variation in the effect of treatment across the population. The company provided economic results for the severe population. This analysis was subject to a number of limitations (see Section 4.2.3.1 and 5.2).
Special considerations including issues related to equity or equality	None specified	N/A	N/A	Treatment with olipudase alfa was not anticipated to affect inequity in protected groups.

Abbreviations: AE, adverse event; ASMD, acid sphingomyelinase deficiency; CS, company submission; EAG, External Assessment Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; HRQoL, health-related quality of life; N/A, not applicable; NICE, National Institute for Health and Care Excellence

3. CLINICAL EFFECTIVENESS

The sections below provide the EAG appraisal of the evidence submitted by the company in support of the clinical effectiveness and safety of olipudase alfa for the treatment of children and adults with ASMD Type B or A/B.

The EAG reviewed the details provided on:

- the methods implemented to identify, screen, extract data and assess the risk of bias in the relevant evidence
- the clinical efficacy of olipudase alfa for the stated indication and
- the safety profile of olipudase alfa for the stated population.

Detailed information from the CS is only provided where the EAG disagreed with the company's assessment or proposal, or where there was a particular area of concern that the EAG considered necessary to highlight to the NICE committee. Otherwise, the EAG signpost to the relevant part of the CS.

3.1. Critique of the methods of the review

The company undertook a single SLR to identify evidence reporting on the efficacy/effectiveness and safety of olipudase alfa for the treatment of children or adults with ASMD types B or A/B.

A summary of the EAG's critique of the methods implemented in the SLR is presented in Table 8. Overall, the EAG found the SLR to be of reasonable quality and it was likely that the key studies relevant to the company's decision problem were identified.

The EAG was concerned about the quality appraisal conducted by the company and disagreed with the company's overall ratings of trial quality. This issue is discussed further in section 3.2.2.6.

Table 8: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	CS B.2.1, Table 9	The EAG was broadly satisfied that searches identified all relevant literature, however, the EAG

	CS Appendix D.1.1 Company clarification response to questions A1 – A3.	noted the following limitations: the subject heading for Niemann-Pick Diseases was not exploded to include narrower terms in the MeSH hierarchy; and the use of 'Article' and 'Article in Press' limits excluded conference abstracts from Embase search results. At clarification, the company provided additional information about methods for searching grey literature sources. The EAG considered that these methods missed some relevant sources, and restrictions on search terms and limits in clinicaltrials.gov could have resulted in missing relevant evidence. However, the EAG conducted additional searches (see Section 3.4.1) and did not identify any relevant studies that should have been included.
Inclusion criteria	CS Appendix D.1.1, Table 83 Company clarification response to questions A4–A5	Inclusion and exclusion criteria were broad, and reasonably aligned with the company's decision problem. The EAG noted that the broad inclusion criteria (i.e. including all non-medical interventions) resulted in the inclusion of a study (NCT00410566) where olipudase alfa was not given at the licensed maintenance dose. The EAG also noted that the comparator in the NICE scope was best supportive care, but non-medical comparators were excluded from the SLR for clinical and safety outcomes. Following clarification, the company provided justification for this: non-medical interventions aim to reduce symptom burden rather than treating ASMD. The EAG noted that concomitant non-medical interventions would have been permitted for participants in the included trials. Additionally, the EAG agreed that it is unlikely any studies focusing on a non-medical intervention as a comparator were available and excluded from the SLR.
Screening	CS B.2.1, Table 9 CS Appendix D.1.1	Standard appropriate methods. The EAG highlighted that the SLR included studies reporting the population of interest as a subgroup, or for which 80% of the population matched the population of interest. Given the rarity of the condition, the EAG agreed that this was methodologically appropriate.
Data extraction	CS B.2.1, Table 9 CS Appendix D	Standard appropriate methods.
Tool for quality assessment of included study or studies	CS B.2.1, Table 9 CS Appendix D Company clarification response to question A6	The EAG noted that whilst appropriate methods were used to assess the ASCEND trial, the ROBINS-I was used to assess the single-arm trials. The ROBINS-I was designed for non-randomised comparative studies and was, therefore, not the best choice of tool to evaluate

		and highlight the constraints of single-arm studies. The EAG had concerns with the critical appraisal ratings determined by the company and considered that the evidence base for olipudase alfa was limited in ways not considered in the company assessment.
Evidence synthesis	CS B.2.1, Table 9 CS Appendix D	The EAG agreed that, due to the paucity of studies, data pooling across studies was not feasible.

Abbreviations: CS, Company submission; EAG, Evidence Assessment Group

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described four trials of olipudase alfa (Table 9). Three of the trials included unique patient populations: ASCEND (a double-blind RCT with adults), [9,10] ASCEND-Peds (an open-label single arm trial with children) [11,12] and DFI13412 (an open-label single arm trial with adults). [13] The fourth trial, LTS13632, was an open-label extension of the latter two trials (ASCEND-Peds and DFI13412). [14] The company reported clinical effectiveness and safety data for all four trials: data for ASCEND (and its extension), ASCEND-Peds and DFI13412 were reported in Section B.2.6. of the CS. Data for LTS13632 were reported in Section B.2.11 of the CS.

The EAG noted that further data are being collected for olipudase alfa and/or for outcomes relevant to understanding the humanistic burden and potential value of olipudase alfa for treating ASMD type B and A/B. Data collection for LTS13632 is ongoing and is expected to generate data at four- and 6.5-year follow-up for paediatric and adult participants, respectively (within the CS, data were reported at 6.5-years for five adult participants, and at four-years for spleen and liver volume in seven paediatric participants). In addition, the company was conducting a prospective/retrospective cohort study to map disease course, disease burden, HRQoL, resource use, and to validate patient-reported outcome measures (PROs) in ASMD, which was expected to complete in April 2023 [NCT04106544]. Finally, the EAG understood that olipudase alfa was being reimbursed in France as part of an early access program with evidence generation, which will complete in January 2025 [NCT05359276].

Table 9: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Follow-up	Study type
ASCEND DFI12712 [NCT02004691] [10,15,16]	Double-blind international RCT plus double-blind extension (all participants receiving placebo switched to treatment)	Adults with ASMD type B (N=36)	Olipudase alfa	Placebo	52 weeks plus 1-year extension	Phase II/III efficacy and safety evaluation
ASCEND-Peds DFI13803 [NCT02292654] [11,12]	Open-label international single-arm	Children with ASMD not identified as type A (N=20)	Olipudase alfa	NA	52 weeks	Phase I/II efficacy and safety evaluation
DFI13412 [NCT01722526] [13,17]	Open-label, single arm trial	Adults with ASMD (N=5)	Olipudase alfa	NA	26 weeks	Phase I safety and tolerability evaluation
LTS13632 [NCT02004704] [14,18-21]	Open-label extension to ASCEND-Peds and DFI13412	Participants from selected centres recruited to ASCEND-Peds and DFI13412 (N=25)	Olipudase alfa	NA	4- and 6.5-years for paediatric and adult participants, respectively	Phase II long-term efficacy and safety evaluation. Trial ongoing (expected completion July 2024)

Abbreviations: ASMD, acid sphingomyelinase deficiency; CS, company submission; NA, not applicable; RCT, randomised controlled trial

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

For adults, the CS reported an RCT evaluating olipudase alfa (ASCEND) alongside a small single-arm study (DFI13412) and a single-arm extension study involving the DFI13412 participants (LTS13632).

The company stated that an RCT design was not considered appropriate for those <18 years of age for ethical reasons. The paediatric evidence base for olipudase alfa was, therefore, limited to a single-arm study (ASCEND-Peds) from which participants were also eligible to enter the extension study LTS13632. Key design features of these studies are provided in Table 10.

Table 10: Summary of key olipudase alfa study design characteristics

	ASCEND	ASCEND-Peds	DFI13412	LTS13632
Design	Double-blind RCT	Single-arm	Single-arm	Single-arm extension
Blinding	During PAP + ETP	Open-label	Open-label	Open-label
Comparator	Placebo (0.9% sodium chloride)	None	None	None
Total N	36	20	5	25
ASMD Type	B[a]	A/B and B	B	A/B and B
Adult/Paediatric	Adult	Paediatric [b]	Adult	Both
Location(s)	17 countries in North and South America, Australasia, Europe, and Asia	6 countries (Brazil, France, Germany, Italy, the UK, US)	2 countries (UK, US)	7 countries (Brazil, Belgium, France, Germany, Italy, the UK, US)
Sites	23 (one in the UK)	6 (one in the UK)	2 (one in the UK)	9 (two in the UK)
PAP	52 weeks (randomly allocated treatment period)	52 weeks	26 weeks	Ongoing[c]
ETP	52 weeks (all participants switched to olipudase alfa)	Eligible to participate in LTS13632	Eligible to participate in LTS13632	NA

Abbreviations: PAP, primary analysis period; ETP, extension period; NA, not applicable.
Notes: [a] Although the summary of product characteristics (SmPC) for olipudase alfa reported that 25% of participants in ASCEND had neurological symptoms consistent with a clinical diagnosis of ASMD type A/B; [b] Split into three age groups: adolescents (n=4), children (n=9), and infants/early children (n=7); [c] Data reported in the CS were principally available at 6.5 years for adult and 4 years for paediatric populations.

A discrepancy in the information provided by the company was noted in that an additional study location was reported for LTS13632 despite all participants having been recruited from the ASCEND-Peds and DFI13412 studies.

The company defined multiple different analysis sets for both ASCEND and ASCEND-Peds, including a modified-ITT (m-ITT) population, a per protocol set, a safety set, and outcome-specific analyses using patients with available data. At clarification (question A20) the company confirmed that all clinical data reported in the CS from these trials were based on the mITT population and all safety data were based the safety population, but that these populations were identical (no participant received a treatment other than the one they were allocated to receive).

The EAG considered that the data from LTS13632 may be unreliable due to the small number of participants reaching the 6.5-year and four-year time points and the high levels of missing data in the paediatric population at the latest data cut prior to this appraisal (data were available for 7/20 participants [35%]). In response to clarification (question A18) the company also reported a high rate of missing data for key outcomes at 2-year follow-up (see Section 3.2.2.5). Additionally, the EAG highlighted that, in the CS (p.169), the company claimed that data up to 9-years were available from LTS13632, but all data reported in the CS were from the earlier time points. Clarification on this was requested (question A23), but no further explanation was provided.

Overall, the EAG considered that the best quality data for olipudase alfa were available at up to one year in both adult and paediatric participants (see Section 3.2.2.6 for the EAG critical appraisal of the included trials).

3.2.2.2. Population

The CS reported limited population eligibility criteria for the included trials. Following clarification (question A16) the company did not provide this information but indicated that this information was not deemed confidential. The EAG, therefore, report further eligibility criteria from the four trial CSRs (Table 11).

No record was made in the trials of ASMD type (A/B or B). The company stated (response to clarification question A15) that this was not necessary because the marketing authorisation for olipudase alfa was for people with either ASMD types A/ B or B. The EAG disagreed with this statement on the basis that it is important to demonstrate effectiveness of olipudase alfa in both conditions covered by the marketing authorisation. Indeed, expert advice to the EAG suggested that the effect of olipudase alfa may differ between these subtypes (the absence of an effect on neurological symptoms may lead to a differential impact on outcomes such as functioning and quality of life). The company also reported that the risk of mortality may be higher for those with ASMD type A/B than type B. The EAG ascertained (response to clarification question A15) that

both adult and paediatric participants with a clinical presentation consistent with type A/B were eligible for inclusion in both ASCEND and ASCEND-Peds (and by default in the paediatric population in LTS13632), and confirmed this using information from the summary of product characteristics (SmPC) for olipudase alfa (produced by the EMA). The SmPC reported that 25% of participants in ASCEND and 40% of participants in ASCEND-Peds had neurological symptoms consistent with a clinical diagnosis of ASMD type A/B (SmPC[22] pages 11 and 14). Despite this, there remains a lack of separate evidence for each ASMD type.

The company reported (document B, Section 2.3) that in ASCEND, 62 people were screened but only 38 were considered eligible for inclusion (i.e. 24 people were excluded at this stage). The EAG requested confirmation that those excluded all had ASMD types B or A/B.

[redacted] Two people did not provide informed consent and one person was recorded as unable to adhere to study requirements. The remaining exclusions were due to not meeting clinical inclusion criteria, such as spleen volume, lung diffusion capacity, comorbid conditions, adequate platelet count, or liver function. Clinical advice to the EAG was that the eligibility criteria were particularly stringent in permitted DLco levels and may have excluded people with higher disease severity. Requirements may also have excluded those at a higher risk of adverse events. Clinical advice also suggested that the trials may have excluded those with mild disease severity. Subgroup analyses conducted within ASCEND did not find an effect of baseline severity on two outcomes (splenomegaly and lung diffusion capacity), though the sample size in subgroup analyses were limited in size. There were mixed views amongst clinicians about whether the treatment effect of olipudase alfa may vary according to disease severity, though there was some speculation that this may be true for some outcomes and not others (for example, some symptoms may be irreversible where there has been extensive organ damage). Overall, the EAG considered it plausible that the treatment effect of olipudase alfa and its adverse event profile may vary in those excluded in the trial but had no data to substantiate this. The EAG also considered it plausible that the risk of adverse events may be higher in those patients not eligible for the clinical trials.

Table 11: Summary of key inclusion/exclusion criteria for the included trials

	Inclusion criteria	Exclusion criteria
ASCEND	Adults aged ≥18 years with a clinical diagnosis of ASMD type B and: DLco ≤70% of predicted normal value Spleen volume ≥6 multiples of normal SRS ≥5 Platelet count ≥ 60 x 103 /μL INR ≤ 1.5 Not pregnant and using effective contraception	Any serious medical condition or a medical condition including significant cardiac disease, hypertension, active hepatitis B or C, HIV, malignancy within the past 5 years Received any major organ transplant Scheduled for surgery during the trial Unwilling to abstain from alcohol around the time each treatment is administered, and unwilling or unable to abstain from certain medications around the time of liver biopsy (at baseline, week 52 and week 104). Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications Patient requires ventilatory support (any invasive or non-invasive for more than 12 hours daily while awake) Patient is breast-feeding
ASCEND-Peds	Children aged <18 years with ASMD without acute or rapidly progressive neurological abnormalities Spleen volume ≥5 multiples of normal Platelet count ≥ 60 x 103 /μL alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤250 IU/L or total bilirubin ≤1.5 mg/dL INR ≤1.5 Height of -1 z score or lower Not pregnant and using effective contraception	Any serious medical condition or a medical condition including significant cardiac disease, active hepatitis B or C, HIV, malignancy within the past 5 years Delayed gross motor skills Received any major organ transplant Scheduled for surgery during the trial Patient requires ventilatory support (any invasive or non-invasive for more than 12 hours daily while awake) Unwilling to abstain from alcohol around the time each treatment is administered Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications

	Inclusion criteria	**Exclusion criteria**
DFI13412	Adults aged 18 – 65 years with documented non-neuronopathic ASMD DLco >20% and ≤80% of predicted normal value Spleen volume ≥6 multiples of normal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤250 IU/L or total bilirubin ≤1.5 mg/dL Receiving a stable dose of lipid-lowering therapy (e.g. statins) Not pregnant and using effective contraception	Any serious medical condition or a medical condition including significant cardiac disease, active hepatitis B or C, HIV, cirrhosis, or malignancy within the past 5 years Received any major organ transplant Unwilling to abstain from alcohol around the time each treatment is administered, and unwilling or unable to abstain from certain medications around the time of liver biopsy Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications Body mass index >30
LTS13632	Patients who completed the treatment period of ASCEND-Peds or DFI13412 and with an acceptable safety profile Not pregnant and using effective contraception	Patient has a new condition or worsening of an existing condition that would make the patient unsuitable for enrollment or would interfere with the patient completing the trial Unwilling to abstain from alcohol around the time each treatment is administered, and unwilling or unable to abstain from certain medications around the time of liver biopsy Patient requires medications that decrease olipudase alfa activity, including certain antidepressant and anti-psychotic medications

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity for carbon monoxide; INR, international normalised ratio; SRS, splenomegaly related score

Source: Trial CSRs

3.2.2.3. Intervention

The evaluated intervention in all included trials was olipudase alfa. Details of the treatment administered, including background care, were not reported in the CS. At clarification (question A17) the EAG requested that the company provide information of the dose received, mean dose duration, dose modifications, and background care received by participants in all trial arms. In response, the company provided some of this information, as follows:

- The mean [redacted] and median [redacted] cumulative dose of olipudase alfa received by patients in the initial trial period of olipudase alfa (i.e. not the extension phase), and the number and proportion of participants not achieving the target olipudase alfa dose of 3mg/kg (n=1; 5.6%).
- The mean [redacted] and median [redacted] number of infusions received by participants in ASCEND-Peds (i.e. not the mean/median dose received, as requested by the EAG), and the number and proportion of participants not achieving the target olipudase alfa dose of 3mg/kg (n=0).
- A table summarising concomitant treatments during the initial ASCEND trial period (Table 4 in the company response to clarification question A17), and during ASCEND-Peds (Table 5 in the company response to clarification question A17). People with ASMD typically experience a range of comorbid conditions resulting from the impact of their condition, and the background care received by participants in ASCEND and ASCEND-Peds provided by the company at clarification (question A17) appeared to be consistent with this. The EAG noted some differences in background care between the trial arms in ASCEND but considered that these likely due to the small absolute numbers of participants.

3.2.2.4. Comparator

Only one of the trials (ASCEND) used a comparator, which was a matched placebo. The EAG highlighted that the lack of a comparator in the remaining three trials seriously increased the risk of bias in these studies (see Section 3.2.2.6).

3.2.2.5. Outcomes

The outcomes measured in the four trials, and where these data can be found in the CS, are summarised in Table 12. Key outcomes specified in the NICE scope were available for all four

studies, although data from DFI13412 and LTS13632 were primarily used to supplement safety data from ASCEND and ASCEND-Peds.

The company conducted subgroup analyses on data for two outcomes in ASCEND: for DLco, the company compared the outcome according to baseline DLco severity, baseline ALT or AST abnormality, and total bilirubin abnormality; for spleen volume, the company compared the outcome according to baseline ALT or AST abnormality, total bilirubin abnormality, spleen severity, and the presence of portal hypertension. At clarification (question A25) the EAG requested that the company provide a rationale for why these subgroups were selected over other prognostic or demographic markers. The company did not provide a rationale for the selected subgroups, instead stating that the subgroup analyses were requested by the FDA without explanation. Expert advice to the EAG was that these subgroups were appropriate for consideration and provided some indication of whether the effect of treatment may vary according to disease severity and organ damage. However, a broader range of analyses may have been informative as there was no universally accepted measure of disease severity and there are other markers of organ damage. Furthermore, clinical advice was that baseline severity may affect response to some outcomes over others, and therefore subgroup analyses across a broader range of outcomes may have been more informative.

Table 12: Map of the location of outcomes data in the company submission

Outcome	ASCEND	ACSEND-Peds	DFI13412	LTS13632
% change in DLco	CS Document B, Table 22, Figure 6, Figure 13, Figure 14	CS Document B, Table 29, Figure 10	Not reported in CS	CS Document B, Figure 19
% change in spleen volume	CS Document B, Table 23, Figure 7, Figure 15, Figure 16	CS Document B, Table 30, Figure 11	CS Document B, Table 34, CS Appendix M.1.4	CS Document B, Figure 17
% change in liver volume	CS Document B, Table 24, Figure 8	CS Document B, Table 31, Figure 12	CS Document B, Table 34, CS Appendix M.1.4	CS Document B, Figure 18
% change in platelet counts	CS Document B, Table 25, Figure 9	Not reported	Not reported in CS	CS Document B.2.11
% change in liver function (ALT and AST)	CS Document B, Table 26, CS Appendix N.6	CS Document B, Table 32, CS Appendix N.6	Not reported in CS	CS Appendix O.1
% change in lipid profile (cholesterol and triglycerides)	CS Document B, Table 26, Appendix N.6	CS Document B, Table 32, CS Appendix N.6	Not reported in CS	Not reported in CS
% change in Pulmonary function (FVC, FEV1, lung capacity, and O2 uptake during exercise)	CS Document B, Table 26, Appendix N.6	CS Document B, Table 32, CS Appendix N.6	Not reported in CS	Not reported in CS
Biomarker reduction (chitotriosidase, angiotensin enzyme, CCL18, safety biomarkers)	CS Document B, Table 26, CS Appendix N.6 and N.8	CS Document B, Table 32, CS Appendix N.6 and N.8	Not reported in CS	CS Appendix O.5
HRQoL	CS Document B, Tables 27-28; CS Appendix N.7	CS Document B, Table 33	Not reported in CS	CS Appendix O.6
Adverse effects	CS Document B, Tables 35 and 36	CS Document B, Tables 37 and 38	CS Document B, Table 34, CS Appendix M.1.6	CS Document B, Table 41
Neurological and physical observations and imaging	CS Appendix N.1-N.4	CS Appendix N.1-N.4	Not reported in CS	CS Appendix O.3 and O.4
Paediatric physical outcomes (height, weight, puberty onset)	Not applicable	CS Document B, Table 32 CS Appendix N.5 and N.6	Not applicable	CS Appendix O.2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCL18, chemokine ligand 18; CS, company submission; DLco, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume; FVC, forced vital capacity; HRQoL, health-related quality of life;

In response to clarification (question A18), the company reported that the availability of follow-up data in ASCEND varied across outcomes due to participant non-attendance or technical faults with certain assessments. The company further reported the number of participants available at follow-up for some outcomes (shown in Table 13). These data showed that attrition of ≥30% was present for key clinical outcomes in the olipudase alfa arm at year two (spleen volume, DLco, liver volume, platelet count), with attrition particularly high (50%) for DLco. The EAG considered this to be a high rate of attrition for these key outcomes, and considered this issue in its appraisal of the quality of the trial (see Section 3.2.2.6).

Table 13: Number of participants available at follow-up timepoints in ASCEND

Outcome	Follow-up timepoint	Number of participants available			
		Placebo/olipudase alfa N=18		**Olipudase alfa/olipudase alfa N=20**	
% predicted DL_{CO}	Year 1	17	94.4%	17	85.0%
	Year 2	10	55.6%	10	50.0%
Spleen volume (MN)	Year 1	17	94.4%	18	90.0%
	Year 2	11	61.1%	14	70.0%
Liver volume (MN)	Year 1	17	94.4%	17	85.0%
	Year 2	11	61.1%	14	70.0%
Platelet count (10^9/L)	Year 1	16	88.9%	18	90.0%
	Year 2	15	83.3%	13	65.0%
Lung HRCT ground glass appearance score	Year 1	17	94.4%	18	90.0%
	Year 2	14	77.8%	16	80.0%
ALT (IU/L)	Year 1	16	88.9%	18	90.0%
	Year 2	15	83.3%	12	60.0%
HDL cholesterol (mg/dL)	Year 1	16	88.9%	18	90.0%
	Year 2	14	77.8%	12	60.0%
LDL cholesterol (mg/dL)	Year 1	15	83.3%	18	90.0%
	Year 2	14	77.8%	12	60.0%

Source: Company response to clarification A18. The table was amended by the EAG to show the percentage of participants available.

Abbreviations: ALT, alanine aminotransferase; DLco, diffusing capacity of carbon monoxide; HDL, high-density lipoprotein; HRCT, high-resolution computed tomograph; LDL, ow-density lipoprotein; MN, multiples of normal

3.2.2.6. Critical appraisal of the design of the studies

The company usedthe Cochrane risk-of-bias (RoB) tool version 2.0 to assess the quality of ASCEND, and the ROBINS-I to assess the remaining three olipudase alfa studies. Three additional single-arm studies used to inform inputs in the company's economic analysis were also assessed using the ROBINS-I: Bembi 1992 (amniotic epithelial cell implantation), [23] Liu 2019 (liver transplantation) [24] and NCT00410566 (olipudase alfa). [25]

The EAG broadly agreed with the company's assessment that ASCEND was at a low risk of bias as assessed using the Cochrane RoB 2.0 (CS Appendix D.1.3, Table 2). [26] However, the EAG highlighted two additional considerations:

- At clarification (question A9), the company confirmed that overall quality appraisal ratings were considered relevant to all trial outcomes. However, as noted in Section 3.2.2.5, there was a high rate of missing participants at 2-year follow-up for several key clinical outcomes (attrition ≥30% in the olipudase alfa arm at year 2 for spleen volume, DLco, liver volume and platelet count; attrition 50% for DLco.). The company did not consider this in their quality appraisal. Based on the Cochrane risk of bias tool v2, the EAG considered these outcomes to be at severe risk of bias. This rating is based on the view that it is plausible that missingness in these outcomes could relate to the outcome, for example high rates of participant non-attendance could be due to the effect of treatment. The severe rating remains even though the EAG did not have sufficient information to judge whether this was likely.

- There were no baseline data provided for ASCEND on the number of participants with type A/B ASMD in each of the trial arms. It is, therefore, unclear whether an imbalance between trial arms exists in this baseline characteristic.

With regard to the single-arm studies, the EAG considered that the company's assessment that these (ASCEND-Peds, DFI13412 and LTS13632) were at a low risk of bias was incorrect. This was largely because the assessments did not fully account for the lack of a comparator in these trials. The ROBINS-I tool[27] used to assess these studies was initially developed to appraise the quality of non-randomised comparative trials rather than single-arm studies. It is, therefore, not possible for the trial analyses to fully account for confounders in a way required by the tool criteria. Furthermore, the EAG did not consider that the company had provided sufficient justification for its statements that ASCEND-Peds was representative of the target patient

population, accounted for confounding factors, and that the findings were sufficiently precise. Data available to the EAG suggested that these statements were questionable.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Baseline characteristics of participants in the included trials

The CS presented baseline characteristics of participants included in ASCEND, ASCEND-Peds, and DFI13412 (see Table 12). Baseline data for LTS13631 were not presented in the CS (participants were those included in ASCEND-Peds and DFI13412). Table 14 summarises the key baseline data from the four trials. Demographic data presented in the CS from the olipudase alfa trials were judged to be generally consistent with the population in UK clinical practice (as far as it is possible to ascertain for such a rare condition). However, the EAG identified several considerations:

- As noted in Section 3.2.2.2, a breakdown of participants by ASMD subtype was not presented for any of the trials. Although the SmPC reported that 25% of participants in ASCEND and 40% in ASCEND-Peds exhibited neurological symptoms consistent with type A/B ASMD, these rates were not provided separately for the trial arms in ASCEND. The EAG could not, therefore, determine whether ASMD type was balanced between the trial arms.

- Baseline weight of participants in the trials was lower than would be expected for the general population in England and Wales. For ASCEND, weight data for trial participants was reported in the CS but were not available in the CSR and could not be verified. Clinical expert advice indicated that although some people with ASMD are slightly smaller than the average population, this would not necessarily lead to a major difference in weight across the population. With successful treatment, growth may be expected to be comparable to the general population.

- Baseline age at first infusion reported for the paediatric and adult populations in LTS13631 were not consistent with those given for ASCEND-Peds and DFI13412 (see Table 14). This may simply be due to rounding errors.

- Age at diagnosis was higher in ASCEND than in the adult population in DFI13412 (see Table 14). Clinical expert advice to the EAG indicated that a lower age at diagnosis may be

expected with time (due to improvements in understanding of the condition and cascade testing of asymptomatic siblings).

- In ASCEND, when compared with controls, a numerically higher proportion of participants in the olipudase alfa arm had severe splenomegaly (>15 MN) at baseline (27.8% versus 16.7%), although this is likely due to the small numbers of participants involved (n=5 versus n=3).

Table 14: Key baseline characteristics for the included trials

	ASCEND		**ASCEND-Peds**	**DFI13412**	**LTS13631**	
	Olipudase alfa N=18	Placebo N=18	N=20	N=5	Paediatric N=20	Adult N=5
Age, mean years (SD), range	36.2 (12.7), 18.8 – 59.9	33.5 (17.1), 18.6 – 65.9	8.2 (4.4), 1.5 – 17.5	32.6 (9.4), 23 - 48	[redacted]	[redacted]
Weight (kg), mean (SD)	67.4 (14.1)	61.6 (13.4)	23.4 (10.8)	[redacted]	As per ASCEND-Peds	As per DFI13412
Sex, n (%)	Male 9 (50%) Female 9 (50%)	Male 5 (28%) Female 13 (72%)	Male 10 (50%) Female 10 (50%)	Male 3 (60.0%) Female 2 (40.0%)	As per ASCEND-Peds	As per DFI13412
Race, n (%)	White 16 (89%) Asian 1 (6%) Other 1 (6%)	White 16 (89%) Asian 1 (6%) Other 1 (6%)	White 17 (85%) SE Asian 2 (10%) Other 1 (5%)	White 5 (100%)	As per ASCEND-Peds	As per DFI13412
Ethnicity, n (%)	Not Hispanic or Latino 12 (67%) Hispanic or Latino 5 (28%) NR 1 (6%)	Not Hispanic or Latino 12 (67%) Hispanic or Latino 6 (33%)	Not Hispanic or Latino 19 (95%) Hispanic or Latino 1 (5%)	Not Hispanic or Latino [redacted] Hispanic or Latino [redacted]	As per ASCEND-Peds	As per DFI13412
Age at ASMD diagnosis, mean years (SD), range	21.4 (20.3), [redacted]	14.6 (16.1), [redacted]	2.5 (2.5), [redacted]	7.2 (5.0), [redacted]	As per ASCEND-Peds	As per DFI13412
Severe splenomegaly (>15 MN), n (%)	5 (27.8%)	3 (16.7%)	12 (60%)	[redacted]	NR	NR
Severely reduced DLco (<40%), n (%)	3 (16.7%)	4 (22.2%)	1 (11.1%)	[redacted]	NR	NR

Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusing capacity for carbon monoxide; kg, kilogram; MN, multiples of normal; NR, not reported; SD, standard deviation. Source: Trial CSRs[10,11,13,14]; Wasserstein et al. 2022[15]

3.2.3.2. Clinical effectiveness results

Percentage change in DLco

Participants who received olipudase alfa in all included trials showed an overall improvement in lung diffusion capacity. By year one all groups showed a mean improvement of >20%, and there was an apparent trend for DLco to increase over time (though longer follow-up points included small numbers of participants, DLco exceeded 30% for adults and 40% for children). In comparison, no change in DLco was evident for adults who received placebo. The EAG therefore concluded that olipudase alfa had an overall clear clinical benefit in improving lung diffusion capacity compared to BSC.

A remaining uncertainty for the EAG was the number of participants in the trials who did not respond to treatment or did not achieve a clinically significant improvement in DLco (defined by the company as an improvement ≥15%). The EAG understood that the effect of treatment may vary across the population, for example due to baseline symptom severity or time since diagnosis (as this may affect the extent to which organs have experienced irreversible change). The company conducted a responder analysis showing that only 5/18 (27.8%) of adult participants in ASCEND had shown a clinically significant improvement in DLco by year one (the group LS mean change was 21.97 (95% CI 15.18, 28.76)). While mean improvements in DLco continued to improve over the trial follow-ups, it is uncertain whether this effect was shown in all participants as the company conducted no further responder analyses.

Percentage change in spleen volume

Participants who received olipudase alfa across all the included trials showed a mean reduction in spleen volume. After 6-months of treatment, mean reductions in spleen volume were greater than 25% in all groups, and reductions were stable or reduced further over following timepoints. In comparison, there was no change in spleen volume for adult participants in ASCEND who received placebo. Almost all adult participants (described in the CS as 94.4%, which the EAG assumed was a typo for 16/17 participants [94.1%]) in ASCEND showed a clinically meaningful reduction in spleen volume by 12-months (specified by the company as a change ≥15%). Absolute spleen volume at the longest follow-up stabilised for both adult and child participants at approximately six multiples of normal. Based on the trend in the data showed in Figure 1 below (taken from the CS, p.150), the EAG considered it plausible that spleen volume would remain at this level, at least in the months immediately following the end of trial follow-up. If spleen volume was to remain elevated at this level for the rest of a person's life, clinical experts to the EAG considered that this would nevertheless offer a meaningful clinical benefit to patients' functioning and mental wellbeing.

Figure 1: Spleen volume in long-term follow-up

Percentage change in liver volume

Participants who received olipudase alfa in all included trials showed a mean reduction in liver volume. Mean reductions exceeded 20% following 6-months of treatment, and continued to improve over subsequent follow-up timepoints (see Figure 2 taken from the CS p.151). In contrast, no change in liver volume was evident for participants who received placebo. No responder analysis was conducted by the company to determine how many participants receiving olipudase alfa experienced a clinically meaningful reduction in liver volume.

Figure 2: Liver volume in long-term follow-up

Percentage change in platelet counts

Mean platelet counts increased in adults receiving olipudase alfa in ASCEND, while there was no change amongst participants receiving placebo. There were no data for platelet count for children in ASCEND-Peds, though overall platelet counts for children continuing into LTS13632 did show an increase (N=5). A figure of change in platelet counts in both adult and paediatric participants in ASCEND and ASCEND-Peds was provided in appendices to the LTS13632 trial CSR. [14] The figure showed that adult platelet counts remained fairly stable until final follow-up, though in children mean platelet counts showed high variance and appeared to reduce back towards baseline measurements in the last few months of follow-up. Given the small sample size available in the long-term follow-up, and the increased stability of platelet counts in the adult population, the EAG were hesitant to conclude that the effect of olipudase alfa on platelet count reduced after four-years. However, the EAG considered that the effect of olipudase alfa

for platelet counts may vary across paediatric participants for unclear reasons, and that further data collection is needed to reduce uncertainties in the effect of treatment beyond four years.

Additional efficacy outcomes

Additional efficacy outcomes measured in ASCEND suggested that participants receiving olipudase alfa also showed improved liver function (ALT and AST), reduced cholesterol and triglyceride, and improved pulmonary function (FVC and O^2 uptake during exercise). Data for disease markers showed [redacted] in chitotriosidase, there was also a [redacted] angiotensin enzyme and CCL18, though [redacted]

Positive findings were also reported for additional outcomes measured in ASCEND-Peds, though there was no comparison group and variance was high, particularly in age-specific groups where sample sizes were small. Improvements were shown in liver function (ALT and AST), pulmonary function (FVC), cholesterol and triglyceride, and exercise capacity. Data for disease markers also showed [redacted]

The EAG did not have validated thresholds to determine whether changes in the above outcomes in the adult and paediatric populations were clinically meaningful. Clinical advice to the EAG was that in the paediatric population, these effects may lead to overall improved functioning, which would have benefits for children's school life and wellbeing.

Health-related quality of life

In ASCEND, HRQoL at baseline for each treatment arm was below the general population norms for all subscales. At six- and 12-months, there was no difference between treatment arms in HRQoL measured either by the EQ-5D or the SF-36. The company argued that these findings were inconsistent with improvements in clinical outcomes and with statements by participants who received olipudase alfa and described benefits of treatments for fatigue, productivity and pain. The EAG agreed that the lack of a change in HRQoL seemed inconsistent with improvements in clinical outcomes such as reductions in splenomegaly and platelet count, which may be expected to impact on fatigue. The company argued that clinical benefits of olipudase alfa improve HRQoL through reductions in fatigue and pain, and through increased ability to function; however, the EAG noted that measures selected by the company to assess these outcomes showed no difference between treatment arms at up to one year follow-up. The

EAG considered it possible that while olipudase alfa may have clinical health benefits for adult participants, the impact of these changes on their overall HRQoL had not been demonstrated.

In ASCEND-Peds, participants exhibited an improvement in HRQoL that in many cases exceeded established minimally important differences (MIDs) for the PedsQL generic outcome.[28,29] For children aged 5-7 years' old the effect was not present until after one year of treatment, and mean improvement in HRQoL hovered close to the MID threshold. However, children between eight and 18-years of age showed mean improvements in HRQoL above the MID by six-months, with a further increase by 12-months. Given the company's argument that generic HRQoL measures are insensitive to change in the adult population, at clarification (QA26) the EAG asked the company if they had a rationale for why this may be different for the paediatric population. The company responded that they considered generic HRQoL in both adults and paediatric patients to be insensitive, and that without a comparator arm in ASCEND-Peds they were unable to conclude whether there is a real effect of treatment on HRQoL. The EAG accepted that there was no control arm and therefore it was not possible to ascribe the improvements in HRQoL shown in paediatric participants to the benefits of olipudase alfa. The EAG also noted that HRQoL measures completed within open-label trials present a significant risk of bias (see Section 3.2.2.6). However, the EAG nevertheless considered these data to suggest that improvements in clinical outcomes shown in ASCEND-Peds may have meaningful benefits in HRQoL, particularly for children over 5-years of age. This was consistent with advice from experts to the EAG, who suggested that improvements in clinical outcomes would be expected to improve children's functioning at school and home.

Subgroup analyses

Subgroup analyses comparing outcomes between those with severe DLco and spleen volume at baseline were highly limited due to the small number of participants in ASCEND who were considered to have severe symptoms (DLco: three and four participants in the olipudase alfa and placebo arms, respectively; spleen volume: five and three participants in the olipudase alfa and placebo arms, respectively). Other analyses had a more balanced sample size, though were still limited by small samples. Subgroup analyses did not show a clear difference in effect based on baseline severity in the outcome or other subgroup categories.

Adverse effects

The CS primarily reported adverse reactions to olipudase alfa that occurred in the ASCEND and ASCEND-Peds trials (CS B.2.10). Adverse events data were also provided from LTS13632 (CS B.2.11, Table 41) and DFI13412 (CS B.2.6, Table 34). The EAG have checked the data provided in the CS against the CSRs for the four studies.

Treatment-emergent adverse events (TEAEs)

Overviews of the safety data from ASCENDS and ASCEND-Peds were provided in CS B.2.10, Tables 35 and 37 respectively, with summaries of the most common TEAEs provided in CS B.2.10, Tables 36 and 38 respectively.

CS B.2.10 stated that all participants in both the ASCEND safety population and the ASCEND-Peds safety population experienced at least one TEAE. In ASCEND, treatment-related TEAEs were more common in the olipudase alfa group than in the placebo group (n=12 (67%)) versus n=6 (33%) respectively), but serious TEAEs were similar across the two groups and none were thought to be related to the study drug. The EAG noted that this applied to the primary analysis period for the study, and that the ASCEND CSR[10] specified that one participant (previously in the placebo group but switched to olipudase alfa as part of the study extension) experienced a serious TEAE of extrasystoles that was related to the study drug. This participant had pre-existing cardiomyopathy. In ASCEND-Peds, five participants experienced 12 serious adverse events. Five of these (in three participants) were treatment-related serious adverse events. These all occurred in the youngest study cohort (infant/early child).

For brevity, the EAG consolidated the data on the most commonly observed adverse events observed in ASCEND (primary analysis period) and ASCEND-Peds (see Table 15). For a breakdown of the ASCEND-Peds results by age category, refer to CS B.2.10 Table 38. In ASCEND, headache was the most frequently observed TEAE during the primary analysis period with infections and infestations being the most commonly observed organ class of adverse events. In ASCEND-Peds pyrexia occurred in more participants than any other TEAE during the treatment period.

Table 15: Summary of the most common treatment-emergent adverse events in ASCEND PAP and ASCEND-Peds

	ASCEND				**ASCEND-Peds**	
	N (%)	Events	N (%)	Events	N (%)	Events
Any class†	18 (100%)	270	18 (100%)	242	20 (100%)	798
Pyrexia	--	--	--	--	15 (75.0%)	56
Contusion	--	--	--	--	6 (30.0%)	88
Scratch	--	--	--	--	4 (20.0%)	44
Infections and infestations	15 (83.3%)	36	15 (83.3%)	45	--	--
Nasopharyngitis	6 (33.3%)	8	8 (44.4%)	18	11 (55.0%)	28
Upper RTI	4 (22.2%)	6	6 (33.3%)	8	8 (40.0%)	17
Nervous system disorders	9 (50.0%)	40	13 (72.2%)	71	--	--
Headache	8 (44.4%)	32	12 (66.7%)	64	8 (40.0%)	38
Musculoskeletal and connective tissue disorders	11 (61.1%)	26	12 (66.7%)	23	--	--
Arthralgia	3 (16.7%)	3	4 (22.2%)	10	--	--
Respiratory, thoracic, and mediastinal	5 (27.8%)	15	9 (50.0%)	14	--	--
Cough	2 (11.1%)	3	5 (27.8%)	5	14 (70.0%)	31
Nasal congestion	--	--	--	--	6 (30.0%)	18
Epistaxis	--	--	--	--	4 (20.0%)	17
Urticaria	--	--	--	--	4 (20.0%)	24
Rash	--	--	--	--	3 (30.0%)	17
Vomiting	--	--	--	--	12 (60.0%)	38
Diarrhea	--	--	--	--	11 (55.0%)	22
Stomach pain	--	--	--	--	6 (30.0%)	20

Abbreviations: PAP, primary analysis period; PT, preferred term; RTI, respiratory tract infection; SOC, system organ class

† Includes treatment-emergent adverse events with percentages of events >= 2% and number of patients >= 2; --Not reported in the CS for this study. Source: CS B.2.10, Table 36 and Table 38

CS B.2.6, Table 34 reported that there were no serious TEAEs in DFI13412, with 97% of TEAEs assessed as mild, which was consistent with the data in the CSR. The CSR specified that the

most common TEAEs in DFI13412 were headache (n = 18), arthralgia (n = 16), abdominal pain (n = 14), and nausea (n = 14) and that there were six moderate events in two participants (pyrexia, abdominal gas pain, spleen pain, nausea, headache, and migraine). LTS13632 included the five participants from DFI13412, and separate longer-term data from DFI13412 were provided in CS B.2.11, Table 41.

For the LTS13632 study as a whole, CS B.2.11, Table 41 reported that [redacted] (99.7%) of TEAEs (in the adult and paediatric population) were of mild or moderate severity (data up until 78 months. [redacted] Details of these serious TEAEs were not provided in the CS, but were given in the CSR: [redacted]

Adverse events of special interest

In ASCEND, the percentage of patients with a protocol defined infusion associated reaction (IAR) was higher in the olipudase alfa group compared with the placebo group (44.4% and 27.8%, respectively; CS B.2.10, Table 35). CS B.2.10, Table 37 states that 55% of the participants in ASCEND-Peds had a protocol defined IAR. The CSR for LTS13632 reported that 80% of adult and 65% of paediatric participants experienced a protocol-defined IAR, with the most common protocol-defined IAR events being headache, nausea, and arthralgia in adults and urticaria, pyrexia, and vomiting in children. These events were highest during year one of treatment and declined gradually. The CSR for DFI13412 reported that 80% of participants experienced an IAR (55 events in four participants), with the most commonly reported IAR events being headache, nausea, abdominal pain, and musculoskeletal pain.

CS B.2.10, Table 35 reported that there were no treatment-emergent pregnancies or symptomatic overdoses in either group of the ASCEND study or in the ASCEND-Peds study. The CSR for LTS13632 reported that there were no pregnancies or symptomatic overdoses during the study.

Discontinuations and dose reductions

The CS reported that there were no discontinuations or withdrawals due to TEAEs in any of the four studies reporting adverse events data (ASCEND, ASCEND-Peds, DFI13412 and

LTS13632). Following clarification, the company confirmed that there were no discontinuations due to the study drug in ASCEND (of the two discontinuations in people receiving olipudase alfa, [redacted]

CS B.2.10 stated that three out of the 18 participants in each safety group of ASCEND experienced a TEAE that lead to a temporary interruption in treatment. In ASCEND-Peds, two of the 20 participants experienced an event that led to the visit being stopped (but then continued and completed the study) and three participants experienced 25 events where infusions had to be paused and resolved.

CS B.2.10 also reported that, in ASCEND, one participant in the olipudase alfa group experienced a TEAE (alanine aminotransferase increased) that led to a temporary dose reduction and in ASCEND-Peds, there were eleven dose reduction events. For LTS13632, CS B.2.11, Table 41 specified that there were [redacted] These data were consistent with the CSRs for these studies.

Deaths

CS B.2.10 stated that no deaths occurred in the ASCEND or ASCEND-Peds trials, CS B.2.6, Table 34 stated that there were no deaths in DFI13412, and CS B.2.11, Table 41 reported no TEAEs leading to death in LTS13632. This was consistent with the CSRs for these studies.

Safety biomarkers

Safety biomarker data (ceramide levels in plasma, calcitonin, high sensitivity C-reactive protein (hsCRP), ferritin, IL-6, IL-8, iron and cardiac troponin) were provided in CS Appendix N.8, Tables 30 and 31 for ASCEND and ASCEND-Peds respectively.

For ASCEND, the company reported that mean hsCRP, iron, ferritin, calcitonin, cardiac Troponin I, and IL-8 [redacted] In ASCEND-Peds there were three participants who experienced acute phase reactions [redacted]

The company also noted that, at 52-weeks in ASCEND, plasma ceramide was increased in the olipudase alfa arm compared with the placebo arm at both 24- and 48-hours post-infusion. In

the ASCEND-Peds trial, there was an increase in plasma-ceramide from pre-infusion to 24 hours and 48 hours post-infusion, but there was no control group in this study for comparison.

3.3. Critique of the indirect comparison and/or multiple treatment comparison

No other comparators to olipudase alfa were identified, and therefore no indirect comparison was feasible.

3.4. Additional work on clinical effectiveness undertaken by the EAG

The EAG conducted searches of Ovid MEDLINE and Embase (17th August 2022) to confirm that the company's literature searches had identified all relevant studies. The MEDLINE search used the exploded subject heading for Niemann-Pick Diseases to include the relevant MeSH term for Niemann-Pick Disease, Type B/, but this search did not retrieve any additional studies. The Embase search tested the impact of the use of 'Article' or 'Article in Press' limits (full search strategies are available in Appendix A). This search identified 19 conference abstracts that were not retrieved by company searches, however, the EAG was satisfied that these abstracts did not provide any further information, and that all relevant studies had been included.

The EAG also noted inconsistent use of terms in grey literature searches for conference abstracts. The EAG completed additional searches of listed sources with missing terms and did not identify any further studies.

3.5. Conclusions of the clinical effectiveness section

Based on the evidence presented by the company, the EAG concluded that olipudase alfa resulted in benefit to clinical outcomes for children and adults with ASMD types B and A/B. These benefits were most notable for outcomes related to splenomegaly and hepatomegaly, but benefits were also demonstrated for respiratory function and platelet count. The benefits of olipudase alfa on clinical outcomes were not reflected in similar benefits in HRQoL and functioning, though clinical advice to the EAG was that the reported change in clinical outcomes would nevertheless have a meaningful benefit to people's functioning and quality of life. The EAG considered it plausible that measures of quality of life and functioning may not be sensitive to change resulting from improvement in the clinical outcomes of ASMD types B and A/B, though the company did not present evidence to substantiate this. Clinical advice to the EAG was that as ASMD types B and A/B are heterogeneous conditions, the magnitude of benefits of treatment to some outcomes may vary across the target population. The adverse event profile

of olipudase alfa appeared acceptable, though the EAG highlighted a high rate of adverse events particularly in very young children treated in ASCEND-Peds. Clinical advice to the EAG was that this may be due to the tapering regimen used in the trial and suggested that more experience with administering olipudase alfa at a slower rate may reduce the number of AEs in this group.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted SLRs to identify existing cost-effectiveness evidence, health-related quality of life (HRQoL) evidence, and cost and resource use evidence for olipudase alfa and comparator interventions. A summary of the EAG's critique of the methods implemented by the company to identify relevant cost effectiveness, HRQoL and healthcare resource use and costs evidence is presented in Table 16. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 16. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence, HRQoL and health care resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	CS Appendix D.1.1	The EAG was broadly satisfied that searches identified all relevant literature, however, the EAG noted the following limitations: the subject heading for Niemann-Pick Diseases was not exploded to include narrower terms in the MeSH hierarchy; and the use of 'Article' and 'Article in Press' limits excluded conference abstracts from Embase search results. The EAG conducted additional searches (see Section 3.4.1) and did not identify further studies.
Inclusion criteria	CS Appendix D.1.1	No issues identified. Health economic evaluations, clinical trials and observational studies were included. The company excluded case reports, non-systematic reviews, pre-clinical studies, non-medical intervention studies, commentary and letters.
Screening	CS Appendices D.1.1, G, H and I	No issues identified. Two independent investigators trained in the objectives of the review screened abstracts and full-text papers to identify relevant studies based on the inclusion/exclusion criteria. Any disagreements were resolved by a third reviewer.
Data extraction	CS Appendices D.1.1, G, H and I	Extraction methods were not explicitly defined, however the company stated that the SLR was conducted in accordance with the high-quality standards required by NICE and reported in accordance with the standards defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
QA of included studies	CS Appendices D.1.1, G, H and I	No economic evaluations of treatments for ASMD were identified in the SLR. No utility values were identified in the SLR. For healthcare resource use and costs, one

		study was identified (SPHINGO-302).[30] The EAG noted that this was not used in the economic analysis, as annual frequencies of resource use were reported to have been derived from a retrospective cohort analysis conducted using IQVIA Open Claims. Full details of the company's SLR methods can be found in appendices G to I.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment; SLR, systematic literature review

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 17: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate and captured the health benefit to patients. Carer disutility was incorporated into the company's model.
Perspective on costs	NHS and PSS	NHS and PSS as appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis. The analysis contained a single comparator and therefore a fully incremental analysis was not required.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model incorporated a lifetime horizon (100-years) for both the paediatric and adult populations. The EAG considered this to be sufficiently long enough to capture important differences in costs and benefits between the treatment arms.
Synthesis of evidence on health effects	Based on systematic review	Modelled transition probabilities used in the economic analysis for both olipudase alfa and BSC treatment arms were estimated from the following key clinical data sources: • ASCEND • ASCEND-peds • SPHINGO-100 • DF131412 • LTS13632

Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs were used as appropriate. The company collected HRQoL data directly from participants in the ASCEND and ASCEND-Peds trials, however data from these trials were not used in the company's base case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utilities for both adult and paediatric patients were derived from a vignette study. Carer disutility was derived from published literature and assumption.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The vignette study was based on [redacted] members of the [redacted] general population. The study appropriately elicited preferences using [redacted]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As part of their base case, the company provided results with unweighted QALYs, which the EAG deemed appropriate. However the company also presented QALY weighted results. The EAG had concerns about the appropriateness of applying QALY weighting, and considered that the NICE committee should determine whether the application of QALY weighting was appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use and costs were largely based on NHS reference costs (2019/20), as appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs were discounted at 3.5% and benefits were discounted at 1.5%. The EAG noted that a differential discount rate is not standard practice.

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal; TTO, time-trade-off

4.2.2. Model structure

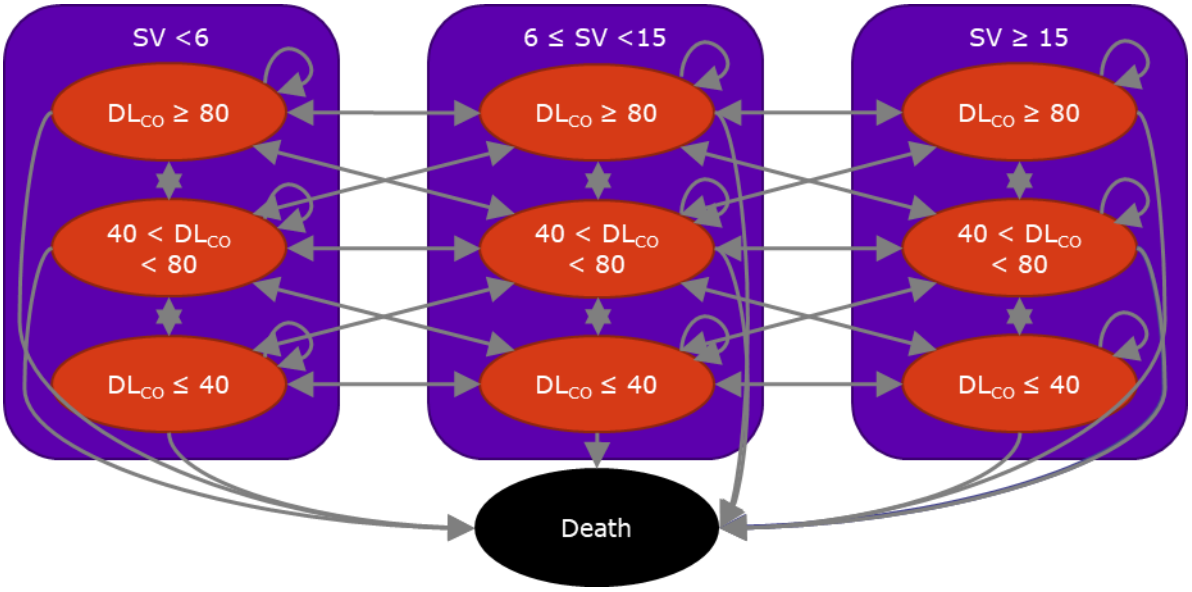
The company presented a cohort-based Markov model whereby patients moved through a series of health states associated with specific costs and utilities. The company defined health states via a combination of patients' spleen volume (splenomegaly) and lung capacity to diffuse carbon monoxide (DLco). The EAG noted that due to the combined nature of the health states, disease severity health states cannot be categorised explicitly according to mild, moderate or severe. However, when considered individually, the model implicitly assumes three levels of spleen volume severity, for example SV <6 MN could be considered mild, SV 6-15 MN as moderate and ≥15 MN as severe. Similarly, the model assumed there to be three levels of

DLco, defined as mild reduction (≥ 80%), moderate reduction (40-80%) and severe reduction (≤40%).

Defining health states via a combination of patients' spleen volume and DLco resulted in nine modelled health states (see Figure 3 below). Patients entered the model according to their baseline distribution in the ASCEND or ASCEND-Peds studies (see Table 19 below). The same model structure was used to model both the adult and paediatric cohort. As outlined in Figure 3, patients could remain in each health state, could improve (i.e. experience a reduced spleen volume and/or increased DLco), or could get worse (i.e. experience an increase in spleen volume and/or decreased DLco). Death could occur in any health state.

The clinical data used to derive transition probabilities in the model were derived from four clinical studies, and was further guided by company assumptions. These are discussed further in Section 4.2.6.

Figure 3: Model structure



On p.165 of the CS, the company stated that spleen volume (splenomegaly) and the lung's capacity to diffuse carbon monoxide (DLco) were selected to inform model health states "*as they are important predictors of disease progression, with a severe impact on the level of disability and QoL of patients, and thus are the primary efficacy endpoints from the ASCEND trial".* The company further stated that the model structure was validated by UK clinical experts with experience in treating ASMD. The EAG noted the lack of cost effectiveness models for ASMD and therefore sought clinical opinion to determine the appropriateness of the model

structure and whether splenomegaly and lung function should be used to inform modelled health states. Clinical opinion to the EAG was somewhat mixed, however, on balance experts considered that both spleen volume and DLco may be reasonable markers of overall disease severity. Impairment in liver functioning was also suggested as a potential indicator of general patient health, though it was noted that liver functioning may also be affected by other conditions, and that impairment in liver function due to ASMD was likely to coincide with spleen enlargement. The EAG noted that two published papers by Jones et al (2020) and Eskes et al (2020), which reviewed prognostic markers of mortality, reported that both spleen volume and DLco were predictors of long term health outcomes.

Overall the EAG considered that the company's approach of defining health states according to spleen volume and DLco was likely to be appropriate, however, the lack of absolute consensus amongst clinicians shold be noted.

4.2.3. Population

Modelled baseline characteristics for paediatric and adult patients are outlined in Table 18, and the distribution of patients across modelled health states is outlined in Table 19. These data were derived from the pivotal studies ASCEND and ASCEND-Peds. The EAG noted that weight for both adults and children was low relative to the general population. Clinical experts to the EAG were unable to clarify the anticipated weight of the target population, though suggested that some children with ASMD types B and A/B may exhibit a lower weight than the general population. However, this would not be expected to be the case in children treated successfully for their condition. Clinical experts were unable to comment on whether adult weight varied from the general population mean, and if so, how this would change with effective treatment.

Table 18: Patient baseline characteristics

	ASCEND-Peds (paediatrics)	**ASCEND (adults)**
Starting age	8 years	34 years
Weight	20.53 kg	64.52 kg

Abbreviations: kg, kilogram

Table 19: **Baseline distribution of patients in the model**

Health state	ASCEND-Peds (paediatrics)	ASCEND (adults)
DL_{CO} ≥80%	0%	0%
DL_{CO} 40 – 80%	88.9%	80.6%
DL_{CO} ≤40%	11.1%	19.4%
Spleen volume <6 MN	0%	0%
Spleen volume 6–15 MN	40%	77.8%
Spleen volume ≥15 MN	60%	22.2%

Abbreviations: DLco, diffusing capacity for carbon monoxide; MN, multiples of normal

Based on one-way sensitivity analysis provided by the company, results were highly sensitive to variation in patient weight and moderately sensitive to patients' starting age (see p.220 and p.221 of the CS). The EAG noted that for adult patients, weight was assumed to be constant over the time horizon. For paediatric patients, the company derived the z-score function based on data from the SPHINGO-100 trial (for children at 8 years; see p.168 in the CS). The EAG considered there to be uncertainty surrounding the company's approach to modelling patient weight in both populations:

- The company used a z-score function to estimate the change in paediatric weight over time (see p.168 and p.169 of the CS). The z-score function (which estimates the change in paediatric weight over time) was applied to weight from UK growth charts. The EAG noted that weights from the growth chart appeared low compared to patient weight data from Health Survey for England (2019).[4] In order to explore uncertainty in patient weight, the EAG conducted a scenario analysis that used patient weight from Health Survey for England. See Section 6.2 for results.

- The patient weight for adults appeared somewhat low relative to mean UK weight and the mean weight estimated by the company for the paediatric equation at 18 years (62kg). Clinical opinion to the EAG was that adults with ASMD types B and A/B were likely to have lower weight compared to the general population mean in the UK. In order to explore uncertainty surrounding modelled adult patient weight, the EAG conducted two scenario analyses. These are discussed further in Section 6.2.

In terms of starting age of patients in the model, clinical opinion to the EAG was that age of diagnosis varied widely across the population. For example, diagnosis will occur earlier in those with more severe disease and in those where there is familial history. Clinical advice to the EAG suggested that diagnosis may commonly occur between two- and six-years of age, though those with mild symptoms may be diagnosed in adulthood. Consistent with heterogeneity in the severity of ASMD across the population, the range in age of diagnosis in the clinical trials was broad, ranging from 0.02 to 11.09 years for children and 1.0 to 58 years for adults. Clinical experts confirmed that typical age of diagnosis for children varies, with experts suggesting average ages ranging between two- to six-years. Clinical experts were unable to determine a representative starting age for adults in clinical practice because of heterogeneity in the population. One expert further noted that diagnosis of those with milder symptoms may occur earlier if a treatment for ASMD became available. In order to explore uncertainty surrounding starting age, the EAG has conducted scenario analyses which reduces the starting age to two-years (in the paediatric population) and 28-years (in the adult population). Section 6.2 for further discussion.

4.2.3.1. Severe patient subgroup

The company provided results for a severe population subgroup (see Section 5.2), though did not provide a rationale for conducting the analysis. In response to clarification question B.3, the company stated that "*patients with severe disease have the poorest prognosis and are likely to benefit most from treatment with olipudase alfa. They would therefore be expected to have differential cost-effectiveness."* The EAG noted that subgroup analyses were conducted for a small number of outcomes in ASCEND, showing no clear difference in effect according to baseline severity. However, it should be noted that the sample size in ASCEND was small and a limited range of outcomes were assessed. Outcomes that may be less amenable to change due to pre-existing damage may not have been included.

The company's approach to modelling the severe population differed to the base case analysis in several respects. For this analysis, 100% of patients were assumed to start in the most severe subgroup SV≥15 MN and DLco<40%. The starting age of paediatric patients was assumed to be two-years (as opposed to eight in the company's base case). The EAG accepted this approach on the basis that those with more severe disease are likely to manifest symptoms earlier and therefore be more likely to receive a diagnosis at a younger age. The company also opted to model mortality using data from McGovern et al (2013), [5] whereby the company

estimated survival by treatment via a parametric extrapolation using a Weibull distribution. The EAG noted several concerns surrounding the subgroup analysis:

- The clinical effectiveness data used to inform transitions were not derived from patients with severe ASMD. Instead, the company assumed that 100% of patients began in the severe health state and applied transition probabilities from the overall population. Based on clinical opinion to the EAG, this assumption did not appear to be appropriate, see Section 4.2.7
- The company used an alternative published literature source to estimate mortality for severe patients (McGovern et al, [5] see Section 4.2.8 for further description). The EAG considered there to be a lack of transparency in the company's approach to estimating survival. For both the severe adult and paediatric populations, the company did not justify use of a Weibull distribution to the mortality data, AIC/BIC statistics were not presented, and no attempt was made to discuss visual fit of alternative functions.
- Limited sensitivity analyses were conducted i.e. the company tested uncertainty via probabilistic sensitivity analysis (PSA), however no scenario analysis or one-way sensitivity analysis (OWSA) was presented in the CS for this subgroup.

Overall, the EAG considered there to be significant uncertainty surrounding the severe population subgroup and considered that results should be interpreted with caution.

4.2.4. Interventions and comparators

There were no alternative curative treatments for ASMD in the UK. The company therefore compared olipudase alfa (plus BSC) to best supportive care (BSC). Within the economic model, BSC consisted of routine care including healthcare professional visits, monitoring and laboratory tests, medications, vaccinations and organ transplants (lung and liver). Clinical opinion to the EAG confirmed that BSC as outlined by the company was the appropriate comparator. The intervention, olipudase alfa, is administered as an IV infusion at a recommended maintenance dose of 3mg/kg every 2 weeks. Clinical advice to the EAG was that treatment would likely be administered in hospital initially, but that after a period of time some people may prefer to be treated at home. See Section 4.2.10 regarding assumptions with respect to treatment dosing and administration.

4.2.5. Perspective, time horizon and discounting

The economic analysis was conducted from an NHS and PSS perspective as consistent with the NICE reference case. The time horizon used in the economic analysis was 100-years for both adult and paediatric populations. The EAG considered this to be reasonable and sufficiently long enough to capture the differences in costs and effects between treatment arms. The cycle length used in the analysis was six-monthly (for the first year) and then yearly thereafter. The company stated that this is broadly reflective of monitoring in UK clinical practice. Based on clinical input to the EAG, there was some variability with respect to monitoring, however using a yearly cycle length was considered to be broadly appropriate.

The EAG noted that non-reference case (differential) discounting was used in the company's base case: costs were discounted at 3.5% and benefits were discounted at 1.5%. The company justified this approach on the basis that it reflected HM Treasury Green Book advice.[31] Whilst the EAG acknowledged the advice in the HM Treasury Green Book, differential discounting was nevertheless inconsistent with the NICE process and methods manual (2022),[32] as per the NICE reference case. Differential discount rates typically improve the cost effectiveness of most medical interventions, particularly treatments with high upfront costs or delayed benefits. Differential discounting could therefore potentially allow for the higher pricing of treatments, thus increasing NHS costs. As outlined in a 2020 report by the Centre for Health Technology and Evaluation (CHTE), this methodology remains an area of academic debate.

The company provided a scenario analysis where both costs and benefits were discounted at 1.5%, resulting in an increased ICER in both paediatric and adult populations (see Section 5.3.3). The NICE process and methods manual (2022) specified that the reference case may be supplemented with alternative analyses to apply a discount rate of 1.5% to both costs and benefits if all of the following criteria are met:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

On p.10 of the 2017 NICE interim process and methods guidance for HSTs[33] it is stated that *"a discount rate of 1.5% for costs and benefits may be considered by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are*

likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs".

The EAG did not consider the use of a 1.5% discount rate to be appropriate given the lack of robust long term data supporting the impact of olipudase alfa on patient morbidity and mortality (see Section 4.2.6 and 4.2.8). The EAG preference was therefore for a 3.5% discount rate to be used for costs and benefits.

4.2.6. Treatment effectiveness and extrapolation

The clinical data used to derive treatment probabilities for adult and paediatric patients in the olipudase alfa and BSC arms were derived from trials of olipudase alfa (ASCEND[10,16], ASCEND-Peds[11,34], LTS13632[14] and DF131412[13]) and from an observational study of outcomes in people with ASMD (SPHINGO-100)[35].

For paediatric patients, olipudase alfa transition probabilities in the first year were calculated based on ASCEND-Peds trial data. For BSC, these were estimated based on the paediatric patients in the SPHINGO-100 study. For subsequent years, olipudase alfa transition probabilites were estimated by combining data from ASCEND-Peds and LTS13632. For subsequent year BSC transitions, data from SPHINGO-100 was used.

For adult patients in year one, transition probabilities for olipudase alfa were estimated by combining data from ASCEND and DF131412, whereas for BSC, ASCEND and SPHINGO-100 were used. For subsequent years, olipudase alfa transition probabilites were estimated by combining data from ASCEND and LTS13632, and BSC transitions were estimated from SPHINGO-100. Olipudase alfa transition probabilies used in the model are presented in Table 20 and Table 21 (see p.172 and p.173 of the CS for BSC transitions).

Table 20: Olipudase alfa transition probabilities for spleen volume

Start state		End state		
		<6 MN	**6–15 MN**	**≥15 MN**
0–6 months				
Children	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	26.2%	73.8%	0.0%
	≥15 MN	7.9%	43.6%	48.5%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	36.2%	63.9%	0.0%

	≥15 MN	21.3%	64.5%	14.2%
6–12 months				
Children	<6 MN	97.6%	2.4%	0.0%
	6–15 MN	11.3%	88.7%	0.0%
	≥15 MN	4.3%	59.3%	36.5%
Adult	<6 MN	97.5%	2.5%	0.0%
	6–15 MN	12.5%	87.5%	0.0%
	≥15 MN	3.5%	45.2%	51.3%
Year 2+				
Children	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	100.0%	0.0%	0.0%
	≥15 MN	100.0%	0.0%	0.0%
Adult	<6 MN	100.0%	0.0%	0.0%
	6–15 MN	100.0%	0.0%	0.0%
	≥15 MN	100.0%	0.0%	0.0%

Abbreviations: MN, multiples of normal; SV, spleen volume.
Source: Company submission (p.160 and p.161)

Table 21: Olipudase alfa transition probabilities for DLco

Start state		End state		
		≥80%	**40–80%**	**≤40%**
0–6 months				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	0.0%	100.0%	0.0%
	≤40%	0.0%	0.0%	100.0%
6–12 months				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	24.7%	75.3%	0.0%
	≤40%	0.0%	0.0%	100.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	6.3%	93.7%	0.0%
	≤40%	2.9%	72.0%	25.1%

Year 2+				
Children	≥80%	100.0%	0.0%	0.0%
	40–80%	100.0%	0.0%	0.0%
	≤40%	100.0%	0.0%	0.0%
Adult	≥80%	100.0%	0.0%	0.0%
	40–80%	100.0%	0.0%	0.0%
	≤40%	100.0%	0.0%	0.0%

Abbreviations: DL_{CO}, diffusing capacity for carbon monoxide.
Source: Company submission (p.160 and p.161)

4.2.7. Long term extrapolation of treatment effectiveness

In the company's base case analysis, 100% of patients who receive olipudase alfa are assumed to transition to the least severe health state (SV<6MN and DLco≥80% health states) from year two and remain there for the duration of the modelled time horizon (subject to mortality). In contrast, patients in the BSC arm are assumed to transition in every cycle until the end of the time horizon or death. The company did not provide justification for this assumption in the CS. Based on clinical expert opinion to the EAG, the long-term efficacy assumption for olipudase alfa may be plausible. Stable, long-term efficacy has been shown for enzyme-replacement therapy (ERT) in gaucher disease, which is another lysosomal storage disorder. Not all ERTs have shown long-term efficacy, though clinicians advising the EAG were hopeful that olipudase alfa may be as effective as for gaucher disease. However, two clinical advisers suggested that there may be a reduced effect (some treatment waning) in severe patients due to antibody resistance.

The EAG considered it to be plausible that olipudase alfa may have long-term benefit for the target population, though due to the lack of long-term treatment effectiveness data and the potential for the assumption to overestimate the incremental QALY gain associated with olipudase alfa, there was a high degree of uncertainty surrounding this assumption. The EAG conducted three scenario analyses using alternative long-term efficacy assumptions for olipudase alfa (see Section 6.2.1). As part of the EAG preferred base case, it was assumed that transition probabilities for patients receiving olipudase alfa would be frozen at two-years.

4.2.8. Mortality

Mortality was modelled via standardised mortality ratios (SMRs) using clinical data from the SPHINGO-100 study, [3] the prospective longitudinal study which collected disease related morbidity and mortality data over an 11-year period. The company estimated mortality according

to the presence or absence of severe splenomegaly: for patients without severe splenomegaly, the SMR was estimated to be 4.3, whilst for those with severe splenomegaly the SMR was 43.1 (i.e. patients with severe splenomegaly have a death rate 10 times higher than those without severe splenomegaly). These SMRs were estimated by comparing the observed mortality in the SPHINGO-100 study, with the expected mortality of the general US population (using US life tables). In order to calculate adjusted survival probabilities in the model, the SMR was applied to the mortality rates of the general UK population, as a multiplier.

The EAG noted several issues with the company's approach to modelling mortality, including the following:

- The EAG queried the company's decision to use splenomegaly as the key determinant of mortality (given ASMD impacts multiple organs including liver and lung function) during clarification. In response to question B.11, the company stated that "*all available clinical parameters were tested as potential predictors of survival, defined as the time from the date of birth to the date of last visit or death. The only parameter that presented a statistically significantly association with survival was severe splenomegaly as defined using the published threshold of 15 multiples of normal".* Clinical advice to the EAG about the validity of this approach was somewhat mixed, however on balance splenomegaly appeared to be a reasonable proxy/beacon of disease severity. While an enlarged spleen may not be a common cause of death, there is a positive correlation between an enlarged spleen and disease severity (including lung and liver involvement). Furthermore, the EAG noted two recently published papers, which examined prognostic markers for mortality, identified splenomegaly as a predictor of survival; Jones et al (2020) [36] and Eskes et al (2020). [37]

- Clinical opinion to the EAG suggested that there was uncertainty surrounding the company's assumption that paediatric patients die from ASMD. Two clinicians treating paediatric patients were unable to recall any deaths amongst children with ASMD types B or A/B in their care.

- The EAG noted that data from SPHINGO-100 were derived from a small sample (n=58) with correspondingly low event rates (e.g. deaths n=9), which may lead to unreliable estimates of risk. Three deaths occurred in the paediatric population, which represented 33.3% of deaths within the study. The primary cause of death for all three deaths was pneumonia. To validate these data, the EAG sought to identify additional mortality data from the international Niemann-Pick Disease Alliance (INPDA), who manage a data registry

including people with ASMD types B and A/B. These data were not available during the timeframe of the EAG appraisal, though the evidence may become available to the EAG and/or NICE committee at a later stage during this appraisal.

Overall, the EAG considered there to be some uncertainty surrounding the mortality data used in the company's base case and considered that the incremental life-years gained reported for olipudase alfa should be interpreted with caution. In order to test the impact of mortality on the base case ICER, the EAG conducted a scenario analysis in which the SMR for severe splenomegaly was reduced by 50%. Results were not sensitive to this change (see Section 6.2). Furthermore, on the basis of clinical opinion, a scenario analysis was conducted in which disease-related mortality in the paediatric population was removed i.e. only backgroud mortality was considered (until the patient reached adulthood). This analysis was included as part of the EAG preferred base case (see Section 6.2 and 6.3).

As part of a scenario analysis (and for the subgroup analysis in the severe population), the company used an alternative mortality data source, a published study by McGoven et al (2013).[5] This natural history study, which included 103 patients with ASMD type B, assessed morbidity and mortality. At entry, 61 participants were considered paediatric (≤21 years) and 42 were adults. Eighteen patients died during the study, of whom 12/18 (67%) were children and 6/18 (33%) were adults, leading to a mortality rate of 19% and 14%, respectively.

The EAG identified the following concerns surrounding the use of McGovern et al. as a source of alternative mortality data, and in the company's modelling approach in general:

- A significant minority of the deaths reported in the trial were due to complications following treatment (bone marrow and stem cell transplants, 25%) rather than due to the disease itself. The EAG noted that these may not reflect routine operational procedures for people with ASMD types B and A/B within the NHS.The McGovern study was also reasonably dated (conducted from 1992-2012), and the EAG queried whether care will have changed substantially since that time so that health outcomes are no longer generalisable. There were differing views amongst clinical experts as to whether care and health outcomes had changed substantially in the past ten- or twenty-years.

- The study did not report whether participants had 'severe disease', and did not categorise participants according to spleen volume or lung function (as per the company's base case approach). In the paper the authors stated that the mortality data suggested that there were

two cohorts: those with more severe disease who have a higher mortality rate during childhood and those with milder disease who are more likely to survive into adulthood. The EAG noted that this assumption introduced uncertainty given that data were not derived from a population with confirmed severe status based on important prognostic factors like spleen volume and DLco.

- The EAG considered there to be a lack of transparency surrouding the company's approach to extrapolating overall surivival data. The company stated that a Weibull parametric function was used, however no rational or supporting evidence was provided for selecting the Weibull i.e. curve selection did not appear to be validated using clinical opinion, AIC/BIC statistics or visual inspection. The EAG considered this to introduce considerable uncertainty into the analysis, as it was a veritable 'black box'.

For the reasons outlined above, the EAG considered the mortality estimates from McGovern et al. to be subject to uncertainty and may overestimate mortality, particulalry in the paediatric cohort.

4.2.9. Health-related quality of life

There was a lack of published HRQoL data for people with ASMD types B and A/B. The company collected HRQoL data directly from participants in the ASCEND and ASCEND-Peds trials. The company stated that HRQoL in the ASCEND trial was assessed after 52-weeks of olipudase alfa treatment, using the EQ-5D-5L and SF-36 generic preference-based measures. The company also presented data for a disease-specific measure named the NPB-HAQ, which reportedly assessed fatigue, pain, respiratory, abdominal complaints and quality of life (as well as questions specific to ASMD symptoms and physical activity). HRQoL-specific data from the NPB-HAQ were not included in the company's model. No citation for the NPB-HAQ was provided by the company (and the EAG were unable to locate one), therefore the EAG were unclear whether this measure had been appropriately developed and validated before use in the trial. The company stated that the primary instruments (EQ-5D-5L or SF-36) lacked sensitivity to change in adults with ASMD, noting that there was no statistically significant difference in HRQoL following treatment with olipudase alfa despite change in disease severity markers. As noted on p.177 of the CS, the company stated that neither instrument (EQ-5D-5L or SF-36) assessed the "*important aspects*" of ASMD, such as spleen volume and pulmonary function, and further noted that the utilities derived from both instruments produced counterintuitive results e.g. baseline utilities from both instruments were lowest for the least severe health

states. The company suggested that one potential reason for counterintuitive results was that the small sample size may not be sufficiently large enough to reflect the different health states within ASMD, or because patients may adjust to their condition over time. Overall, the EAG considered that the company's decision to not use HRQoL data for adults from the ASCEND trial in the economic analysis trial may be appropriate given the short follow up in the trial (which the EAG considered partly explained the counterintuitive HRQoL results). Using the trial results within the model was likely to have introduced further uncertainty to the analysis.

In the ASCEND-Peds trial, treatment with olipudase alfa resulted in a significant improvement in the PedsQL Generic Core Scale and Multidimensional fatigue scale for the majority of subsets at week-52 compared to baseline. However, the company did not use HRQoL data from the trials in their economic model. The company stated that despite the improvement in HRQoL noted in the ASCEND-Peds trial, they nevertheless considered that generic HRQoL measures were insensitive to change in the population. Furthermore, in their response to clarification (question A26), the company noted that the paediatric trial did not have a comparator arm, thereby preventing the evaluation of the treatment related benefit on HRQoL.

Due to the limitations surrounding the trial HRQoL data, the company conducted a vignette study[38] to generate HRQoL data for the economic model. In the absence of robust trial data (and values in published literature), well-conducted vignette studies are an appropriate means for eliciting health state values and are in line with the NICE manual for process and methods (2022). [32] In this instance, the company's vignette study appeared reasonably well-conducted: the study included a pilot phase (including [redacted] patients) to test the validity of the planned methodology and health states; and adult and child health state descriptions used in the main study were based on discussions with clinicians, patients, carers, and on the basis of data from literature reviews and clinical trials. In order to validate health state descriptions (and how well they match the modelled health states), the EAG sought clinical expert opinion (see Table 22 below for health state descriptions). Based on clinical input to the EAG, the vignette health states were considered to be broadly appropriate and were reflective of the modelled states.

Table 22: Modelled health states (corresponding to vignette states)

Modelled health state	Vignette health states
Spleen volume (1-6): DLco (100-80)	ASMD without impairment
Spleen volume (1-6): DLco (80-40)	ASMD with mild/moderate impairment in DL_{CO}

Spleen volume (6-15): DLco (100-80)	ASMD with mild/moderate spleen and liver volume increase
Spleen volume (6-15): DLco (80-40)	Mild/moderate ASMD
Spleen volume (>15): DLco (100-80)	ASMD without DL_{CO} impairment with severe spleen and liver volume increase
Spleen volume (1-6): DLco (<40)	ASMD with severe DL_{CO} impairment and without spleen and liver volume increase
Spleen volume (>15): DLco (80-40)	ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase
Spleen volume (6-15): DLco (<40)	ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase
Spleen volume (>15): DLco (<40)	Severe ASMD

The main study[38] included [redacted] participants and interviews were conducted in-person. The [redacted] was used to elicit health state utilities The EAG noted several benefits of using the vignette study rather than using HRQoL data from the trials:

- the study included [redacted] only
- the relatively large number of respondents may be likely to produce more robust estimates (versus the small number of patients included in the trials).
- eliciting values from the [redacted]

Health state utility values used in the model are outlined in Table 23. Given the lack of published utility values for ASMD, the EAG sought clinical expert opinion on the face validity of these values. Based on clinical opinion to the EAG, values for both populations appeared to make logical sense (decreasing with disease severity) and could be considered broadly reasonable. However, one of the EAG's clinical experts who had experience with paediatric patients stated that utility values for people with Gaucher disease (a lysosomal storage disorder that has similarities with ASMD types B and A/B) were lower. The EAG attempted to identify utility values for Gaucher disease used in the NICE HST appraisal of eliglustat (HST5 for treatment of type 1 Gaucher disease), but these were redacted and could not be provided by NICE. Therefore, it was not possible to cross-validate values using this appraisal.

Table 23: Health state utilities (derived from the vignette study)

Health state	Adults	Children
A1: ASMD without impairment	[redacted]	[redacted]
A2: ASMD with mild/moderate impairment in DL_{CO}	[redacted]	[redacted]
A3: ASMD with mild/moderate spleen and liver volume increase	[redacted]	[redacted]
A4: Mild/moderate ASMD	[redacted]	[redacted]
A5: ASMD without DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]
A6: ASMD with severe DL_{CO} impairment and without spleen and liver volume increase	[redacted]	[redacted]
A7: ASMD with mild/moderate DL_{CO} impairment with severe spleen and liver volume increase	[redacted]	[redacted]
A8: ASMD with severe DL_{CO} impairment with mild/moderate spleen and liver volume increase	[redacted]	[redacted]
A9: Severe ASMD	[redacted]	[redacted]

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

4.2.9.1. Carer disutility and disutility associated with death

The model included carer disutility for health states in the BSC arm only. On p.180 of the CS, the company stated that this treatment-specific approach to carer disutility was justified *"given the treatment-mediated impact on patients' symptoms and manifestations, and the potential reduction in caregiver burden this brings".* For each health state, a disutility of -0.150 was applied. The carer disutility chosen by the company was based on a published study by Simon et al., [1] which estimated health utilities and parental quality of life for three rare conditions in new-borns (Krabbe disease, Pompe disease and Pheylketonuria). Specifically, the company opted to use the parental disutility for Pompe disease (non-ventilator dependent infants) stating that Pompe disease and ASMD share similarities including respiratory issues, reduced growth and fatigue. Furthermore, the company made two key assumptions with respect to carer disutility: the implementation of a carer disutility associated with patient death (assumed to be -0.50); and the number of carers (1.8 for paediatric patients and 1 for adults).

The EAG had several key concerns surrounding the company's approach to estimating carer disutility in the model:

- Clinical opinion to the EAG was that the disease burden of Pompe disease is greater than in ASMD, as most patients with Pompe are immobile and unable to feed, unlike those with ASMD. The EAG therefore considered that the expected burden on these families and carers would be considerably higher and that the disutility selected by the company appeared to overestimate the impact of ASMD on carer HRQoL.

- The EAG considered the application of carer disutility only to the BSC arm to lack plausibility, given that carer HRQoL will depend on the severity of the patient's disease rather than the treatment received. That is, carers for patients in the severe health state (who are receiving either olipudase alfa or standard of care) will have reduced quality of life. The EAG conducted a scenario analysis whereby carer disutility was applied to all modelled health states regardless of treatment (see Section 6.2). The EAG incorporated this approach into its preferred base case.

- The EAG considered the company's decision to apply a single disutility to all modelled health states to be a simplifying assumption that was not adequately justified. For example, a carer disutility of -0.15 was applied to all health states including the least severe health state (where a patient has spleen volume of 1-6 MN and DLco 100-80). This implied that carers of patients with mild symptoms will experience a severe disutility of -0.15). Clinical opinion to the EAG was that this assumption did not appear to be appropriate, and that the HRQoL burden for carers was likely to increase with respect to disease severity. It was considered that a more plausible approach would be to use dynamic disutilities, whereby a separate (higher) carer disutility is applied to the most severe state and lower disutilities are applied for mild/moderate health states. The EAG conducted scenario analyses to explore this (see Section 6.2.3).

- In the base case analysis, the company assumed that paediatric patients (patients <18 years) would require 1.78 carers (based on the UK average number of parents per child) [39] and adults would require one carer. The company stated that this assumption was in line with a prior HST appraisal of voretigene neparvovec (HST 11) [2] for treating inherited retinal dystrophies caused by RPE65 gene mutations. Children eligible for treatment with voretigene neparvovec have significant visual impairment and for this appraisal the EAG considered that a school-age child would typically require more than one carer. In the

absence of data, a mean of 1.78 carers using the same source was used.[39] The EAG did not consider that the conditions were sufficiently similar with respect to disease activity, and therefore did not consider it appropriate to assume generalisability with respect to carer burden.

Furthermore, the 'QALY penalty' associated with caring responsibilities can be thought of as comprising two components: (i) the impact of caring duties themselves, and (ii) the emotional burden of caring for a sick child. With respect to (i), the EAG felt that where there are two parents, the caring duties would be divided between both parents rather than doubled: the sum total of carer burden would be the same irrespective of whether there was one or two parents. Clinical advice to the EAG was that an assumption of one carer was likely appropriate with regards to caring responsibilities. With respect to (ii) the EAG accepted that the emotional burden would, of course, fall on both parents. However, it would also affect siblings, extended family and friends. To inform a fair comparison to allocate finite resources across the NHS, the EAG proposed that such impacts be limited to a single carer rather than an arbitrary higher number. On this basis and informed by clinical expert advice, the EAG considered that 1.8 carers per child was likely to be an overestimation and preferred to assume one carer would be standard in its base case.

- The company's model included a carer disutility associated with patient death. The company assumed this to be -0.50 and applied this as a multiplier to the number of deaths in each cycle (which was assumed to continue over the entire modelled time horizon). As a means of justifying this disutility, the company stated that this value had been used in published cancer models, referring to a study by Hornberger et al. (2012).[40] Upon review the EAG noted that this study (which was a cost effectiveness analysis of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia) applied a carer utility decrement of 0.60 if the patient died and assumed a one-year bereavement period). This carer disutility assumption was notably different to that used by the company within this appraisal, whereby the disutility value of -0.50 was applied throughout the modelled time horizon. For the paediatric population, this assumption contributed to a total loss of [redacted] QALYs in the olipudase alfa arm, and [redacted] QALYs in the BSC arm. For the adult population, this assumption contributed to a total loss of [redacted] QALYs in the olipudase alfa arm and a total loss of [redacted] QALYs in the BSC arm. The EAG also noted that within Hornberger et al., it was not clear how carer

decrements were calculated as no information was provided regarding carer disutility elicitation methods.

Sources (published literature and HTA assessments) have explored the impact of including carer disutility associated with patient death, including a published study (Song et al.)[41] and NICE TA588 (Nusinersen for treating spinal muscular atrophy, where a disutility of -0.04 was applied). However, the inclusion of carer disutility associated with patient death was not an approach recommended by NICE at the time. Ultimately, the EAG considered it to be a highly speculative assumption that potentially biased the analysis in favour of olipudase alfa (given the higher mortality rate in the BSC arm in the model). The EAG conducted a scenario analysis that removed carer disutility associated with death. This scenario analysis was incorporated into the EAG base case (See Section 6.2 and 6.3 for results).

Overall, the EAG considered the company's approach to modelling carer disutility included numerous inappropriate assumptions. Based on the scenario analyses conducted by the EAG, carer disutility was considered to be a key driver of results (see Section 6.2).

4.2.9.2. Disutility associated with complications and adverse events

The model included disutilities associated with common complications of ASMD B and A/B, shown in Table 24. Complications were modelled as one-off events (assigned at the start of the event). The company noted that this is likely to be a conservative assumption, given that ASMD complications are likely to have lasting long-term effects. The duration of adverse events was assumed to be one-year for all complications, apart from hospitalised pneumonia.

Due to the paucity of utility data with respect to ASMD-related complications, modelled values were derived from numerous published literature sources (UK and non-UK):

- respiratory complications: disutility was derived from a study in pneumococcal disease (disutility is reflective of having hospitalised pneumonia)[42]
- liver disease complications: disutility was assumed to reflect decompensated cirrhosis in hepatitis C[43]
- Spleen complications: disutility was assumed to reflect splenectomy in patients with immune thrombocytopenic purpura[44]

- cardiovascular disease complications: disutility was assumed to reflect angina in patients with diabetes-related chronic conditions[45]
- major bleeding: disutility was assumed to reflect thrombocytopenia in patients with immune thrombocytopenic purpura in the UK.[46] The company stated that thrombocytopenia was chosen as the closest proxy, as bleeding in patients with ASMD is also related to thrombocytopenia, as a result of splenomegaly

The EAG considered that the use of disutility data from diseases the company considered 'analogous' to ASMD introduced uncertainty as it was unclear whether these disease complications could be considered sufficiently similar to ASMD. However, in the absence of robust ASMD data, the approach of using proxy values to capture the impact of complications on patient HRQoL was reasonable. The company tested disutility associated with complications via one-way sensitivity analysis (varying parameters by +/- 20%), however results were not sensitive to this. The EAG did not consider disutility associated with complications to be a key driver of incremental results.

Table 24: Disutility associated with complications

Complication	Utility decrement	Source
Respiratory	-0.034	Galante et al (2011)[42]
Liver disease	-0.237	McLernon et al (2008)[43]
Spleen	-0.080	Snyder et al (2008)[44]
Cardiovascular disease	-0.230	Sullivan et al (2016)[45]
Major bleeding	-0.129	Szende et al (2010)[46]

Finally, the company did not include disutilities due to adverse events in the base case and justified this on the basis that these events were not assumed to have a long-term impact on patients' quality of life. The EAG considered that the approach was not consistent with the company's approach to modelling costs, whereby adverse event costs associated with olipudase alfa were included in the model. However, due to short duration of treatment-emergent adverse events, it was considered that including adverse event disutility was likely to have a minimal impact on the results.

4.2.10. Resources and costs

4.2.10.1. Drug costs

The model included drug acquisition costs for olipudase alfa. The list price for a 20mg vial was stated to be [redacted]. A patient access scheme (PAS) discount for olipudase alfa that reduced the list price by [redacted] was agreed with NHS England and included in the company analyses. Including the PAS discount, the price per 20mg vial of olipudase alfa was [redacted]. There were no active treatment costs applied to the BSC arm in the model, which was considered reasonable given that no active comparator to olipudase alfa was available and background care interventions would be received by participants in both arms.

Olipudase alfa is administered via IV infusion every two-weeks. For both adult and paediatric patients, the model estimated drug costs for two periods, a dose escalation period and a maintenance period. On p.163 of the CS (Document B), the company reported that the dosing corresponds to the ASCEND and ASCEND-Peds trials (see Table 25). The EAG noted that there was an error in the company's estimation of paediatric dosing in the model i.e. the company overestimated the mg/kg for weeks 6, 10, 12 and 14. The EAG amended this error, however this did not have a material impact on the ICER (see Section 6.1). Once patients entered the maintenance period, it was assumed that they receive 3mg/kg for the duration of treatment (which is considered the highest tolerated dose). The EAG noted that the proportion of patients achieving the highest tolerated dose was derived from the ASCEND and ASCEND-Peds trials for the adult and paediatric populations, respectively i.e. 94.40% of adults and 100% of paediatric patients achieved the highest tolerated dose.

Table 25: Dosing used in the model

Dose	Adults (≥18 years old)	Paediatrics (0 to < 18 years old)
First dose (Day 1/Week 0)	0.1 mg/kg	0.03 mg/kg
Second dose (Week 2)	0.3 mg/kg	0.1 mg/kg
Third dose (Week 4)	0.3 mg/kg	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg	0.3 mg/kg
Fifth dose (Week 8)	0.6 mg/kg	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg	0.6 mg/kg
Seventh dose (Week 12)	2 mg/kg	1 mg/kg

Eighth dose (Week 14)	3 mg/kg (recommended maintenance dose)	2 mg/kg
Ninth dose (Week 16)	-	3 mg/kg (recommended maintenance dose)

For both the paediatric and adult populations, annual drug acquisition costs for olipudase alfa were calculated based on the estimated total annual dose and compliance rate (see Table 59 on p.185 of the CS, Document B). The compliance rate used in the analysis was 90% for both populations, based on data from ASCEND and ASCEND-Peds. Based on clinical opinion to the EAG, 90% may represent a reasonable minimum compliance rate as, like other ERTs, olipudase alfa may ultimately be administered at home by a clinician and missed doses may be uncommon. As an exploratory analysis, the EAG conducted a scenario analysis that increased the compliance rate to 100%. See Section 6.2 for further details and results.

The EAG also noted that the model did not assume the occurrence of drug wastage. Based on the company's response to clarification question A11, ERT doses are routinely rounded to the nearest vial to avoid wastage. For example, if weight is halfway between two vials, clinicians would round down the dose one week and round up the dose the following week in order to avoid wastage. Based on clinical opinion to the EAG, this assumption was considered to be reasonable.

4.2.10.2. Administration and monitoring

The company included administration costs associated with infusion of olipudase alfa for the dose escalation phase and the maintenance phase. In the dose escalation phase, the annual cost was calculated from the biweekly cost of dose escalation consisting of a physician visit and any monitoring (until the highest tolerated dose is achieved). The cost was estimated to be £135 per visit, which appeared to reflect the hourly administration cost for a hospital outpatient clinic setting.

For the maintenance phase, administration costs were based on the mean duration of infusion, which was estimated to be 220 minutes or 3.66 hours (see Table 62 on p.187 of the CS Document B). Clinical expert opinion to the EAG confirmed that the estimated time to administer treatment appeared reasonable. Once on maintenance treatment, 100% of adult and paediatric patients were assumed to have treatment administered at home with a nurse. The hourly cost

for nurse administration was estimated to be £44 and unit costs were derived from Personal Social Services Research Unit (PSSRU) 2020 costs as appropriate.

Annual costs for administering olipudase alfa are shown in Table 26. Administration costs were not considered to be a key driver of the ICER, accounting for just [redacted] of total costs in the olipudase alfa arm.

Table 26: Olipudase alfa annual cost of administration

	Annual cost
Children	
Year 1 (escalation and maintenance)	£3,561.90
Subsequent years (maintenance)	£3,788.16
Adults	
Year 1 (escalation and maintenance)	£3,567.87
Subsequent years (maintenance)	£3,788.16

4.2.10.3. Health state costs

Costs associated with the medical management of ASMD were included in the model, representing health state costs. These applied to both the olipudase alfa and BSC (see Tables 64 to 66 on p.189 to p.192 of the CS). Annual frequencies were derived from a retrospective cohort analysis using IQVIA open claims for patients with confirmed and potential (high probability) ASMD type B. Unit costs were based on 2019/20 NHS reference costs. [47]

The EAG noted that using a retrospective 'activity based costing' approach introduced some uncertainty, and that using a time driven activity-based costing approach (TDABC) or a fuzzy logic (FL) TDABC approach within prospective trials would lead to more accurate resource use estimates, accounting for variation in time. However, this may be considered to be a conservative approach to resource use estimation, as there was assumed to be no difference in healthcare resource use between treatment arms in healthcare visits, laboratory tests, monitoring, medication and vaccine use etc. Clinical opinion to the EAG was that patients on olipudase alfa arm would likely have reduced healthcare resource use in practice, due to the efficacy of treatment.

4.2.10.4. Adverse event and complication costs

The annual costs of treating serious treatment-emergent adverse events were included in the model for the olipudase alfa arm only (see Table 67, p.193 of the CS). Based on the company's model the annual probability of experiencing serious adverse events for children was estimated to be 8.30% in all years, based on incidence data from ASCEND-peds and the long-term extension study LTS13632. This accounted for events such as alanine aminotransferase increase, rash, anaphylactic reaction, urticaria and hypersensitivity, and resulted in an annual cost of £25.66 for olipudase alfa. For adults, the annual probability of experiencing serious adverse events was estimated to be 1.02% in all years, based on the occurrence of serious extrasystoles from ASCEND PAP and ETP. This resulted in an annual cost of £10.51 for olipudase alfa. Unit costs were derived from NHS reference costs 2019/20, as appropriate. Overall, modelled treatment emergent adverse event costs were not a key driver of cost effectiveness, as these were minor relative to the large drug cost associated with olipudase alfa.

The model also included complication costs of respiratory, bleeding (as a result of increased spleen volume), liver, spleen and cardiovascular complications. In each modelled health state, the probability of experiencing complications was based on base annual rate data from SPHINGO-302[30] and odds ratios from SPHINGO 100. [3] The EAG noted that the only difference in complication rates between olipudase alfa and BSC was with respect to liver complications. The annual probability of liver complication was estimated to be 0.3% and 3.4% for olipudase alfa and BSC respectively. To explore uncertainty surrounding modelled complication rates, the EAG conducted a scenario analysis that assumed no difference in liver complication rates between treatment arms. Results were not sensitive to this analysis (see Section 6.2).

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1.1. Company base case results

The discounted results reported by the company including the PAS discount for olipudase alfa are shown in Table 27 to Table 29. The incremental QALY gain associated with olipudase alfa in both the paediatric and adult populations was primarily driven by modelled treatment efficacy i.e. a high proportion of patients were assumed to remain in the SV <6 MN, DLCO ≥80% health state and therefore experience lower mortality (increased life-years) and higher utility relative to patients on BSC (see CS Appendix J for disaggregated results). The QALY loss associated with BSC was due primarily to carer QALY loss (see Section 4.2.9.1 for the EAG's critique of the company's approach to modelling carer HRQoL). In terms of incremental costs, these are driven by olipudase alfa drug costs. The company presented results for a mixed population (weighted average of adult and paediatric patients). The EAG did not consider a mixed population to be appropriate for decision making, however for completeness, results are presented in Table 29.

The company provided supplementary base case results using QALY weighting, however no justification was provided for this. In response to clarification question B.12, the company stated that the approach was in line with NICE guidance and that *"olipudase alfa offers significant QALY gains, with discounted QALY gains of 24.95 in paediatric patients and 16.44 in adult patients despite likely conservative assumptions regarding mortality and patient and family/carer utilities".* The EAG noted that based on NICE guidance (Interim Process and Methods of the Highly Specialised Technologies Programme, 2017), [33] in order for QALY weighting to be considered there would need to be compelling evidence that the treatment offered significant QALY gains. As discussed in Sections 4.2.6, 4.2.8 and 4.2.9.1, the EAG highlighted considerable uncertainty surrounding modelled assumptions including long-term treatment efficacy, impact on mortality, and patient and carer utilities. The EAG, therefore did not consider that it was appropriate to apply QALY weighting given the uncertainty surrounding the incremental QALY gain associated with olipudase alfa. However, for completeness, the results incorporating undiscounted QALYs are reported in Appendix B.

Table 27: Company base case results (paediatric population)

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	8.81	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Company probabilistic base case							
Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	8.07	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]

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

Table 28: Company base case results (adult population)

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	7.42	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Company probabilistic base case							
Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	6.24	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]

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

Table 29: Company base case results- Mixed population (paediatrics and adults)

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	8.12	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Company probabilistic base case							
Olipudase alfa	[redacted]	[redacted]	[redacted]	[redacted]	7.16	[redacted]	[redacted]

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]

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

5.2. Subgroup analysis

As discussed in Section 4.2.3.1, the company presented a subgroup analysis in patients with severe disease. The company's results for this subgroup, including the PAS discount for olipudase alfa, are presented in Table 30. As previously noted, these results are considered highly uncertain and should be interpreted with caution.

Table 30: Company base case results (Severe subgroup)

	Incremental costs	Incremental LYs	Incremental QALYs	ICER	ICER (weighted)
Paediatric	[redacted]	[redacted]	47.42	[redacted]	[redacted]
Adult	[redacted]	[redacted]	17.83	[redacted]	[redacted]
Mixed population	[redacted]	[redacted]	32.62	[redacted]	[redacted]

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

5.3. Company's sensitivity analyses

5.3.1. One-way sensitivity analysis (OWSA)

The company conducted OWSA for both adult and paediatric populations that varied certain model parameters by +/- 20% including baseline patient characteristics, drug administration and acquisition costs, maintenance costs, complication costs, compliance rates, treatment related adverse events, routine care costs and utilities. Results were presented via tornado diagrams (see p221 and p.222 in the CS Document B). The EAG noted that although the company provided a separate model for the subgroup population, OWSA results for the severe subgroup were not provided in the CS.

The EAG noted that parameters such as caregiver disutilities, number of caregivers and mortality were omitted from the company's sensitivity analysis. There were also discrepencies in the calcualtion of boundaries of the sensitivity analysis for respiratory complication rate and carer disutility parameters. After resolving the general discrepencies of the model and amending

the company's OWSA, the results were most sensitive to variation in adult patient weight, drug unit costs, compliance, number of caregivers for adults, mortality ratios, starting age, and utilities.

5.3.2. Probabilistic sensitivity analysis

The company conducted probabilistic sensitivity analysis (PSA) for both the paediatric and adult populations. Distributions used for model parameters can be found in Table 73 on p.213 of the CS Document B. As with the company's OWSAs, the EAG noted that parameters such as caregiver disutilities, number of caregivers and mortality had been excluded from the company's PSA. Threre were also discrepencies in the formulas used to caclulate the PSA sample number for carer disutility. After resolving general discrepencies in the model and implementing the EAG PSA corrections, the model was run for 1000 simulations. The results showed that for the paediatric population, olipudase alfa had a [redacted] probability of being cost effective at a willingness to pay of £300,000. For adults, olipudase alfa had a [redacted] probability of being cost effective at a willingness to pay of £300,000. The maximum willingness to pay threshold for HSTs is £100,000. Using this threshold, there is a [redacted] probability of olipudase alfa being cost effective in either adults or children.

5.3.3. Scenario analyses

A limited number of scenario analyses were provided by the company in the CS (see Table 74, p.222 of the CS Document B). For both the paediatric and adult populations, the company conducted the following scenario analyses:

- Discounting costs at 1.5%. When both costs and benefits were discounted at 1.5% the ICER increased i.e. olipudase alfa became less cost effective due to higher total costs (see question B.17 of the company clarification response).

- Alternative mortality assumptions based on a published study by McGovern et al (2013).[5] This analysis resulted in improved cost effectiveness for olipudase alfa i.e. there was a minor downward impact on the ICER for the adult population and a large downward impact on the ICER for the paediatric population (resulting from a large incremental LY and QALY gain). As noted in Section 4.2.8, the EAG considered the company's approach to extrapolating survival using McGovern et al, to be associated with considerable uncertainty.

- Treatment discontinuation in week 80 (at a rate of 5.56%). The company stated that this reflected the participants in the ASCEND trial who discontinued during the extended trial period. This resulted in an increased ICER for olipudase alfa in both adults and children.
- Patient compliance increased to 95%. Increasing compliance to olipudase alfa resulted in increased ICERs in both adults and paediatric patients as a result of higher drug costs (see question B.17 of the company clarification response).

Although the company provided rationale for testing each of the aforementioned scenarios, it was unclear why a limited subset of results were presented to the EAG. The EAG noted that several key drivers of cost effectiveness uncertainty, including treatment effect and HRQoL assumptions (for both patients and carers), were not tested in the company's scenario analyses. Initially, the company only provided scenario analyses results based on a weighted average population (of paediatric and adults), however during clarification the EAG requested that results be provided seperately for each population (see clarification response B.17).

Overall, the EAG did not consider the scenario analyses conducted by the company to be sufficient to address key aspects of modelled uncertainty.

5.4. Model validation and face validity check

On p.229 of the CS (Document B) the company stated that *"the cost-effectiveness model has undergone validation within a UK advisory board conducted in May 2022 by Sanofi. Five clinical experts participated in the advisory board. Any issues identified were considered in the final model and discussed with a clinical expert".* The company also noted that two external health economists quality-assured the model. However, despite the company's review process, the EAG identified errors within the company's model which were then corrected (see Section 6.1 for a complete list).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The EAG identified limitations with the company's base case and therefore explored the impact of using alternative parameter values and assumptions.

Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis.

The scenario analyses presented in Section 6.2 focused on exploring the following issues and uncertainties:

- **The extrapolation of the olipudase alfa treatment effect**. The company assumed that 100% of patients who receive olipudase alfa transition to the SV <6MN and DLco ≥80% health states from year 2 onwards i.e. all patients move into the least severe health state and remain there for the duration of the modelled time horizon (subject to mortality). The EAG explored alternative long-term effectiveness assumptions for olipudase alfa (discussed in Section 4.2.6).
- **Mortality in paediatric patients**. The company assumed that paediatric patients die due to ASMD-related complications. The EAG explored the impact of removing disease-related mortality in paediatric patients (discussed in Section 4.2.8).
- **The SMR associated with severe splenomegaly**. The company estimated the SMR for severe splenomegaly to be 43.1. The EAG assessed the impact of using a reduced SMR of 21.5, an approximately 50% reduction (discussed in Section 4.2.8).
- **Modelled carer disutility assumptions**. The EAG assessed the impact of assuming alternative model carer disutility assumptions (discussed in Section 4.2.9.1).
- **Compliance rates**. The company modelled treatment compliance based on rates within the clinical trials ASCEND and ASCEND-Peds. In this scenario the EAG assessed the impact of assuming 95% compliance i.e. no missed/interrupted doses (discussed in Section 4.2.10.1).

- **Discounting of costs and benefits**. The company employed differential discounting in their base case analysis (costs were discounted at 3.5% and benefits at 1.5%). In this scenario analysis both costs and benefits were discounted at 3.5%.
- **Age of starting treatment**. For this scenario the EAG assumed a lower treatment starting age (reducing the age by six years in both adult and paediatric patients).
- **Liver complication rates**. The EAG assumed no difference in liver complication rates between olipudase alfa and BSC.

In Section 6.3, the EAG preferred base-case is presented incorporating a combination of the exploratory analyses presented in Section 6.2.

6.1. EAG corrections and adjustments to the company's base case model

The EAG identified errors within the company's model. These included the following:

- general population utility was updated based on the latest NICE algorithm[48];
- an inappropriate correction for cycle length for the two first cycles in AE calculations;
- an inappropriate use of probabilities rather than rates in calculation of complications;
- an inappropriate correction for cycle length for the first two cycles for liver, spleen and CV complications;
- an inappropriate formula to calculate complication QALYs for all types of complications;
- dosing escalation data for children for week 6, 10, 12 and 14 were incorrectly inputted in the model.

The EAG corrected company base case results are outlined in Table 31. The costs and QALYs reported in all tables are for olipudase alfa.

Table 31: EAG-corrected company base case results and impact of model corrections (paediatric population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
Model corrections					

General population utility	[redacted]	[redacted]	[redacted]	26.06	[redacted]
AE calculation	[redacted]	[redacted]	[redacted]	24.95	[redacted]
Respiratory complications	[redacted]	[redacted]	[redacted]	24.94	[redacted]
Liver complications	[redacted]	[redacted]	[redacted]	24.96	[redacted]
Spleen complications	[redacted]	[redacted]	[redacted]	24.95	[redacted]
CV complications	[redacted]	[redacted]	[redacted]	24.95	[redacted]
Bleeding complications	[redacted]	[redacted]	[redacted]	24.95	[redacted]
Dosing (children)	[redacted]	[redacted]	[redacted]	24.95	[redacted]
EAG corrected company base case	[redacted]	[redacted]	[redacted]	26.05	[redacted]
EAG corrected company probabilistic base case					
Model corrections					
General population utility	[redacted]	[redacted]	[redacted]	25.21	[redacted]
AE calculation	[redacted]	[redacted]	[redacted]	24.05	[redacted]
Respiratory complications	[redacted]	[redacted]	[redacted]	24.03	[redacted]
Liver complications	[redacted]	[redacted]	[redacted]	24.07	[redacted]
Spleen complications	[redacted]	[redacted]	[redacted]	23.94	[redacted]
CV Complications	[redacted]	[redacted]	[redacted]	23.74	[redacted]
Bleeding Complications	[redacted]	[redacted]	[redacted]	23.75	[redacted]
Dosing (Children)	[redacted]	[redacted]	[redacted]	24.14	[redacted]
EAG corrected company base case	[redacted]	[redacted]	[redacted]	25.15	[redacted]

Abbreviations: AE, adverse event; CV, cardiovascular; EAG, external assessment group; QALYs, quality adjusted life years

Table 32: EAG-corrected company base case results and impact of model corrections (adult population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
Model corrections					
General population utility	[redacted]	[redacted]	[redacted]	17.60	[redacted]
AE calculation	[redacted]	[redacted]	[redacted]	16.44	[redacted]
Respiratory complications	[redacted]	[redacted]	[redacted]	16.43	[redacted]
Liver complications	[redacted]	[redacted]	[redacted]	16.44	[redacted]
Spleen complications	[redacted]	[redacted]	[redacted]	16.44	[redacted]
CV complications	[redacted]	[redacted]	[redacted]	16.43	[redacted]
Bleeding complications	[redacted]	[redacted]	[redacted]	16.44	[redacted]
Dosing (children)	[redacted]	[redacted]	[redacted]	16.44	[redacted]
EAG corrected company base case	[redacted]	[redacted]	[redacted]	17.59	[redacted]
EAG corrected company probabilistic base case					
Model corrections					
General population utility	[redacted]	[redacted]	[redacted]	16.41	[redacted]
AE calculation	[redacted]	[redacted]	[redacted]	15.34	[redacted]
Respiratory complications	[redacted]	[redacted]	[redacted]	15.20	[redacted]
Liver complications	[redacted]	[redacted]	[redacted]	15.19	[redacted]
Spleen complications	[redacted]	[redacted]	[redacted]	15.28	[redacted]
CV complications	[redacted]	[redacted]	[redacted]	15.05	[redacted]

Bleeding complications	[redacted]	[redacted]	[redacted]	15.34	[redacted]
Dosing (children)	[redacted]	[redacted]	[redacted]	15.52	[redacted]
EAG corrected company base case	[redacted]	[redacted]	[redacted]	16.49	[redacted]

Abbreviations: AE, adverse event; CV, cardiovascular; EAG, external assessment group; QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted a list of scenario analyses to test the impact of alternative model assumptions on the ICER. These are discussed in the Sections below.

6.2.1. Olipudase alfa long term treatment effect

As noted in Section 4.2.6, there was a lack of long-term data supporting the company's assumption of effect of olipudase alfa after two years i.e. 100% of patients who received olipudase alfa were assumed to transition to the best health states (SV <6MN and DLco ≥80%) from year two onwards. The EAG considered that this assumption was subject to uncertainty and potentially overestimated the QALY gain associated with olipudase alfa. To explore the impact of alternative effectiveness assumptions, the EAG conducted the following scenarios:

- **Observed benefit was frozen for olipudase alfa**: In this scenario patients on olipudase alfa remained in the same health state they were in after two years' of treatment. Given the lack of long-term effectiveness data, the EAG considered this effectiveness assumption to be more plausible than the assumption used by the company in their base case, which may be optimistic. Results were highly sensitive to this analysis. This analysis was incorporated into the EAG preferred base case.

- **Observed benefit continued for olipudase alfa**: In this scenario analysis transition probabilities were replayed in the olipudase alfa arm at two years i.e. after year two patients moved through health states based on the transition probabilities observed in year two of the trials. Results were sensitive to this analysis.

- **Treatment effect waning**: In this scenario it was assumed that all patients receiving olipudase alfa followed BSC transitions from year two onwards. The EAG considered this

scenario to be exploratory and pessimistic as there was no empirical basis to support the assumption that treatment effectiveness would be equivalent to BSC after year two. Results were highly sensitive to this analysis.

6.2.2. Mortality

To test the impact of alternative mortality assumptions, the EAG conducted the following scenario analyses:

- **Removed mortality associated with ASMD (for paediatric patients)**. Based on clinical advice that the risk of mortality was very low in children with ASMD types B and A/B (see Section 4.2.8), in this scenario paediatric patients were assumed to follow general background mortality until the age of 18, whereupon ASMD mortality would re-apply. Results were not very sensitive to this scenario, resulting in a minor increase in the ICER. This analysis was incorporated into the EAG preferred base case.
- **Reduced the SMR associated with severe splenomegaly**. As discussed in Section 4.2.8, the EAG noted limitations surrounding the SPHINGO-100 study used to estimate SMRs in the model. In this scenario, the EAG reduced the SMR for severe splenomegaly by 50%, to 21.5. This analysis had a small upward impact on the ICER in both populations.

6.2.3. Modelled carer disutility assumptions

As noted in Section 4.2.9.2, the EAG conducted scenario analyses to test the impact of alternative/more plausible carer disutility assumptions on the ICER.

- **Application of carer disutility to model health states (irrespective of treatment)**. This scenario analysis had a large upward impact on the ICER for both populations. As noted in Section 6.2.8, the EAG considered this assumption to be more appropriate for decision-making. This analysis was incorporated into the EAG preferred base case.
- **Application of a dynamic disutility approach** i.e. applied higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility). The EAG considered this assumption to be more appropriate for decision-making. For the paediatric population, the disutility for mild/moderate health states was derived from Al Janabi et al. (where the value reflected carer disutility for patients with meningitis who have mild/moderate learning disability), [49] whilst disutility for the severe health state was from Wittenberg et al. (*reflecting carer disutility for patients of children with*

activity limitation).[50] For adult patients, the disutility for mild/moderate health states was derived from Wittenberg et al. (where carer disutility is representative of all chronic conditions within the Wittenberg systematic review),[50] whilst disutility for the severe health state was from Acaster et al. (reflecting carer disutility for patients with Stage 2 MS; patients who are symptomatic).[51] The disutilities selected by the EAG are outlined in Table 33. For this scenario analysis the EAG made several assumptions: first, the severe health state was assumed to be defined by SV ≥15 MN and all other health states were considered under the category 'mild/moderate'; second, the disutilities associated with these proxy conditions were assumed to be generalisable to people with ASMD. Finally, carer HRQoL was not assumed to adapt over time. One expert comment to the EAG noted that carer HRQoL may change over time due to an adaptation effect. The EAG acknowledged that whilst this may happen, incorporating such an additional assumption into the model (without robust data) would introduce further uncertainty. A simplifying assumption was therefore made that assumed that carer disutility would remain constant. This scenario analysis had a moderate/large upward impact on the ICER. This analysis was incorporated into the EAG preferred base case.

Table 33: Dynamic carer disutility values used by the EAG

Population	Mild/moderate health states (all health states other than severe)	Severe health state (SV ≥ 15MN)
Paediatrics	-0.023	-0.080
Adults	-0.010	-0.045

Abbreviations: SV, spleen volume

- **Remove carer disutility associated with death of patient**. This scenario analysis had a large upward impact on the ICER. The EAG considered this assumption to be more appropriate for decision-making. This analysis was incorporated into the EAG preferred base case.

- **Assume 1 carer in each health state (for paediatric patients)**. This scenario analysis had a relatively minor upward impact on the ICER. The EAG considered this assumption to be more appropriate for decision-making. This analysis was incorporated into the EAG preferred base case.

6.2.4. Compliance rate

As noted in Section 4.2.10.1, the company used a compliance rate of 90% in both the paediatric and adult populations (data from the ASCEND and ASCEND-Peds trials). The EAG noted that altering compliance in the model to 100% impacted on costs only i.e. QALYs were not affected. Based on this analysis, the ICER increased by approximately 10% in the paediatric population and 11% in the adult population.

6.2.5. Discount rate

The EAG did not consider the use of differential discounting to be appropriate (see Section 4.2.5). This scenario analysis applied NICE reference case discounting (3.5%) to both costs and benefits. The ICER was highly sensitive to this analysis, resulting in a large upward impact. This analysis was incorporated into the EAG preferred base case.

6.2.6. Starting age

To explore uncertainty surrounding the starting age, the EAG reduced the starting age in both subgroups. The starting age for paediatric patients was reduced to two years and the starting age of adults was reduced to 28-years. Results were not sensitive to this analysis and the ICER decreased in both populations. The EAG noted that for the paediatric population, this scenario resulted in reduced incremental costs, which appeared to be due to differential discounting (of costs and benefits).

6.2.7. Liver complication rate

In the company's base analysis, the annual base rate for spleen, liver and CV complications were derived from SPHINGO-302. [30] The EAG noted that both olipudase alfa and BSC were modelled to have the same probability of spleen and CV complications, however for olipudase alfa, the company estimated a lower complication probability for liver complication (0.3% vs 3.4%). In this scenario, the EAG assumed no difference in liver complication rates between arms i.e. the rate was set to 3.4% for both olipudase alfa and BSC. Results were not overly sensitive to this analysis.

6.2.8. Modelled Patient weight

The EAG noted some uncertainty surrounding the company's modelling of patient weight in both the paediatric and adult populations (see Section 4.2.3). As dosing of olipudase alfa is weight-

based, assumptions about population weight may be influential on drug costs. The following scenario analyses were conducted to test the impact of using alternative weight assumptions.

For paediatrics:

- In order to explore the impact of using an alternative source to estimate paediatric weight in the model, the EAG opted to use weight data from paediatrics in the Health Survey for England report 2019. [4] This scenario analysis had a moderate upward impact on the ICER.

For the adult population:

- Mean patient weight was updated based on UK general population estimates (using data from Health Survey for England report 2019). [4] The UK mean weight was adjusted to reflect the male/female split from the ASCEND trial. This resulted in a mean weight of 77.27kg. The ICER was sensitive to this analysis.

- Mean patient weight was updated based on UK general population estimates (using data from Health Survey for England report 2019). [4] Based on clinical input to the EAG, patients with ASMD may be likely to have lower weight than the UK average population. To account for reduced weight as a result of ASMD, the z-score for 18-year olds (as estimated by the company) was applied, resulting in a weight of 68.52 kg. This scenario analysis had a moderate upward impact on the ICER. This analysis was incorporated into the EAG preferred base case.

6.2.9. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.8. Each change was made individually. The results of the EAG's exploratory analyses are provided in Table 34.

Table 34: Deterministic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	26.05	[redacted]	[redacted]
Olipudase alfa long-term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	22.57		[redacted]

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	23.71	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	12.11	[redacted]	[redacted]
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	25.86	[redacted]	[redacted]
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	23.87	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	19.22	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.94	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.62	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	25.00	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	26.05	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	15.36	[redacted]	[redacted]
Starting age					
Reduced to 2 years	6.2.6	[redacted]	26.40	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	25.87	[redacted]	[redacted]
Modelled patient weight					

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	26.05	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 35: Probabilistic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	16.1	[redacted]	25.06	[redacted]	[redacted]
Olipudase alfa long-term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	21.60	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	23.03	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	11.52	[redacted]	[redacted]
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	24.88	[redacted]	[redacted]
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	23.26	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.28	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the	6.2.3	[redacted]	20.94	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)					
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.28	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	23.94	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	25.20	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	15.01	[redacted]	[redacted]
Starting age					
a. Reduced to 2 years	6.2.6	[redacted]	25.77	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	25.26	[redacted]	[redacted]
Modelled patient weight					
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	25.15	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 36: Deterministic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	17.59	[redacted]	[redacted]
Olipudase alfa long-term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	13.99	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	14.63	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	10.37	[redacted]	[redacted]
Mortality					
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	16.04	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	13.67	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	15.18	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.88	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	17.59	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	12.25	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	19.50	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	17.49	[redacted]	[redacted]
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	17.59	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	17.59	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 37: Probabilistic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	16.32	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	12.84	[redacted]	[redacted]
b. Observed benefit continues: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	13.57	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	9.42	[redacted]	[redacted]
Mortality					
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	15.10	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	12.32	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	13.69	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.25	[redacted]	[redacted]
Compliance rate					

	Section in EAG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Rate set to 100%	6.2.4	[redacted]	16.36	[redacted]	[redacted]
Discount rate					
3.5% for both costs and benefits	6.2.5	[redacted]	11.47	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	18.15	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	16.22	[redacted]	[redacted]
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	16.37	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	16.57	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

6.3. EAG's preferred assumptions

The EAG preferred deterministic and probabilistic base case ICERs are provided in Table 38 to Table 41. Incremental costs and QALYs are discounted (undiscounted QALYs are provided in Appendix B.

Table 38: EAG's deterministic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.95	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	26.05	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	15.36	[redacted]	[redacted]
Removed carer disutility associated with death of patient	6.2.3	[redacted]	21.62	[redacted]	[redacted]

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	22.57	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	19.22	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.94	[redacted]	[redacted]
c. Assume 1 carer in each health state	6.2.3	[redacted]	25.00	[redacted]	[redacted]
Removed disease-related mortality (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	25.86	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	26.05	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.57	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 39: EAG's probabilistic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	24.07	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	25.06	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	14.90	[redacted]	[redacted]

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Remove carer disutility associated with death of patient	6.2.3	[redacted]	21.29	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	21.86	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.41	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	20.87	[redacted]	[redacted]
c. Assume 1 carer in each health state	6.2.3	[redacted]	24.21	[redacted]	[redacted]
Disease related mortality removed (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	24.81	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	25.20	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	7.29	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 40: EAG's deterministic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	16.44	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	17.59	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually) 6.2.1					

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	12.25	[redacted]	[redacted]
Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.88	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2-years	6.2.1	[redacted]	13.99	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	13.67	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	15.18	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	17.59	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	5.30	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

Table 41: EAG's probabilistic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	15.39	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	16.32	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually)					
Costs and benefits discounted at 3.5%	6.2.5	[redacted]	11.46	[redacted]	[redacted]

Remove carer disutility associated with death of patient	6.2.3	[redacted]	13.33	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.36.2.1	[redacted]	13.74	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	12.48	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	13.60	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	16.27	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	4.83	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TP, transition probability

6.4. Conclusions of the cost-effectiveness section

There was a lack of robust clinical data to inform the company's economic model, which the EAG considered was largely due to the rarity of the condition. Consequently, however, the company's base case analysis contained assumptions that the EAG considered to be associated with a high degree of uncertainty. Key model inputs and assumptions were tested by the EAG via scenario analysis, as noted in Section 6.2, which showed that results were sensitive to alternative treatment efficacy, carer HRQoL, patient weight and discounting assumptions.

Based on the EAG preferred base case results, olipudase alfa was not considered to be cost effective compared to BSC at a willingness to pay threshold of £100,000 in either adults or

children. Although the EAG did not consider QALY weighting to be appropriate, an appendix is provided which contains undiscounted QALYs for NICE's consideration.

References

1. Simon N-J, Richardson J, Ahmad A, Rose A, Wittenberg E, D'Cruz B, et al. Health utilities and parental quality of life effects for three rare conditions tested in newborns. Journal of Patient-Reported Outcomes. 2019;3(1):4.

2. National Institute for Health and Care Excellence (NICE). Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. HST guidance, HST11. Published 9th October 2019. Last accessed July 2022. Available from: https://www.nice.org.uk/guidance/hst11.

3. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet Journal of Rare Diseases. 2021;16(1):212.

4. NHS Digital. Health Survey for England: Overweight and obesity in adults and children. 2019.

5. McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann-Pick disease. Genetics in Medicine. 2013;15(8):618-23.

6. Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, et al. Prevalence of lysosomal storage diseases in Portugal. European Journal of Human Genetics. 2004;12(2):87-92.

7. Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, et al. Newborn screening for lysosomal storage disorders in Illinois: The initial 15-month experience. Journal of Pediatrics. 2017;190:130-5.

8. Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, et al. The frequency of lysosomal storage diseases in The Netherlands. Human Genetics. 1999;105(1-2):151-6.

9. Wasserstein M, Arash-Kaps L, Barbato A, Gallagher R, Giugliani R, Guelbert N, et al. OP093 - One-year results of the placebo-controlled ASCEND trial of olipudase alfa enzyme replacement therapy in adults with chronic acid sphingomyelinase deficiency. Molecular Genetics and Metabolism. 2021;132:S64-S5.

10. Sanofi. CSR: DFI12712 (ASCEND). A Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, repeat dose study to evaulate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency. Data on file. 2021.

11. Sanofi. CSR: DFI13803 (ASCEND-Peds). A Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency. Data on file. 2020.
12. Diaz GA, Jones SA, Scarpa M, Mengel KE, Giugliani R, Guffon N, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genetics in Medicine. 2021;23(8):1543-50.
13. Sanofi. CSR: DFI13412. An open-label, multicenter, ascending dose study of the tolerability and safety of recombinant human acid sphingmyelinase (rhASM) in patients with acid sphingomyelinase deficiency (ASMD). Data on file. 2014.
14. Sanofi. CSR: LTS13632. A long-term study to assess the ongoing safety and efficacy of olipudase alfa in patients with acid sphingomyelinase deficiency. Data on file. 2021.
15. Wasserstein M, Lachmann R, Hollak C, Arash-Kaps L, Barbato A, Gallagher RC, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. Genetics in Medicine. 2022;24(7):1425-36.
16. Villarrubia J, Wasserstein M, Barbato A, Gallagher RC, Giugliani R, Guelbert NB, et al. Olipudase alfa for adults with acid sphingmyelinase deficiency: improvements in crossover placebo patients and further improvements in original olipudase alfa patients after 2 years in ASCEND trial. HemaSphere. 2022;6(Suppl):2183-4.
17. Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL, et al. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Molecular Genetics and Metabolism. 2015;116(1-2):88-97.
18. Wasserstein MP, Diaz GA, Lachmann RH, Jouvin MH, Nandy I, Ji AJ, et al. Olipudase alfa for treatment of acid sphingomyelinase deficiency (ASMD): safety and efficacy in adults treated for 30 months. Journal of Inherited Metabolic Disease. 2018;41(5):829-38.
19. Thurberg BL, Diaz GA, Lachmann RH, Schiano T, Wasserstein MP, Ji AJ, et al. Long-term efficacy of olipudase alfa in adults with acid sphingomyelinase deficiency (ASMD): Further clearance of hepatic sphingomyelin is associated with additional improvements in pro- and anti-atherogenic lipid profiles after 42 months of treatment. Molecular Genetics and Metabolism. 2020;131(1-2):245-52.
20. Lachmann R, Diaz GA, Wasserstein MP, Rawlings AM, Yarramaneni A, Kim Y. Sustained and continued improvements in pulmonary function, hepatosplenomegaly, dyslipidemia, and disease biomarkers in 5 adults with chronic acid sphingomyelinase deficiency

after 6.5 years of olipudase alfa enzyme replacement therapy. Molecular Genetics and Metabolism. 2022;135(2):S70.

21. Diaz GA, Giugliani R, Guffon N. Continued improvement in pulmonary, visceral, biomarker and growth outcomes in children with chronic acid sphingomyelinase deficiency treated with olipudase alfa enzyme replacement therapy: 2-year results of ASCEND-Peds. Molecular Genetics and Metabolism. 2022;135:S37.

22. EMA. SmPC olipudase alfa. Available from: https://www.ema.europa.eu/en/documents/product-information/xenpozyme-epar-product-information_en.pdf.

23. Bembi B, Comelli M, Scaggiante B, Pineschi A, Rapelli S, Gornati R, et al. Treatment of sphingomyelinase deficiency by repeated implantations of amniotic epithelial cells. American Journal of Medical Genetics. 1992;44(4):527-33.

24. Liu Y, Luo Y, Xia L, Qiu B, Zhou T, Feng M, et al. The effects of liver transplantation in children with Niemann-Pick Disease Type B. Liver Transplantation. 2019;25(8):1233-40.

25. McGovern MM, Wasserstein MP, Kirmse B, Duvall WL, Schiano T, Thurberg BL, et al. Novel first-dose adverse drug reactions during a phase I trial of olipudase alfa (recombinant human acid sphingomyelinase) in adults with Niemann-Pick disease type B (acid sphingomyelinase deficiency). Genetics in Medicine. 2016;18(1):34-40.

26. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

27. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

28. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003;3(6):329-41.

29. Hilliard ME, Lawrence JM, Modi AC, Anderson A, Crume T, Dolan LM, et al. Identification of minimal clinically important difference scores of the PedsQL in children, adolescents, and young adults with type 1 and type 2 diabetes. Diabetes Care. 2013;36(7):1891-7.

30. Sanofi. Data on File. SPHINGO-302 Clinical Trial.

31. HM Treasury. The Green Book. Central Government Guidance on Appraisial and Evaluation. Available at: . Last accessed August 2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1063330/Green_Book_2022.pdf.

32. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual, 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741.
33. National Institute for Health and Care Excellence (NICE). Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. 2017.
34. Diaz G, Giugliani R, Guffon N, Jones S, Mengel E, Scarpa M, et al. Children treated with olipudase alfa for chronic acid sphingomyelinase deficiency show meaningful improvement on clinically relevant outcomes and an overall favorable safety profile: 1-year results of the ASCEND-Peds trial. Molecular Genetics and Metabolism. 2021;132:S33-S4.
35. Sanofi. CSR: MSC12840 (SPHINGO-001-00). A prospective, cross-sectional survey study to collect natural history data in patients with Niemann-Pick B disease. Data on file. 2015.
36. Jones SA, McGovern M, Lidove O, Giugliani R, Mistry PK, Dionisi-Vici C, et al. Clinical relevance of endpoints in clinical trials for acid sphingomyelinase deficiency enzyme replacement therapy. Molecular Genetics and Metabolism. 2020;131(1-2):116-23.
37. Eskes ECB, Sjouke B, Vaz FM, Goorden SMI, van Kuilenburg ABP, Aerts J, et al. Biochemical and imaging parameters in acid sphingomyelinase deficiency: Potential utility as biomarkers. Mol Genet Metab. 2020;130(1):16-26.
38. Sanofi. Data on file. Assessment of Health State Utilities Associated with Acid Sphingomyelinase Deficiency (ASMD). 2022.
39. Office for National Statistics. Families and Households. 2017.
40. Hornberger J, Reyes C, Shewade A, Lerner S, Friedmann M, Han L, et al. Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. Leukemia & Lymphoma. 2012;53(2):225-34.
41. Song J, Floyd FJ, Seltzer MM, Greenberg JS, Hong J. Long-term Effects of Child Death on Parents' Health Related Quality of Life: A Dyadic Analysis. Fam Relat. 2010;59(3):269-82.
42. Galante J, Augustovski F, Colantonio L, Bardach A, Caporale J, Marti SG, et al. Estimation and comparison of EQ-5D health states' utility weights for pneumococcal and human papillomavirus diseases in Argentina, Chile, and the United Kingdom. Value Health. 2011;14(5 Suppl 1):S60-4.
43. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Medical Decision Making. 2008;28(4):582-92.

44. Snyder CF, Mathias SD, Cella D, Isitt JJ, Wu AW, Young J. Health-related quality of life of immune thrombocytopenic purpura patients: results from a web-based survey. Current Medical Research and Opinion. 2008;24(10):2767-76.

45. Sullivan PW, Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. Value Health. 2016;19(8):1002-8.

46. Szende A, Brazier J, Schaefer C, Deuson R, Isitt JJ, Vyas P. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. Current Medical Research and Opinion. 2010;26(8):1893-903.

47. NHS. National Schedule of NHS costs - Year 2019-20 - NHS trust and NHS foundation trusts.

48. Hernandez A, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU report. 2022.

49. Al-Janabi H, van Exel J, Brouwer W, Coast J. A Framework for Including Family Health Spillovers in Economic Evaluation. Med Decis Making. 2016;36(2):176-86.

50. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. Pharmacoeconomics. 2013;31(6):489-500.

51. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. BMC Health Serv Res. 2013;13:346.

Appendix A: Search strategies for Ovid MEDLINE and Embase

A summary of additional searches completed by the EAG are reported in 3.4.

Search strategy for Ovid MEDLINE:

1	niemann pick disease/	1711
2	(acid sphingomyelinase deficien$ or ASMD or Niemann-Pick).ti,ab,kw.	4078
3	1 or 2	4489
4	type C*.ti.	17610
5	3 not 4	3320
6	5 not ((exp animal/ or nonhuman/) not exp human/)	2794
7	(case report or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	870892
8	case report/ or case study/ or case reports.jw.	2322536
9	6 not (7 or 8)	2338
10	(ephemera or "introductory journal article" or news or "newspaper article" or editorial or comment or overall).pt. or in vitro techniques/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3254601
11	9 not 10	2178
12	review.pt. not (guideline/ or practice guidelines/ or practice guidelines as topic/ or guideline.ti. or (((systematic or meta) and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.)	2878862
13	11 not 12	1692
14	Niemann-Pick Diseases/	1711
15	Niemann-Pick Disease, Type B/	95
16	((visceral or neurovisceral) adj2 NPD).ti,ab.	3
17	(ASM adj deficien*).ti,ab.	94
18	Niemann-Pick.ti,ab,kw.	3983
19	niemann pick.ti,ab,kw.	3983
20	NiemannPick.ti,ab.	3
21	14 or 15 or 16 or 17 or 18 or 19 or 20	4451
22	21 not 3	44

Search strategy for Ovid Embase:

1	niemann pick disease/	5043
2	(acid sphingomyelinase deficien$ or ASMD or Niemann-Pick).ti,ab,kw.	5336
3	1 or 2	6837
4	type C*.ti.	19792
5	3 not 4	5227
6	5 not ((exp animal/ or nonhuman/) not exp human/)	4301
7	(case report or woman or man or child or adolescent or female or male or bou or girl or infant).ti.	952339
8	case report/ or case study/ or case reports.jw. or case reports.jx.	2854453
9	6 not (7 or 8)	3651

10 (ephemera or "introductory journal article" or news or "newspaper article" or editorial or comment or overall).pt. or in vitro techniques/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti. 3433333
11 9 not 10 3343
12 limit 11 to (article or article in press) 1498
13 review.pt. not (guideline/ or practice guidelines/ or practice guidelines as topic/ or guideline.ti. or (((systematic or meta) and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.) 2721272
14 12 not 13 1498
15 ((visceral or neurovisceral) adj2 NPD).ti,ab. 6
16 (ASM adj deficien*).ti,ab. 132
17 Niemann-Pick.ti,ab,kw. 5186
18 niemann pick.ti,ab,kw. 5186
19 NiemannPick.ti,ab. 12
20 15 or 16 or 17 or 18 or 19 5253
21 20 not 3 54
22 type B.ti,ab. 33907
23 4 and 22 118
24 2 and 23 9
25 11 not 12 1845 [results not retrieved by use of Article, Article in Press limit]
26 olipudase alfa/ 49
27 olipudase alfa.ti,ab. 38
28 26 or 27 53
29 25 and 28 31
30 (prevalence or incidence or natural history or complication* or mortality).ti. 719318
31 25 and 30 17
32 exp health economics/ 974892
33 exp economic evaluation/ 338707
34 exp "health care cost"/ 323866
35 exp pharmacoeconomics/ 221790
36 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 1285287
37 (expenditure$ not energy).ti,ab. 47306
38 (value adj2 money).ti,ab. 2809
39 budget$.ti,ab. 44444
40 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 1900228
41 (metabolic adj cost).ti,ab. 1749
42 ((energy or oxygen) adj cost).ti,ab. 4850
43 ((energy or oxygen) adj expenditure).ti,ab. 35485
44 41 or 42 or 43 40910
45 40 not 44 1891789
46 25 and 45 88
47 Quality-Adjusted Life Years/ 32388
48 (quality adjusted or adjusted life year$).ti,ab,kf. 31254
49 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 25008
50 (illness state$1 or health state$1).ti,ab,kf. 13601
51 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2866
52 (multiattribute$ or multi attribute$).ti,ab,kf. 1414
53 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 29594
54 utilities.ti,ab,kf. 14100

55 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. 28068
56 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 8184
57 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 43549
58 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. 3295
59 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. 30688
60 quality of life/ and ec.fs. 53881
61 quality of life/ and (health adj3 status).ti,ab,kf. 19411
62 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 6492
63 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 231876
64 25 and 63 22
65 overall survival.ti. 13772
66 25 and 65 1
67 randomized controlled trial/ 727333
68 random*.ti,ab. 1832911
69 RCT.ti,ab. 48577
70 67 or 68 or 69 1952480
71 25 and 70 32
72 71 not 29 25

WORLDSymposium, 2021

https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/132/issue/2

Searched used CTRL+F: Niemann. All highlighted records relate to Niemann-Pick C. No additional records retrieved.

WORLDSymposium, 2022

https://www.sciencedirect.com/journal/molecular-genetics-and-metabolism/vol/135/issue/2

Searched used CTRL+F: Niemann. All highlighted records relate to Niemann-Pick C. No additional records retrieved.

European Society of Human Genetics-2021

https://www.abstractsonline.com/pp8/#!/10372

Searched using search box: Niemann. No additional relevant records retrieved.

Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, 2021

https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12458

Searched PDF with CTRL+F: sphingomyelinase. Kapetanakis (P-173) retrieved by EAG's additional searches in Ovid Embase. No additional records identified.

Appendix B: Results based on undiscounted QALYs

The following section presents the EAG scenario analyses and EAG preferred base case results based on undiscounted QALYs.

EAG scenario analyses using undiscounted QALYs

Table 42: Deterministic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	42.68	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	37.21	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	39.03	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	17.64	[redacted]	[redacted]
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	42.45	[redacted]	[redacted]
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	38.79	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	32.77	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	37.12	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	33.85	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	41.55	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	42.68	[redacted]	[redacted]
Starting age					
Reduced to 2 years	6.2.6	[redacted]	44.75	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	42.43	[redacted]	[redacted]
Modelled patient weight					
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	42.68	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 43: Probabilistic EAG scenario analysis (paediatric population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	16.1	[redacted]	40.69	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	35.50	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	37.55	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	16.77	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Mortality					
a. Remove ASMD related mortality for paediatric patients	6.2.2	[redacted]	40.69	[redacted]	[redacted]
b. Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	37.30	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	30.65	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	35.14	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	32.95	[redacted]	[redacted]
d. Assume 1 carer in each health state	6.2.3	[redacted]	39.73	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	40.55	[redacted]	[redacted]
Starting age					
Reduced to 2 years	6.2.6	[redacted]	43.45	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	40.76	[redacted]	[redacted]
Modelled patient weight					
Paediatric weight estimated based on data from the Health Survey for England report	6.2.8	[redacted]	41.08	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 44: Deterministic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	24.03	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	19.25	[redacted]	[redacted]
b. Observed benefit continued: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	20.11	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	13.84	[redacted]	[redacted]
Mortality					
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	21.92	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.92	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.05	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	18.50	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	24.03	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	27.78	[redacted]	[redacted]
Liver complication rate					

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	23.90	[redacted]	[redacted]
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	24.03	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	24.03	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 45: Probabilistic EAG scenario analysis (adult population)

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
EAG corrected company base-case	6.1	[redacted]	22.21	[redacted]	[redacted]
Olipudase alfa long term treatment effect					
a. Observed benefit is frozen: no further transitions after 2 year	6.2.1	[redacted]	17.47	[redacted]	[redacted]
b. Observed benefit continues: replay TPs in the olipudase alfa arm at 2 years	6.2.1	[redacted]	18.44	[redacted]	[redacted]
c. Treatment effect waning: from 2 years, assume that all olipudase alfa patients follow BSC transitions	6.2.1	[redacted]	12.36	[redacted]	[redacted]
Mortality					
Reduce SMR for severe splenomegaly to 21.5	6.2.2	[redacted]	20.41	[redacted]	[redacted]
Modelled carer disutility assumptions					
a. Application of carer disutility to model health states	6.2.3	[redacted]	17.21	[redacted]	[redacted]

	Section in EAG report	Incremental discounted costs	Incremental undiscounted QALYs	ICER £/QALY	+/- EAG corrected company base case
(irrespective of treatment)					
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	18.96	[redacted]	[redacted]
c. Remove carer disutility associated with death of patient	6.2.3	[redacted]	17.87	[redacted]	[redacted]
Compliance rate					
Rate set to 100%	6.2.4	[redacted]	22.19	[redacted]	[redacted]
Starting age					
Reduced to 28 years	6.2.6	[redacted]	25.56	[redacted]	[redacted]
Liver complication rate					
Olipudase alfa set to be the same as BSC	6.2.7	[redacted]	22.40	[redacted]	[redacted]
Modelled patient weight					
a. Patient weight based on UK mean weight (weighted for split of male/females in the ASCEND study)	6.2.8	[redacted]	22.53	[redacted]	[redacted]
b. Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	22.09	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

EAG's preferred assumptions (undiscounted QALYs)

The EAG preferred deterministic and probabilistic base case ICERs are provided in Table 46 to Table 49.

Table 46: EAG's deterministic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	40.72	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	42.68	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					
Removed carer disutility associated with death of patient	6.2.3	[redacted]	33.85	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	37.21	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	32.77	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	37.12	[redacted]	[redacted]
c. Assume 1 carer in each health state	6.2.3	[redacted]	41.55	[redacted]	[redacted]
Removed disease-related mortality (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	42.45	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	42.68	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	21.78	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 47: EAG's probabilistic preferred assumptions and ICER (paediatric population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	38.79	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	40.69	[redacted]	[redacted]
EAG preferred base case assumptions (applied individually)					
Removed carer disutility associated with death of patient	6.2.3	[redacted]	32.95	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 years	6.2.1	[redacted]	35.50	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	30.65	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	35.14	[redacted]	[redacted]
c. Assume 1 carer in each health state	6.2.3	[redacted]	39.73	[redacted]	[redacted]
Disease related mortality removed (assumed to follow background mortality until adulthood)	6.2.2	[redacted]	40.69	[redacted]	[redacted]
Weight on adulthood based on UK mean weight 2019	6.2.8	[redacted]	40.53	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	20.83	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 48: EAG's deterministic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	22.44	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	24.03	[redacted]	[redacted]
EAG Preferred base case assumptions (applied individually) 6.2.1					
Remove carer disutility associated with death of patient	6.2.3	[redacted]	18.50	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2-years		[redacted]	19.25	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	18.92	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	21.05	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	24.03	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	10.44	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 49: EAG's probabilistic preferred assumptions and ICER (adult population)

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
Company's base case	5.1	[redacted]	20.74	[redacted]	[redacted]
EAG corrected company base case	6.1	[redacted]	22.21	[redacted]	[redacted]

	EAG report section	Incremental cost	Incremental QALYs	ICER (applied individually)	ICER (cumulative)
EAG Preferred base case assumptions (applied individually)					
Removed carer disutility associated with death of patient	6.2.3	[redacted]	17.86	[redacted]	[redacted]
Observed benefit is frozen: no further transitions after 2 year	6.2.36.2.1	[redacted]	17.81	[redacted]	[redacted]
Alternative approach to modelling carer disutility					
a. Application of carer disutility to model health states (irrespective of treatment)	6.2.3	[redacted]	16.97	[redacted]	[redacted]
b. Application of a dynamic disutility approach i.e. apply higher disutility to the severe health state and lower disutility for other states (alternative published literature sources used for carer disutility)	6.2.3	[redacted]	18.85	[redacted]	[redacted]
Patient weight based on UK mean weight (z-score for 18-year olds applied) to account for lower patient weight due to ASMD	6.2.8	[redacted]	22.37	[redacted]	[redacted]
Cumulative impact of EAG's preferences	6.3	[redacted]	9.24	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

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Highly Specialised Technology

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

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If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **the morning** on **Thursday 31st August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Technical engagement response form

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

About you

Table 1: About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Sanofi
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

As part of this response Sanofi are also submitting an outline of a Managed Access Agreement proposal (separate document).

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case	Yes	Sanofi believe that costs and benefits should be discounted using different rates in line with the HM Treasury's Green Book. Although we acknowledge that the differential discounting is not consistent with the NICE reference case, based on the guidance provided in the NICE health technology evaluations manual, there is a strong case to apply a discount of 1.5% to both costs and benefits, if a differential rate is not accepted. In consideration of the comments in the external assessment group's (EAG's) report, a case for using a 1.5% discount rate for both costs and health effects is presented, based on the criteria provided in Section 4.5 of the NICE health technology evaluations manual. Results using 1.5% discounting for both costs and outcomes are provided in Section 3.10.3.1 of the company submission and are provided as the company's revised base case in Table 4 below. The technology is for people who would otherwise die or have a very severely impaired quality of life Severe and progressive somatic multi-systemic manifestations, including splenomegaly (present in >90% of patients), hepatomegaly (present in >70% of patients), lung disease (present in >80% of patients), and gastrointestinal (GI) issues (present in >75% of patients), are indicative of acid sphingomyelinase deficiency (ASMD) type A/B and type B, which worsen in the absence of disease-

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		modifying treatment. These manifestations cause irreversible organ damage and result in substantial morbidity and mortality, leading to reduced life expectancy in patients with ASMD. Early onset of the disease is also associated with an increased risk of early mortality. There are no patients over 60 years of age currently living with ASMD in the UK, with most patients dying in or before their 50s. Reduced life expectancy is particularly apparent with paediatric onset ASMD. There are three studies highlighted in Document B that reported worldwide mortality outcomes in adult and paediatric patients with ASMD along with a chart review and pooled data analysis of patients with ASMD (n=270) in Germany, France, the USA and Brazil (1-4). These studies consistently show shorter life expectancy in patients with ASMD (1-4). The standardised mortality ratio (SMR) from the pooled chart data analysis was [redacted] (using 2018 as reference) (4). There is a substantial burden with ASMD. Patients must make changes to their lifestyle, including nutritional, social, employment, and activity adaptations due to an enlarged spleen and/or liver, pulmonary impairment, excessive bleeding, and growth deficits. Patients with ASMD experience a substantial impact on their mental health including depression, anxiety, and psychosis due to the severe limitations imposed by their disease. Additionally, ASMD negatively impacts physical, self-esteem, emotional, personal care, and social function and relationship quality of life (QoL) domains. In addition to the burden to the patient, there is a substantial impact on the QoL of caregivers of patients with ASMD. More detail on caregiver burden is provided in Key Issue 3. <u>It is likely to restore them to full or near full health</u> The clinical results from the ASCEND and ASCEND-Peds trial demonstrate that olipudase alfa is associated with significant improvements in multisystemic clinical manifestations of ASMD (including respiratory function, spleen volume, and liver volume) in both adults and children, with increased growth and musculoskeletal development in children.

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		In the ASCEND trial, treatment with olipudase alfa resulted in a significant improvement in diffusing capacity of the lung, as measured by percent predicted lung diffusion of carbon monoxide (DL_{CO}), compared with placebo at Week 52 (least squares [LS] mean difference of 19.01%, p=0.0004). Additionally, olipudase alfa treatment resulted in a significant reduction in liver volume (LS mean difference of –26.60%; p<0.0001) and a significant increase in platelet count (LS mean difference of 14.33%; p=0.0185) at Week 52 compared with placebo. In the ASCEND-Peds trial, treatment with olipudase alfa resulted in a statistically significant improvement in diffusing capacity of the lung, as measured by percent predicted DL_{CO}, compared with baseline at Week 52 (32.94%; p=0.0053) and a statistically significant reduction in spleen volume (SV) and liver volume at Week 52 compared with baseline (-49.21% and 40.56%, respectively; p<0.0001). A recent international study conducted on behalf of National Niemann-Pick disease Foundation (NNPDF), Niemann-Pick UK (NPUK), and the International Niemann-Pick Disease Registry (INPDR), which involved an online survey and semi-structured interviews with 10 patients or their caregivers, reported that olipudase alfa was associated with improvements in all non-neurologic manifestations of ASMD (Figure 1) (5). Results from this study highlighted the impact of olipudase alfa on the range of symptoms experienced by paediatric patients with ASMD.

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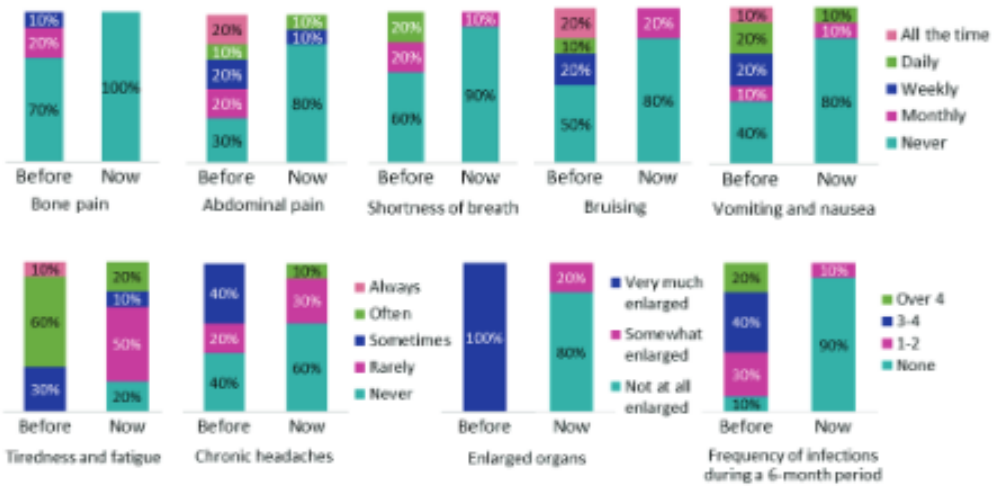
Figure 1: Frequency of ASMD symptoms before (n=10) and after (n=10) treatment with olipudase alfa



Abbreviations: ASMD, acid sphingomyelinase deficiency.

Clinical opinion was sought after the initial submission on the long-term efficacy of olipudase alfa. Clinicians indicated that patients continue to improve in clinical parameters during treatment and approach normal range over time. In particular, they noted that DL_{CO} shows improvement and normalises over time. Liver and spleen volume approach normal range over time and patients are expected to stabilise at a lower spleen and liver volume compared to prior to treatment.

The benefits are likely to be sustained over a very long period

At the latest data cut off ASCEND (01 March 2021), data were available for up to 6.5 years of follow-up for adult patients and 4 years of follow-up for paediatric patients (6). The company believes that effects will be sustained long-term, in line with what has been observed in Gaucher disease where there is evidence showing patients continue to maintain response 20 years after initiation of treatment (7).

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		This is further supported by clinical opinion provided to both the company and EAG that there is nothing that suggests loss of long-term efficacy in observed patients, with normalisation/improvement in key clinical outcomes over extended treatment, and no indication of antibody response. An updated base case analysis is provided for a discount rate of 1.5% for both costs and benefits in Table 4. Sensitivity analyses for differential discount rates and 3.5% discount rate for costs and benefits are shown in Table 5 and Table 6 respectively.
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	Yes	At the latest data cut of ASCEND (01 March 2021), data were available for up to 6.5 years of follow-up for adult patients and 4 years of follow-up for paediatric patients. Results from the clinical trials indicate that patients are 'normalised' (i.e. restored to full or near full health) at the latest data cut. The company has no reason to believe that treatment effects will not be sustained long-term. This is further supported by clinical expert opinion obtained both by the company and EAG and similar results have been shown with long-term enzyme replacement therapy (ERT) in Gaucher disease, another lysosomal storage disorder. Therefore, in the absence of longer-term data, our base case assumption is appropriate. However, following the technical engagement meeting where the reservations regarding a transition to a normalised health state after two years were discussed, the company would like to provide alternative methodology and additional scenario analyses that address the long-term treatment effect in the model. In the original company base case, patients receiving olipudase alfa can only transition to an alternative health state for up to 2 years, after which (from year 3 onwards) they all transition to the SV <6 / DL_{CO} >80 state and remain there until the end of the time horizon or death. We have revised our base case so that patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which all patients transition to the SV <6 / DL_{CO} >80 state from year 10 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth

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		linear change in patients' probability to transition to the 'SV <6 / DL_{CO} >80' state from the other health states between year 2 and year 10. In scenario analysis transition probabilities at year 2 are applied each year until the end of the time horizon or death. In other words, patients are no longer all assigned to the 'SV <6 / DL_{CO} >80' state from year 3 onwards. The probability of patients reaching this state over time is driven by the transition probabilities that applied during year 2 and are assumed to be constant afterwards. Sensitivity analyses are provided to demonstrate the effect of modelling long-term treatment effect on the model results. Please see Table 7 and Table 8 for results.
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL	Yes	ASMD has a profound impact on not only patients, but also on their families. Due to the severe and progressive somatic multi-systemic manifestations and the high morbidity and mortality, particularly associated with the paediatric population, it is assumed that there is a meaningful detrimental impact on the QoL of caregivers of patients with ASMD. Caregivers face the grief of losing a loved one prematurely, and this is especially true for those caring for children. In addition to facing grief, caregivers have difficulty maintaining their emotional and mental state, along with preserving social activities and relationships. The caregiving burden directly impacts the QoL of the caregiver. Caregiving responsibilities including the requirement to attend medical appointments, changing daily routines, and maintaining the overall wellbeing of their loved one are associated with a substantial caregiver burden, and in turn this impacts QoL. Physical exhaustion and pain from the caregiving process decreases the ability of caregivers to socialise resulting in further emotional impact. The extreme financial burden resulting from caregiving duties and the associated inability to work can also contribute to feelings of low self-worth, further increasing the caregiving burden and decreasing the caregiver's QoL. Physical symptoms associated with ASMD include respiratory symptoms (shortness of breath, requirement for supplemental oxygen), abdominal symptoms

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		(pain and discomfort [resulting in sleep disturbances], enlarged and distended abdomen), musculoskeletal symptoms (muscle weakness, bone pain, and joint pain), fatigue, excessive bleeding and bruising, gastrointestinal symptoms and headaches, which are all indicative of the substantial clinical burden that requires the involvement of caregiver(s). <u>Carer disutility</u> We agree with the EAG that modelling carer disutility is an area where insufficient methodological guidance currently exists. Furthermore, there are no published estimates of disutility for caregivers of patients with ASMD or analogue conditions such as Gaucher disease. As discussed in response to Key Issue #1, results from the clinical trials indicate that patients treated with olipudase alfa are 'normalised' (i.e. restored to full or near full health). Additionally, clinicians indicated that the clinical parameters of patients in trials continue to improve over time and approach a normal range. As patients quickly approach full or near full health with olipudase alfa treatment, it is also anticipated that the impact on caregivers diminishes to a very low level and therefore in the absence of data disutilities are applied to the BSC arm only. As highlighted above, no caregiver disutilities were identified for ASMD or Gaucher disease, which could be considered an analogue. Therefore, other disease areas were used to obtain disutility values for scenario testing. We acknowledge that there are limitations to the use of caregiver disutilities from Pompe disease (company analysis), as well as those used by the EAG, which were derived from conditions such as multiple sclerosis and meningitis. *1.78 carers for children* Providing care for patients with ASMD is a time-consuming task and often involves and affects the entire family. As has been considered appropriate in other appraisals (e.g. highly specialised technology [HST] guidance HST 3, HST 9, HST 10, HST 11), the inclusion of utilities for multiple caregivers has been considered appropriate. In this ASMD model, we account for an average of

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		1.78 caregiving parents per child with ASMD, in line with HST 11 (8). This is likely an underestimate of the true impact of the condition, as does not take into account the real impact on the extended family and friends of ASMD patients. Although very limited evidence exists in ASMD, publications in Duchenne muscular dystrophy indicate that both parents are involved in caregiving duties (9, 10). There is further a substantial impact on the QoL of siblings of patients with chronic disease. While siblings' emotional experiences are characterised by diverse and contradictory feelings (11), the QoL of siblings of patients with chronic conditions is lower than that of patients whose siblings had no chronic conditions (12, 13). Healthy siblings of children with chronic disease are affected physically and psychosocially (12), and their health-related QoL is lower in well-being, social support, and financial dimensions compared with their peers (13). A web-based survey of Duchenne muscular dystrophy caregivers showed that siblings are perceived to have to give up time with friends, sports and/or extracurricular activities, and holiday-related activities (14). Further, caregivers report that there may be insufficient finances for siblings' educational or other activities (14). According to a report on the impact of a rare disease on sibling experience conducted by Alexion, the QoL of a sibling of a person with a rare disease is negatively affected due to the presence of the rare disease in the family unit (15). Although siblings are generally not the primary carer, they do provide care and support, and this increases with age and maturity, as does the impact on their mental health (15). Siblings are unable to experience the same QoL as that of their peers; this can be due to feeling overlooked as their parents devote a large amount of time to caring for their sibling, constant feelings of worry for their family, or the stress of feeling the need to protect their sibling (15). We therefore believe this should be reflected in the economic model by the inclusion of siblings in the mean number of caregivers. The mean number of siblings in the UK in 2021 was 1.77 (16). This gives an overall average of 2.6 carers affected per patient.

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		Impact of patient death on carer disutility The exclusion of disutility due to bereavement from the model leads to spurious results suggesting that parent QoL increases following the death of their child. In fact, publications highlight the substantial impact on QoL experienced by carers of patients with chronic and severe disease approaching death. Carers experience reduced mental QoL when caring for ill family members (17-24). More specifically, patients with a high level of anticipatory grief had a lower QoL (17). Carers of patients with advanced cancer, or disorder of consciousness reported poorer physical and mental health than the general population (18, 20, 22, 24). In a survey focusing on symptoms of grief and depression to determine the extent of overall functional impairment in caregivers of terminally ill patients in Denmark, 51% of caregivers reported overall functional impairment before the death of the patient (22). Depressive symptoms were a common characteristic observed in caregivers of patients with chronic or severe disease approaching death (20, 22). The importance of bereavement in rare diseases is reflected by its inclusion in over 30% of HST appraisals. In a study of 23 HST appraisals, eight included considerations involving bereavement. Grief and bereavement were included in company submissions (n=2), patient advocacy group submissions (n=3), and company and patient advocacy group submissions (n=3). The impact of grief and bereavement on caregivers and the carer disutility due to bereavement was included in two appraisals (25). HST 7 (an economic evaluation of a meningitis vaccine) modelled family quality-adjusted life year (QALY) loss resulting in an incremental cost-effectiveness ratio (ICER) decrease of 9%; the additional QALY loss experienced by a bereaved family was assumed to be 9% of the child's QALY loss (26). Appraisal ID800 included a caregiver disutility in the base case which corresponded to the most severe health state; the Extended Disability Status Scale illustrated that the caregiver disutility increased as the disease becomes more severe (27). Although the publications documenting disutilities associated with grief and bereavement are scarce, there is evidence that grief and bereavement profoundly

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		influence caregiver QoL. We therefore believe it is appropriate to include a carer disutility associated with death of the patient in the economic model. Sensitivity analyses are provided for health state-specific carer disutilities applied from a proxy disease area, Pompe (28). Please see Table 9 for the utility values used and Table 10 for results.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	Yes	ASMD is a disease that shortens overall survival. There is consistent evidence of this from the SPHINGO-100 study, and from the pooled data analysis of patients with ASMD included in the Addendum. This was further confirmed in advice received from clinical experts. Regarding low paediatric mortality rates proposed by the EAG, clinical opinion suggests the assumption that paediatric patients with ASMD type B would die sooner than the general population is correct, but noted the incidence of these deaths would likely be underreported, given these patients transition to adult care services at 16 years and thus any deaths after this point would not be recorded. Advice from clinical experts supported the use of parametric fits based on the pooled analysis forming the basis of the Addendum, as these reflected the underlying data. It was also considered that the population included in the study was generalisable to patients with ASMD in the UK, as the treatment paradigm is similar across the world due to the lack of disease modifying treatments.
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	No	On average, patients with ASMD are lighter than the general population, as shown by trial data, clinical expert interviews, and compassionate use requests received by the company. The EAG preferred assumption of using the mean UK population weight is not representative of patients with ASMD. Data from the pivotal ASCEND and ASCEND-Peds trials shows that weight for both children and adults was low relative to the general population due to the nature of the disease. In addition,

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		according to a retrospective chart review of 100 patients with ASMD (Cox et al., 2018), growth was subnormal throughout childhood for all patients with chronic neurovisceral disease and for 50% of patients with chronic visceral disease; weight gain was impaired over time in patients with ASMD (2). A publication by Diaz et al. (2022), indicated that the short stature and low weight associated with patients with ASMD is correlated with large organ volumes, delayed bone age, and low serum insulin-like growth factor 1 concentrations (29). These additional publications support the rationale for the patient weight used in the model. Following compassionate use requests, Sanofi have provided olipudase alfa to [redacted] UK patients who were severely affected by ASMD type B and A/B. The maximum weight of these patients recorded at baseline was [redacted]. This information further substantiates the rationale that patients with ASMD have a lower weight than the general population.
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations	No	We acknowledge that there are limitations in carrying out a subgroup analysis based on the small sample size in ASCEND. The severe subgroup analysis was provided for illustrative purposes, to explore the cost-effectiveness of olipudase alfa in particularly severe patients. In addition, this analysis is likely conservative, as it uses transition probabilities from the broad patient population.

Abbreviations: AIC, Akaike information criterion; ASMD; acid sphingomyelinase deficiency; BIC, Bayesian information criterion; BSC, best supportive care; CI, confidence interval; DL_{CO}, lung diffusion of carbon monoxide; DSU, Decision Support Unit; EAG, external assessment group; ERT, enzyme replacement therapy; HST, highly specialised technology; ICER, incremental cost-effectiveness ratio; INPDR, International Niemann-Pick Disease Registry; KOL, key opinion leader; LS, least squares; NICE, National Institute for Health and Care Excellence; NNPDF, National Niemann-Pick disease Foundation; NPUK, Niemann-Pick UK; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; QoL, quality of life; RARE sibling, sibling of a person with a rare disease; SMR, standardised mortality ratio; SV, spleen volume.

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Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3: Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Potential impact of antibody resistance mentioned by clinical advisers to EAG in Section 4.2.7 of the EAG report	Section 4.2.7 of the EAG report	Yes	Immunogenicity data In response to the potential impact of antibody resistance mentioned by clinical advisers to EAG in Section 4.2.7 of the EAG report, Sanofi would like to submit a report on the immunogenicity of olipudase alfa which supports the maintenance of response with long-term olipudase alfa treatment of patients with ASMD, demonstrating that olipudase alfa has a low risk of immunogenicity impacting clinical outcomes (30). [redacted]

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			[redacted]

Abbreviations: EAR, external assessment report; NA, not applicable.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	After provision of the initial evidence submission to NICE in August 2022, further data relevant to the decision problem have become available. A chart review and subsequent pooled data analysis of patients with ASMD (n=270) in Germany, France, the USA, and Brazil provides new survival estimates for adults and children with ASMD (31). Clinicians consulted by Sanofi confirmed that the population included in this study was generalisable to patients with ASMD in the UK (32).	New survival data were used to generate survival curves and were incorporated into the model. Please see company addendum to the HST submission for further details.	The original submitted unweighted ICER (£/unweighted QALY gained) for the paediatric population was £[redacted] The original submitted unweighted ICER (£/unweighted QALY gained) for the adult population was £[redacted] The original submitted weighted ICER (£/weighted QALY gained) for the paediatric population was £[redacted]The original submitted weighted ICER (£/weighted QALY gained) for the adult population was £[redacted]

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Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
			The original submitted unweighted ICER (£/unweighted QALY gained) for the paediatric population was £[redacted]The original submitted unweighted ICER (£/unweighted QALY gained) for the adult population was £[redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is £[redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is £[redacted]
EAG key issue #1:The company used differential discounting, which is not consistent with the NICE reference case	Sanofi believe that costs and benefits should be discounted using different rates in line with the HM Treasury's Green Book.	We acknowledge that differential discounting is not consistent with the NICE reference case, based on the guidance provided in the NICE health technology evaluations manual, but that there is a strong case to apply a discount of 1.5% to both costs and benefits, if a differential rate is not accepted.	When added to the change outlined above: The updated unweighted ICER (£/unweighted QALY gained) for the paediatric population is [redacted] The updated unweighted ICER (£/unweighted QALY gained) for the adult population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is [redacted]

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Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
			The updated weighted ICER (£/weighted QALY gained) for the adult population is [redacted]
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	In the company base case, patients receiving olipudase alfa can only transition to an alternative health state for up to 2 years, after which (i.e., from year 3 onwards) they all transition to the SV <6 / DL_{CO} >80 state and remain there until the end of the time horizon or death.	We have revised our base case so that patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which all patients transition to the SV <6 / DL_{CO} >80 state from year 10 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients' probability to transition to the 'SV <6 / DL_{CO} >80' state from the other health states between year 2 and year 10.	When added to the change outlined above: The updated unweighted ICER (£/unweighted QALY gained) for the paediatric population is [redacted] The updated unweighted ICER (£/unweighted QALY gained) for the adult population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is £[redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is £[redacted]
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL	In the company's base case model, we account for an average of 1.78 caregiving parents per child with ASMD, in line with HST 11. This is likely to be an underestimate of the true impact of the condition, as it does not take into account the real impact on the extended	We therefore believe this should be reflected in the economic model by the inclusion of siblings in the mean number of caregivers. The mean number of siblings in the UK in 2021 was 1.77 (16). This gives an overall average of 2.6 carers per patient.	When added to the change outlined above: The updated unweighted ICER (£/unweighted QALY gained) for the paediatric population is [redacted] The updated unweighted ICER (£/unweighted QALY gained) for the adult population is [redacted]

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Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
	family and friends of ASMD patients.		The updated weighted ICER (£/weighted QALY gained) for the paediatric population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is £[redacted]
Company's base case following technical engagement (or revised base case)	Paediatric population Incremental unweighted QALYs: 37.38 Incremental weighted QALYs: 112.13 Adult population Incremental unweighted QALYs: 20.62 Incremental weighted QALYs: 61.85	Paediatric population Incremental costs: [redacted] Adult population Incremental costs: [redacted]	The cumulative result of the updates to the company's base case model as a result of the changes outlined in this table is as follows: The updated unweighted ICER (£/unweighted QALY gained) for the paediatric population is [redacted] The updated unweighted ICER (£/unweighted QALY gained) for the adult population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is £[redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is £[redacted]

Abbreviations: EAR, external assessment report; ICER, incremental cost-effectiveness ratio; NICE, The National Institute for Health and Care Excellence; QALY, quality-adjusted life year.

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Sensitivity analyses around revised base case
The company would like to provide sensitivity analyses to address key issues raised by the EAG.

The scenarios are listed as follows:
- Discounting at 3.5% for costs and 1.5% for benefits
- Discounting at 3.5% for costs and benefits
- Application of year 2 transition probabilities for remainder of the model
- Patients move to SV <6 / DLCO >80 state at 2 years for the reminder of the model
- Disutility values for carers from an alternative source (Pompe)

EAG Key issue #1: Discount rates
As outlined in Table 2, regarding EAG key issue #1, differential discount rates are appropriate in this case. However, 1.5% for both costs and benefits has been adopted in the revised base case.

Two scenarios are provided to demonstrate the effect of discount rates on the model results:
- Scenario 1: Differential discount rate of 3.5% for costs and 1.5% for benefits
- Scenario 2: 3.5% discount rate for costs and benefits

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Table 5: Discount rate of 3.5% for costs and 1.5% for benefits

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/unweighted QALY)	ICER (£/Weighted QALY)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	QALYs (weighted)		
Paediatric	Olipudase alfa	[redacted]	[redacted]	24.93	[redacted]	[redacted]	37.38	112.13	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-12.45	[redacted]	[redacted]	-	-		
Adult	Olipudase alfa	[redacted]	[redacted]	16.31	[redacted]	[redacted]	20.62	61.85	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-4.30	[redacted]	[redacted]	-	-		
Combined	Olipudase alfa	[redacted]	[redacted]	20.62	[redacted]	[redacted]	29.00	86.99	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-8.37	[redacted]	[redacted]	–	–		

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

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Table 6: Discount rate of 3.5% for both costs and benefits

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/unweighted QALY)	ICER (£/Weighted QALY)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Weighted QALYs		
Paediatric	Olipudase alfa	[redacted]	[redacted]	18.03	[redacted]	[redacted]	21.47	64.40	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-3.44	[redacted]	[redacted]	–			
Adult	Olipudase alfa	[redacted]	[redacted]	14.81	[redacted]	[redacted]	12.27	36.82	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	2.53	[redacted]	[redacted]	–			
Combined	Olipudase alfa	[redacted]	[redacted]	16.42	[redacted]	[redacted]	16.87	50.61	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-0.45	[redacted]	[redacted]	–	–		

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

EAG key issue #2: Long-term treatment effect

The company would like to provide an additional scenario analysis that addresses the long-term treatment effect in the model.
In the company's revised base case, it is assumed that patients receiving olipudase alfa can only transition to an alternative health state for up to 9 years, after which they all transition to the SV <6 / DL_{CO} >80 state from year 10 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients' probability to transition to the 'SV <6 / DL_{CO} >80' state from the other health states between year 2 and year 10.

In order to test the assumption on long-term efficacy, a scenario analysis is presented where transition probabilities at year 2 are applied each year until the end of the time horizon or death. In other words, patients are no longer all assigned to the 'SV <6 / DL_{CO} >80' state from year 3 onwards. Their probability to reach this state over time is driven by the transition probabilities that applied during year 2 and are assumed to be constant afterwards.

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An additional sensitivity analysis is presented, in which the company's original base case assumption is used, that is, patients receiving olipudase alfa can only transition to an alternative health state for up to 2 years, after which (i.e., from year 3 onwards) they all transition to the SV <6 / DL_{CO} >80 state and remain there until the end of the time horizon or death.

Table 7: Application of year 2 transition probabilities for remainder of the model

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/unweighted QALY)	ICER (£/Weighted QALY)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Weighted QALYs		
Paediatric	Olipudase alfa	[redacted]	[redacted]	22.88	[redacted]	[redacted]	35.33	105.99	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-12.45	[redacted]	[redacted]	–	–		
Adult	Olipudase alfa	[redacted]	[redacted]	14.34	[redacted]	[redacted]	18.65	55.81	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-4.30	[redacted]	[redacted]	–	–		
Combined	Olipudase alfa	[redacted]	[redacted]	18.61	[redacted]	[redacted]	26.99	80.90	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-8.37	[redacted]	[redacted]	–	–		

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

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Table 8: Patients move to SV <6 / DL_{CO} >80 state at 2 years for the reminder of the model

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/unweighted QALY)	ICER (£/Weighted QALY)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Weighted QALYs		
Paediatric	Olipudase alfa	[redacted]	[redacted]	25.09	[redacted]	[redacted]	37.54	112.61	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-12.45	[redacted]	[redacted]	–	–		
Adult	Olipudase alfa	[redacted]	[redacted]	16.55	[redacted]	[redacted]	20.85	62.55	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-4.30	[redacted]	[redacted]	–	–		
Combined	Olipudase alfa	[redacted]	[redacted]	20.82	[redacted]	[redacted]	29.19	87.58	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-8.37	[redacted]	[redacted]	–	–		

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

EAG key issue #3: Utility values

We have provided a scenario analysis to demonstrate the effect on the economic model results if disutility values from another proxy disease area are used.

The health state specific carer disutility values taken from Pompe as a proxy condition were as follows (taken from Simon et al 2019 (28)) and were incorporated into the model for this scenario analysis.

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Table 9: Disutility values taken from Pompe as a proxy condition

	Spleen volume (MN)		
DL_{CO}	**<6**	**6-15**	**>15**
100 – 80	-0.072	-0.162	-0.18
80 – 40	-0.162	-0.162	-0.18
< 40	-0.18	-0.18	-0.18

Abbreviations: MN, multiples of normal.

Table 10: Alternative caregiver utility scores from Pompe

Population	Technologies	Total			Incremental (olipudase alfa vs BSC)				ICER (£/unweighted QALY)	ICER (£/Weighted QALY)
		Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Weighted QALYs		
Paediatric	Olipudase alfa	[redacted]	[redacted]	20.12	[redacted]	[redacted]	33.22	99.66	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-13.10	[redacted]	[redacted]	–	–		
Adult	Olipudase alfa	[redacted]	[redacted]	13.40	[redacted]	[redacted]	18.28	54.07	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-4.88	[redacted]	[redacted]	–	–		
Combined	Olipudase alfa	[redacted]	[redacted]	16.76	[redacted]	[redacted]	25.75	76.87	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	-8.99	[redacted]	[redacted]	–	–		

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

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References

1. Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases. Mol Genet Metab. 2016 Jul;118(3):206-13.

2. Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of Illness in Acid Sphingomyelinase Deficiency: A Retrospective Chart Review of 100 Patients. JIMD Rep. 2018;41:119-29.

3. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis. 2021 May 10;16(1):212.

4. Sanofi Genzyme. ASMD chart review pooled data analysis. Data on file. 2022.

5. Hopkin J, Donnelly C, Poutney J, Crowe J, Mathieson T, Mbua S. Acid sphingomyelinase deficiency: Burden of disease and real-world impact of enzyme replacement therapy on pediatric patients and caregivers. Poster presented at 19th Annual WORLDSymposium. Orlando, Florida, USA. 2023.

6. Sanofi. Clinical Study Report: LTS13632. A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency. Data on file. 2021.

7. Weinreb NJ, Camelo JS, Charrow J, McClain MR, Mistry P, Belmatoug N. Gaucher disease type 1 patients from the ICGG Gaucher Registry sustain initial clinical improvements during twenty years of imiglucerase treatment. Molecular Genetics and Metabolism. 2021 2021/02/01/;132(2):100-11.

8. NICE. HST 11. Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. Available at https://www.nice.org.uk/guidance/hst11/resources/voretigene-neparvovec-for-treating-inherited-retinal-dystrophies-caused-by-rpe65-gene-mutations-pdf-50216253809605. Accessed 25 August 2023.

9. Chen J-Y, Clark M-J. Family Resources and Parental Health in Families of Children With Duchenne Muscular Dystrophy. Journal of Nursing Research. 2010;18(4):239-48.

10. Siden H, Steele R. Charting the Territory: Children and families living with progressive life-threatening conditions. Paediatrics & Child Health. 2015;20(3):139-44.

11. Haukeland YB, Fjermestad KW, Mossige S, Vatne TM. Emotional Experiences Among Siblings of Children With Rare Disorders. Journal of Pediatric Psychology. 2015;40(7):712-20.

12. Dinleyici M, Çarman KB, Özdemir C, Harmancı K, Eren M, Kirel B, et al. Quality-of-life Evaluation of Healthy Siblings of Children with Chronic Illness. Balkan Med J. 2019 Dec 20;37(1):34-42.

13. Velasco J, Ferraris V, Eymann A, Coccia PA, Ghezzi LR, Sánchez MC, et al. Quality of life among siblings of patients with chronic conditions. Arch Argent Pediatr. 2020 Aug;118(4):252-7.

14. Schwartz CE, Stark RB, Audhya IF, Gooch KL. Characterizing the quality-of-life impact of Duchenne muscular dystrophy on caregivers: a case-control investigation. J Patient Rep Outcomes. 2021 Nov 20;5(1):124.

15. Alexion. The impact of RARE disease on sibling experience. Impact report. Available at https://rare-revolution-wp-images.s3.eu-west-1.amazonaws.com/wp-content/uploads/2023/01/20092626/The-impact-on-RARE-disease-on-siblings-1.pdf. Accessed 24 August 2023.

16. Office for National Statistics. Average number of dependent children per family in England and Wales, 2020 and 2021. 2023. Accessed August 2023. Available online at: [https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/adhocs/15662averagenumberofdependentchildrenperfamilyinenglandandwales2020and2021].

17. Al-Gamal E. Quality of life and anticipatory grieving among parents living with a child with cerebral palsy. International Journal of Nursing Practice. 2013;19(3):288-94.

18. Duggleby WD, Williams A, Holstlander L, Thomas R, Cooper D, Hallstrom LK, et al. Hope of rural women caregivers of persons with advanced cancer: guilt, self-efficacy and mental health. Rural Remote Health. 2014;14:2561.

19. Götze H, Brähler E, Gansera L, Schnabel A, Gottschalk-Fleischer A, Köhler N. Anxiety, depression and quality of life in family caregivers of palliative cancer patients during home care and after the patient's death. European Journal of Cancer Care. 2018 2018/03/01;27(2):e12606.

20. Liew TM, Tai BC, Wee SL, Koh GC-H, Yap P. The Longitudinal Effects of Caregiver Grief in Dementia and the Modifying Effects of Social Services: A Prospective Cohort Study. Journal of the American Geriatrics Society. 2020;68(10):2348-53.

21. Moore KJ, Davis S, Gola A, Harrington J, Kupeli N, Vickerstaff V, et al. Experiences of end of life amongst family carers of people with advanced dementia: longitudinal cohort study with mixed methods. BMC Geriatrics. 2017 2017/07/03;17(1):135.

22. Nielsen MK, Christensen KS, Neergaard MA, Bidstrup PE, Guldin M-B. Exploring Functional Impairment in Light of Prolonged Grief Disorder: A Prospective, Population-Based Cohort Study. Frontiers in Psychiatry. 2020 2020-December-09;11.

23. Persson C, Östlund U, Wennman-Larsen A, Wengström Y, Gustavsson P. Health-related quality of life in significant others of patients dying from lung cancer. Palliative Medicine. 2008 2008/04/01;22(3):239-47.

24. Giovannetti AM, Covelli V, Sattin D, Leonardi M. Caregivers of patients with disorder of consciousness: burden, quality of life and social support. Acta Neurologica Scandinavica. 2015;132(4):259-69.

25. Wentzel H, Malottki K. Capturing the Impact of Grief and Bereavement on Caregivers in National Institute for Health and Care Excellence Highly Specialised Technology Appraisals. Poster presentation at ISPOR EU 2022 Vienna. 2022.

26. NICE. HST 7. Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. Available at https://www.nice.org.uk/guidance/hst7. Accessed 26 June 2023. 2018.

27. NICE. Velmanase alfa for treating alpha-mannosidosis [ID800]. .

28. Simon N-J, Richardson J, Ahmad A, Rose A, Wittenberg E, D'Cruz B, et al. Health utilities and parental quality of life effects for three rare conditions tested in newborns. Journal of Patient-Reported Outcomes. 2019 2019/01/22;3(1):4.

29. Diaz GA, Giugliani R, Guffon N, Jones SA, Mengel E, Scarpa M, et al. Long-term safety and clinical outcomes of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency: two-year results. Orphanet J Rare Dis. 2022 Dec 14;17(1):437.

30. Sanofi. Integrated Summary of Immunogenicity (Acid Sphingomyelinase Deficiency), Olipudase Alfa. Data on File. 2021.

31. Sanofi Genzyme. ASMD Chart review pooled data analysis. November 2022. Sanofi data on file. .

32. Sanofi Genzyme. Clinical opinion. March 2023. Sanofi data on file.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

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

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Monday 18th September 2023** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating acid sphingomyelinase deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Robin Lachmann
2. Name of organisation	University College London Hospitals
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acid sphingomyelinase deficiency? ☐ A specialist in the clinical evidence base for acid sphingomyelinase deficiency or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for acid sphingomyelinase deficiency?	To clear sphingomyelin from visceral tissues, improve the clinical features of the disease and stop future progression.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reductions in visceromegaly and improvements in pulmonary gas exchange
10. In your view, is there an unmet need for patients and healthcare professionals in acid sphingomyelinase deficiency?	Yes. No disease modifying therapy is currently available.
11. How is acid sphingomyelinase deficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients should be seen in highly specialised LSD services. Treatment is supportive. There are some recently published consensus clinical guidelines (Orphanet J Rare Dis. 2023 Apr 17;18(1):85). Olipudase alfa would transform the life of patients with non-neuronopathic ASMD in terms of both quality of life and survival.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology would be use as other enzyme replacement therapies for lysosomal storage disorders. The need for dose escalation might mean that patients would have to receive their infusions in a hospital setting for longer, but I think with experience it would be possible to move much of this phase of care to homecare for many adult patients. In the long-term, infusions would be provided at home.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Olipudase alfa will have dramatic effects on quality of life and survival.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology will have less effect for those with neuronopathic disease. However, for these patients the visceral disease is still a significant cause of morbidity which would respond to treatment with olipudase.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology requires fortnightly intravenous infusions. Similar therapies have proven to be acceptable to patients. We have a well established homecare system for delivering enzyme replacement therapies in the UK and olipudase alfa would be added to that framework.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that the HSS LSD services would be asked to develop rules for starting and stopping treatment. These would be based on clinical features of the disease which are routinely measured anyway. It might be useful for laboratories to offer testing for lyso-sphingomyelin, a biomarker of disease. However, as it is easy to monitor response clinically and with routine investigations this would not be essential.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This is a transformational treatment. Our experience is that many ASMD patients do not realise how their quality of life is affected by their disease until they have been treated. Symptoms which they regarded as normal (limited exercise capacity, pain, fatigue) disappear with treatment and they develop a

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	new understanding of what 'normal' life is. I do not think QALY calculations can fully capture this.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Until now there has been no disease modifying treatment available for ASMD and treatment has essentially be palliative. With olipudase alfa we can now not only prevent progression of visceral ASMD, we can reverse all the clinical features of the disease.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Olipudase alfa has been safe and well tolerated. Infusion related reactions have been easy to manage and self limiting.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials do reflect current UK practice. From the point of view of patient mortality, the effects on liver and lung disease are the most important. We now have almost 10 years experience from the firt patients treated in the phase 1 studies and they continue to show improvements in spleen volume with normalisation of many other parameters including liver volume and pulmonary gas exchange. In adult patients there have been no emergent adverse effects.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I don't think the trials capture the effect the treatment has on patients everyday lives. It would be important to get the experience of patients who have received olipudase alfa.

23. How do data on real-world experience compare with the trial data?	We have not been able to use olipudase alfa outside of clinical trials in the UK
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	The NHS should be able to offer all affected patients access to the treatment.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case • *Is olipudase alfa expected to restore people with acid sphingomyelinase deficiency to full or near-full health?*	Yes, olipudase alfa can restore ASMD patients to full health. The only proviso to this is that if disease is advanced, with organ fibrosis, at the time treatment starts, that can not be reversed by treatment and patients may be left with some residual impairment.
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data. • *Would olipudase alfa's treatment effect be expected to wane over time?*	The patients in the phase 1b study have now been treated for almost 10 years and there is no evidence of any decline in treatment effect.

EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL • *How does acid sphingomyelinase deficiency affect the quality of life of carers?* • *On average, how many carers would you expect for a) adults and b) children with acid sphingomyelinase deficiency?*	I can only comment on adults. This is a slowly progressive disease and adult patients are mostly able to function independently until the very late stages of the disease.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality • *Would you expect disease-specific mortality to be apparent in paediatric population?* • *Are clinical experts aware of any credible mortality data for acid sphingomyelinase deficiency?*	ASMD undoubtedly causes death in children and adults as per the below reference: Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, Imrie J, Mabe P, Takahashi T, Mengel KE, Giugliani R, Cox GF. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases. Mol Genet Metab. 2016 Jul;118(3):206-213. doi: 10.1016/j.ymgme.2016.05.001
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	ASMD causes growth restriction I children, but they do show catch up growth and in my experience adults have a similar weight distribution to the general public.

• *Would you expect the average weight of the population with acid sphingomyelinase deficiency (both adults and paediatrics) to differ from that of the general public? If so, how?*	
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations • *Would you expect response to olipudase alfa to vary by severity of acid sphingomyelinase deficiency?* • *How many people have severe disease in clinical practice and how are these people identified?*	Patients with ASMD show a response to olipudase alfa across the spectrum of disease with clearance of sphingomyelin form then liver and lungs. However, advanced disease is characterised by fibrosis (cirrhosis of the liver and pulmonary fibrosis) and this is not amenable to enzyme replacement therapy. These patients do however still show remarkable clinical benefit from therapy, and personal experience suggest that organ fibrosis does not progress once storage is cleared. As no disease modifying therapy has been available to date, there are currently some patients in our population who have advanced disease. If olipudase alfa were to be made available, then we would no longer expect to se ASMD patients progress to this point of the disease.
Are there any important issues that have been missed in EAR?	I have not seen the EAR so can't comment on this

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

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

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with acid sphingomyelinase deficiency or caring for a patient with acid sphingomyelinase deficiency. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 29 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Living with this condition or caring for a patient with acid sphingomyelinase deficiency

Table 1 About you, acid sphingomyelinase deficiency, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with acid sphingomyelinase deficiency? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with acid sphingomyelinase deficiency? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Niemann-Pick UK (NPUK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with acid sphingomyelinase deficiency? **If you are a carer (for someone with acid sphingomyelinase deficiency) please share your experience of caring for them**	I have held the position of CEO for Niemann-Pick UK (NPUK) since 2005 and have gained experience of providing the patient perspective in over 20 years as a patient advocate, and as the mother of three children affected by Niemann-Pick type C disease. Since my earliest interactions with the ASMD community, I have come to understand the impact of this progressive and life-limiting disease which significantly reduces life expectancy. Representing the views of our patient community is a huge responsibility and one that I take very seriously. Patients and their family members know what is most important to them and what change will have the most impact on their daily lives. I take every opportunity to meet and talk with patients and their families, and I recognise their valuable contribution in shaping the services we provide at NPUK. The following statement is based on my experience, my interactions with ASMD patients and their families and the patient experience data gathered by NPUK throughout the year.
7a. What do you think of the current treatments and care available for acid sphingomyelinase deficiency) on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	One patient explained: “I was diagnosed when I was three years old, and from an early age I knew that I was different, that I was special. Unlike the other kids I was always going into hospital for tests. I had to have blood tests, flu jabs, x-rays, overnight stays at the hospital for monitoring. But the biggest hint was my large tummy that was noticeable from being a toddler.”

	Multiple medical appointments and screening tests often limit a patient and carers ability to go about their daily lives, with time away from school or work impacting on their ability to achieve educational goals or financial stability. In addition, appointments with expert clinicians are limited, usually twice per year, and patients and carers report much lower levels of satisfaction with locally based care. This is related to a lack of knowledge and understanding of their condition, the progressive nature of symptoms and their inability to access suitable symptomatic treatments, supportive aids and/or adaptations in a timely manner. Despite this, patients and their carers report high levels of satisfaction with the care they receive from specialist centres feeling confident and supported by their clinical teams' knowledge and expertise in this rare condition. This confidence is not often shared in relation to care in local centres, which can be challenging due to the rare nature and limited knowledge / experience of treating of ASMD. A caregiver reported: "Bruising was very noticeable at a very early stage, I dreaded putting our son in short trousers as he looked as though he had been beaten, his legs and arms pickled with bruises from normal play, On one occasion after surgery to remove a cyst from his cheek, on returning to the hospital to have his stitches removed, he was whisked off and my husband and I questioned, as they really could not believe that the amount of bruising he had on his face was a result of the surgery, eventually a call to our specialist consultant confirmed that bruising due to low platelets does take place. The nosebleeds happened a lot later, probably when he was 13, alarming at first but we all soon learnt how to cope with them, he had his nose cauterised a couple of times, again though this was due to his low platelets, as a side effect of his enlarged spleen" My reported view on current treatments aligns with the thoughts and experiences of our patient and caregiver community and is reflected within patient experience surveys and case studies collected over many years.

8. If there are disadvantages for patients of current NHS treatments for acid sphingomyelinase deficiency) (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Patients and carers report dissatisfaction with their diagnostic journey, which in some cases is stretched over many years, leading to delays in accessing expert care, practical support, and symptomatic treatments, as well as impacting family planning decisions. Most patients in England receive care at one of the eight designated NHS Specialist Centres providing Highly Specialised Services for patients affected by Lysosomal Storage Disorders. Patients and carers report difficulties in travelling to specialist centres, which are often located far from their home. This is especially so when the disease is more progressed and their burden of disease greater, or when there are family and/or financial constraints. Despite this, patients and their carers report high levels of satisfaction with the care they receive, feeling confident and supported by their clinical teams' knowledge and expertise in this rare condition. However, there are currently no treatment options for ASMD except supportive care. Best supportive care is complex and costly, due to the progressive and multisystemic nature of ASMD and involvement of many different specialities. Treatments, involve symptomatic relief of the disease, including pain relief for musculoskeletal pain, the management of the complications of the disease, (e.g., blood transfusion following bleeding episodes, significantly elevated cholesterol levels and the consequential cardiovascular disease, dietary /digestive aids and invasive surgeries). For patients, this means years of frequent and multiple medical appointments, with regular monitoring and often invasive tests through involving several different clinical teams, including Cardio/respiratory, Endocrinology, Haematology, Hepatology, Physiotherapy, Dietetics. With these clinical teams often located in different locations around the country, the coordination of these appointments can be challenging. In addition, appointments with highly specialised teams are limited, usually twice per year, and patients and carers report much lower levels of satisfaction with locally based GP and hospital care.

	This is related to a lack of knowledge and understanding of their condition, the progressive nature of symptoms and their inability to access suitable symptomatic treatments, supportive aids and/or adaptations in a timely manner.
9a. If there are advantages of olipudase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does olipudase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Following treatment with olipudase alfa, families and carers observed life-changing effects, reporting that their child was no longer exhausted, could attend school for a full day (and parents could resume work), eat normal size meals, walk greater distances without breathlessness and have the energy to enjoy social activities. Furthermore, they could expect to have a far greater life expectancy, with less dependence on healthcare and clinical interventions. Most importantly in my experience of supporting treated patients (ten plus years'), I have observed that treatment with olipudase alfa is transformative and can, over time, reverse (not just stabilise or improve) the effects of ASMD, significantly improving patient and carers' lives and enabling patients to reach and maintain full or near-full health for an extended period of time. Without treatment, parents and carers report feelings of anxiety, stress and depression, linked to their thoughts about keeping their child safe, their health, guilt and feelings of being 'at fault' (for passing on a genetic disease, not spending enough time with siblings, their child's quality of life, what their child is missing out on). Anxieties are exacerbated by constant fatigue and isolation associated with being a caregiver. In addition, sadness that their child was not able to do what they wanted to do and extreme stress in not knowing how the disease would progress, whilst knowing that the outcome was death if it was left untreated. Parents and carers also reported impacts on their work and social life, with many having to give up work entirely or go part time, to care for their child and attend medical appointments, often with severe consequences on family finances. "We questioned and felt a lot of guilt - did we do the right thing to have kids? Should we have done more genetic testing? Were we selfish to think that we didn't have these mutated genes in our cells? There was a lot of stress for us as parents just

	knowing that we brought kids into this world who were going to have an uphill battle." "It is heart-breaking to watch your child go through everything. Really, it puts a lot of stress on us as parents, but also me and my husband's relationship, and it affects all aspects of our lives. Before his infusions and stuff, he required so much care." "You wake up thinking about it. That takes over your life, how am I going to normalize my child's life? How is she going to be able to live normal and not be constantly sick and in the hospital?" "There were times when my wife would go in her bedroom and cry." Sibling speakers at the NPUK Family Conference spoke with great emotion about how they felt growing up - with feelings of guilt (not being affected, not having health issues), how they felt left out, isolated, not knowing what was going on, how they could at times be resentful of the attention that their affected sibling was receiving and their embarrassment when friends came to their homes. They talked of becoming 'young carers' and how they experienced a range of practical, emotional and psychological issues, leading to problems at school, social isolation, feeling neglected and being bullied. They also talked of anxiety for their affected sibling, not feeling able to talk to their parents and worrying about death and dying and what will happen to their sibling as ASMD progresses.
10. If there are disadvantages of olipudase alfa over current treatments on the NHS please describe these. For example, are there any risks with olipudase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	In a recent global survey, "The impacts of olipudase alfa on paediatric patients with ASMD and their families" disadvantages mentioned by patients and families included the treatment not crossing the blood-brain barrier, missing school or work to receive treatment, and the demands and challenges of the clinical trial. All those participating in the survey and those consulted outside of the survey reported that the benefits of the treatment against best supportive care outweighed the risks and disadvantages of olipudase alfa, with most saying: • There were no adverse impacts - benefits outweigh the risks • Side effects were minor issues compared to the effects of ASMD

	• Any concerns about the treatment were addressed by the clinician and vanished once results were apparent • Patients and families adapted easily to the two weekly infusions, at home or in clinic, with homecare the preferred option
11. Are there any groups of patients who might benefit more from olipudase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Clinical data is very strong and published evidence shows clearance of storage and reversal of disease. As it is currently not possible to accurately identify where a patient sits on the spectrum of ASMD disease, outside of very small numbers of classical type A homozygous mutations, treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment. I do not agree with the EAG's assumption that the target population for olipudase alfa would be clearly recognisable to clinicians. In my understanding, it is not easy to determine the clinical distinctions of disease type A/B / disease type B early in the disease course. These distinctions often can't be determined for years, even by the world's experts. The only group that may declare itself in the first year 16 months of life is the most severe cases acute neurovisceral or classical type A mentioned above. In addition, and in relation to the EAG's question regarding clarification that trials of olipudase alfa included participants with ASMD type A/B – I am aware of two paediatric patients with type A/B who were included in the clinical trial, and who have experienced increased physical and mental health benefits. Working in partnership with the National Niemann-Pick Disease Foundation (USA) and the International Niemann-Pick Disease Registry, NPUK commissioned a survey "The impacts of olipudase alfa on paediatric patients with ASMD and their families" to highlight the patient experience and perspective regarding the burden of disease, burden of therapy, benefits of therapy, risks, and tolerance of risk. Four of the patients surveyed had neurological symptoms associated with type A/B. NPUK has provided a copy of the survey report as part of their submission. Phase two of this survey "The impacts of olipudase alfa on adult ASMD patients and their families" has recently been completed. Preliminary results were presented at

	the National Niemann-Pick Disease Foundation (USA) annual conference in July 2023, a copy of this presentation is provided as an appendix to this form.
12. Are there any potential equality issues that should be taken into account when considering acid sphingomyelinase deficiency) and olipudase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	All ASMD patients are disadvantaged by the severe and progressive nature of this condition, and the complex and diverse symptoms and multi-system impacts that prevent them living full lives.
13. Are there any other issues that you would like the committee to consider?	The impact of this technology goes beyond direct health benefits for patients and the cost saving for health systems and includes societal economic benefits such as maintenance of earning potential for the patient and carers. Early diagnosis and treatment for patients with clinically detectable disease will prevent significant and irreversible burden of disease, reduce comorbidity and mortality. The introduction of this technology requires no new specialised equipment or services, IV infusions can be managed in existing clinical centres through current service specifications, or preferably by a home-based infusion service or if appropriate, self-infusion.

	Whilst this technology may be viewed as a 'high-cost treatment' there will be a significant and long-term downstream reduction in healthcare and societal costs over the lifetime of a treated patient. The cost of not treating – patients receiving only best supportive care / symptomatic management, i.e., antibiotics and hospitalisations for respiratory infections, home oxygen needs, medications and treatments to manage bleeding or low platelets, liver transplants, medications to address high cholesterol, portal hypertension and other consequences of a chronic condition - will be much greater. The development of this technology has benefitted from 20plus years of investment from the patient community, including surveys, PROMs, natural history studies, an invasive and burdensome trial protocol – nevertheless, patients and their families have been actively engaged, as this presents the only potential option for patients and evidence shows it can make a huge difference to their quality of life with long term implications. It is important to state the small numbers of patients affected by ASMD and therefore potentially eligible for treatment. In our experience over 30+ years of working with the ASMD community, the number of patients supported in any given year has not exceeded 40. It must be noted that this is a life-limiting and life-shortening disease, and that patients don't have a normal lifespan, and that there will be some who have milder disease and therefore have not yet been diagnosed or may have been misdiagnosed. NPUK currently support 37 ASMD patients 34 with ASMD Niemann-Pick disease type B (16 Children, 18 Adults) and 3 with ASMD Niemann-Pick disease type A. For newly diagnosed patients, genetic counselling should be provided prior to and following diagnosis to assist patient and family understanding and enable informed decisions regarding treatment and family planning, including carrier status and potential impact on future offspring and siblings. This should be included within the service provision and provided in a timely manner. Currently there is no routine screening for ASMD as part of the UK's newborn screening programme. Whilst we understand the Committee or any decision they

	make will not influence or change this, it must be noted that to enable the full benefit of this treatment, inclusion in the NBS programme is highly recommended. In addition, I would ask the Committee to give appropriate and careful consideration to the management of patients currently receiving olipudase alfa post-trial and in any period leading up to and post their decision-making process, to avoid additional and unnecessary anxiety and stress.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case	Based on my long-term experience of supporting ASMD patients and their families, and in consideration of the variable nature and severe impact of this progressive, life-limiting and significantly debilitating condition, I believe that ASMD causes severe impairment. Whilst the lack of data on long-term effectiveness is acknowledged, my experience of supporting treated patients (ten plus years') has shown that olipudase alfa is transformative and can, over time, reverse (not just stabilise or improve) the effects of ASMD, with expert clinical opinion and published evidence supporting our view. With treatment, health is significantly improved and continues to improve, enabling patients to reach and maintain full or near-full health for an extended period of time.
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	Once again, the lack of long-term treatment effectiveness data is acknowledged, however, the clinical advice to the EAG seems to ignore published evidence and expert clinical opinion (it must be noted that the availability of clinical expertise and clinical experience in treating ASMD patients.is severely limited). There is published evidence including data showing sustained benefit and

	continuing improvement following treatment of 6.5 years+ including to liver and lung function, and greatly reduced spleen size and continued improvements to health with long term use: *Lachmann RH, Diaz GA, Wasserstein MP, Armstrong NM, Yarramaneni A, Kim Y, Kumar M. Olipudase alfa enzyme replacement therapy for acid sphingomyelinase deficiency (ASMD): sustained improvements in clinical outcomes after 6.5 years of treatment in adults. Orphanet J Rare Dis. 2023 Apr 25;18(1):94. doi: 10.1186/s13023-023-02700-x. PMID: 37098529; PMCID: PMC10131350.* Whilst longer term, robust data may not be available for many years, patient experience reported to us over a ten-year period speaks volumes and provides meaningful evidence of significant benefit, with severely impacted children and adults now in near or near-full health, able to fully function, live independently, attend and achieve in education or work, and have the energy to participate in social activities.
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL • *How does acid sphingomyelinase deficiency affect the quality of life of carers?* • *On average, how many people are involved in caring for someone with acid sphingomyelinase deficiency? Does this differ by age?* • *Would you expect carer quality of life to improve in people whose disease responded to treatment? If so, how?*	I support the EAG view in regard to the application of carer disutility regardless of treatment arm. I agree that carer disutility is greater for patients in more severe health states, and whilst this will still apply following treatment, we can expect it to be less marked over time. I understand and acknowledge the issues in collecting carer disutility data in ASMD. Whilst I agree that Pompe disease is not a good comparison with ASMD, I disagree that Pompe disease has an overall greater carer burden. ASMD has very different symptoms and challenges, with patients having variable abilities and disabilities, some requiring constant support into adulthood with significant carer burden. Whilst the assumption of 1.78 carers for children could be reduced slightly, I strongly feel it should be above the EAG proposed number of 1 As symptoms are variable and severe, and dependent on disease progression, carer involvement is necessary and can be all-consuming, and emotionally exhausting, considering the frequent and multiple medical appointments, regular monitoring and several different clinical teams, often located in different locations plus the challenges of coordinating appointments at any age / point of progression. Add to this assistance with self-care, including personal care, help to prepare meals and eat, assistance with mobility and daily tasks, which applies to both child and adult patients. I feel 1.5 carers for children and adults would be more appropriate.

Patient expert statement

	Whilst I agree in part with the EAG view on carer disutility associated with patient death, I do not believe that this should be dismissed completely. Undoubtedly, the death of a patient has an impact for a significant period, with carer disutility reducing over time.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	ASMD is a spectrum of disease, with variable presentation and progression. Whilst most ASMD patients are diagnosed in childhood, and experience increasingly severe health issues, there are those (usually (A/B) that experience severe issues and pass away in childhood.
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	ASMD patients are most often under normal weight and shorter in stature than their peers. With treatment, we have seen the normalisation of height and weight over time.
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations	I am not aware of an agreed international classification of severe disease, and I would like to stress that ASMD is multi-systemic and severely life limiting. The inclusion criteria for both the paediatric and adult trials excluded the most ill patients in the patient community, so the severe "subgroups" in the study are actually now healthier than many of the patients in the community. Patients describe reaching a point 'of no return' in their disease progression, where the disease 'creeps up' without early indicators, explaining that they often don't realise how clinically unwell they are, as feeling unwell is their 'normal'. To further assist the EAG with their questions regarding the reliability of mortality data, another source that provides a different approach, looking at causes of death rather than incidence, may be helpful:

	David Cassiman, Seymour Packman, Bruno Bembi, Hadhami Ben Turkia, Moeenaldeen Al-Sayed, Manuel Schiff, Jackie Imrie, Paulina Mabe, Tsutomu Takahashi, Karl Eugen Mengel, Roberto Giugliani, Gerald F. Cox, Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases, Molecular Genetics and Metabolism, Volume 118, Issue 3, 2016, Pages 206-213, ISSN 1096-7192. Olipudase alfa not only appears to halt progression but reverses many aspects of this debilitating and life limiting disease. With evidence that treatment benefits can overcome disease severity and, in some cases, reverse disease impact, we would expect to see the health of treated children continue to improve, to the extent that symptoms in adulthood are significantly or fully reduced. Based on my experience of working with the patient community, it is my understanding that the benefits of treatment for patients with severe disease are significant and may increase over time. Clinical data is very strong and shows clearance of storage and reversal of disease. As it is currently not possible to accurately identify where a patient sits on the spectrum of ASMD disease, outside of very small numbers of classical type A homozygous mutations, I believe that treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment.
Are there any important issues that have been missed in EAR?	Improvements to lung and liver function and the reduction in spleen size following treatment with olipudase alfa have a total body effect and bring multiple benefits for patients, which cannot be overstated. Considering only the statistics of DLCO and spleen volume does not accurately convey the reduction of disease burden and real-life impacts experienced and reported by patients and their carers..

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Monday 21 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Technical engagement response form

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

NICE National Institute for Health and Care Excellence

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

Your name	Toni Mathieson
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Niemann-Pick UK (NPUK)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

About you

Table 1 About you

NICE National Institute for Health and Care Excellence

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case	Yes/No	Whilst we note this issue is resolved, we provide the following comments. Based on our long-term experience of supporting ASMD patients and their families, we understand the variable nature and severe impact of this progressive, life-limiting and significantly debilitating condition. In our opinion, ASMD causes severe impairment. Whilst we acknowledge the lack of data on long-term effectiveness, our experience of supporting treated patients (ten plus years') has shown that olipudase alfa is transformative and can, over time, reverse (not just stabilise or improve) the effects of ASMD, with expert clinical opinion and published evidence supporting our view. With treatment, health is significantly improved and continues to improve, enabling patients to reach and maintain full or near-full health for an extended period of time.
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	Yes/No	Once again, we acknowledge the lack of long-term treatment effectiveness data, but highlight the limited availability of clinical expertise and clinical experience in treating ASMD patients. Therefore, we question the clinical advice to the EAG, which we feel ignores published evidence and expert clinical opinion. This

		includes data showing improved or normalised liver and lung function, greatly reduced spleen size and continued improvements to health with long term use. Whilst longer term, robust data may not be available for many years, patient experience reported to us over a ten-year period speaks volumes and provides meaningful evidence of significant benefit, with severely impacted children and adults now in near or near-full health, able to fully function, live independently, attend and achieve in education or work, and have the energy to participate in social activities.
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL	Yes/No	We support the EAG view in regard to the application of carer disutility regardless of treatment arm. We agree that carer disutility is greater for patients in more severe health states, and whilst this will still apply following treatment, we can expect it to be less marked over time. We understand and acknowledge the issues in collecting carer disutility data in ASMD. Whilst we agree with the clinical advice provided to the EAG, that Pompe disease is not a good comparison with ASMD, we disagree that Pompe disease has an overall greater carer burden. ASMD has very different symptoms and challenges, with patients having variable abilities and disabilities, some requiring constant support into adulthood with significant carer burden. We believe that the assumption of 1.78 carers for children could be reduced slightly, however, we strongly feel it should be above the EAG proposed number of 1. As symptoms are variable and severe, and dependent on disease progression, carer involvement is necessary and can be all-consuming, considering the frequent and multiple medical appointments, regular monitoring and several different clinical teams, often located in different locations plus the challenges of coordinating appointments at any age / point of progression. Whilst we agree in part with the EAG view on carer disutility associated with patient death, we do not believe that this should be dismissed completely.

		Undoubtedly, the death of a patient has an impact for a significant period, with carer disutility reducing over time.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	Yes/No	ASMD is a spectrum of disease, with variable presentation and progression. Whilst most ASMD patients are diagnosed in childhood, and experience increasingly severe health issues, there are those (usually (A/B) that experience severe issues and pass away in childhood.
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	Yes/No	ASMD patients are most often under normal weight and shorter in stature than their peers. With treatment, we have seen the normalisation of height and weight over time.
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations	Yes/No	As we are not aware of an agreed international classification of severe disease, we would like to stress that ASMD is multi-systemic and severely life limiting. Patients describe reaching a point 'of no return' in their disease progression, where the disease 'creeps up' without early indicators, explaining that they often don't realise how clinically unwell they are, as feeling unwell is their 'normal'. Olipudase alfa not only appears to halt progression but reverses many aspects of this debilitating and life limiting disease. With evidence that treatment benefits can overcome disease severity and, in some cases, reverse disease impact, we would expect to see the health of treated children continue to improve, to the extent that symptoms in adulthood are significantly or fully reduced.

		Based on our experience of working with the patient community, it is our understanding that the benefits of treatment for patients with severe disease are significant and may increase over time. Clinical data is very strong and shows clearance of storage and reversal of disease. As it is currently not possible to accurately identify where a patient sits on the spectrum of ASMD disease, outside of very small numbers of classical type A homozygous mutations, we believe that treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

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

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with acid sphingomyelinase deficiency or caring for a patient with acid sphingomyelinase deficiency. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Tuesday 29 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Living with this condition or caring for a patient with acid sphingomyelinase deficiency

Table 1 About you, acid sphingomyelinase deficiency, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with acid sphingomyelinase deficiency? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with acid sphingomyelinase deficiency? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	NPUK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with acid sphingomyelinase deficiency? **If you are a carer (for someone with acid sphingomyelinase deficiency) please share your experience of caring for them**	At 3yrs our son was hospitalised from a severe tonsillitis infection. He was found to have a very enlarged liver and spleen which eventually led to his diagnosis of ASMD. The genetic counselling (whilst we were still trying to cope with the diagnosis and so much unknown about how ill he would be, with no cure nor treatment) resulted in us deciding not to have another child. There was a 1 in 4 chance of having an affected baby and I would not have terminated a pregnancy – I felt it would have been like choosing not to have our son. Following diagnosis, I totally withdrew from my friends and family and found it difficult to function. My husband threw himself into his work. Over the following year, our son had frequent infections, fits (fits only until 7years), hospitalisation, and difficulties eating. I had a very successful and well-paid career, which I clearly could no longer commit to. So, I gave it up when he was 4yrs, to work in the showroom for my husband's small business. That allowed me to be flexible to stay in hospital and be home whenever needed. At that time, I couldn't and didn't consider the big loss in income and loss of a career I had built and enjoyed. Retrospectively though, it was the right decision, as his infections and neutropenia meant that he missed a lot of school and was in hospital a great deal (with me) often 3-14 days, and sometimes 4 times a year. Up to the age of 15yrs old, he had over 25 emergency (unscheduled) hospital admissions to the children's ward, often needing IV antibiotics (needing a stay of at least 3 days) for febrile neutropenia. We were trying to give him as normal life as possible, but it was obvious that visiting crowded places indoors (e.g., cinemas in the winter and seeing family over Christmas), was causing the infections and the resulting hospitalisation. To avoid being admitted to hospital (due to the febrile neutropenia protocol), we never flew abroad and avoided UK holidays where we would

	mix with other children (every holiday he would catch something and end up in a hospital). He would miss school if there was an obvious infection going round the class and not play with peers if their siblings were ill. He was put on prophylactic antibiotics in the winter months and always had lots of mouth ulcers. The severely enlarged spleen also caused low platelets. Through primary school he was covered in bruises and took ages to heal, and the school was always calling me. A knock into him, during play with a friend (not roughly), caused a bleed on his liver. Following this, he became very scared of being knocked in the abdomen. The 'no contact sports' rule (due to his enlarged spleen and liver) had already been very isolating as dodgeball, football and kick-post were the playground games. Following this incident, the school reported that he would isolate himself; "*back into corners"*, *"cover his hands over his belly"* and be "*scared of the more boisterous, unpredictable children"*. He would constantly *"assess risk"* and developed "*tactics like going to the toilet or hiding under the table so he could avoid playground breaks unnoticed"*. We were so worried about this anxiety, but also because he was becoming isolated due to his slow physical development and very tiny size (0.4-2nd centile growth). He became very self-conscious and embarrassed of not being able to reach his feet (I would put his shoes and socks on, wash his feet), not wear normal trousers, not play normal games, couldn't even reach the primary school urinal so would wet himself if the cubicles were full (the Head had a new low one put in especially). Aged 5yrs onwards, we also had to manage; bowel problems (pain, constipation, diarrhoea), eating difficulties (little and often - always feeling weak, sick and full), fatigue (unable to do any after school activities), breathlessness, Vit D and iron deficiency, shin pain (he would drop down and clutch them during a walk), dropped inwards ankles, hamstring and joint pain (advised no anti-inflammatory medication because of his liver), headaches, swelling and burning of hands and feet (which *"really annoyed"* him and interrupted sleep and lessons), discomfort in abdomen (cramps, tenderness, uncomfortable in bed).

	We managed all the clinical appointments as positively as we could for our son. There were usually 8-12 a yr, in 4 different hospitals, including; metabolic, heart, respiratory, liver, gastroenterology, haematology, dietician, physio and the local paediatrician (whose ward we had open-access to for neutropenia). In addition, there were scans (dexa, MRI, CT, Ultrasounds), heart monitors and respiratory and blood tests. On top of that, there was the rushing into hospital with fever admissions and day to day challenges at school. He loved to draw, loved cars, play table tennis, bowls with old people and badminton. Our focus was to make his life as fun as it could be. However, we were finding it very difficult to cope with the emotional stress of his illness during primary school. My husband would say that every time I called him, he would have a sinking feeling and think *"what now?"*. We would solve one challenge then be confronted with the next. We found it so difficult coping with a progressive illness that started from 'normal'. Not just the frustration he had - in not keeping up with peers or being able to do what he used to do. But also, understanding and managing his symptoms. For example, we thought he was a fussy eater so we were always trying to get him to eat when he just couldn't. Also, fatigue was so hard to manage – he would go downhill so rapidly if he didn't eat often enough or over did it (which he did because he wouldn't accept what he couldn't do). This slowly got worse, and each stage crept up on us. I felt confused about how best to manage him and hadn't realised how the disease was progressing until I looked back months later. This made me feel guilty and that I was failing him by not realising. I had pains in my chest that wouldn't go away, panic attacks and whenever I was alone in the car I'd cry. We had attended the annual NPUK conference since diagnosis for education and support. There, I had spoken to other older ASMD patients who described very negative experiences at school, so I fought for a named Senior school on his EHCP (age 11). This was a very small school, in the next road to home, had nurses on site and he'd have a one to one in small classes. This was private so had to be funded by the council. I did this because the local state school was further from home (he would need an ambulance if febrile, as I couldn't get there in time for the protocol), and their risk assessment of his enlarged spleen and liver meant they would be constantly removing him from the

	other children and offering poor access to the curriculum when ill or fatigued. This was a stressful process, as at the same time his disease was progressing, and he was always exhausted. I knew he would need to be at school near home to rest in the day if needed. He couldn't carry his bag any more due to back pain or eat enough calories (was feeling too full and sick all the time), had to rush to the toilet 3 or 4 times a day (would need to be very close or would have an accident), headaches, dizzy and faint with fatigue after walking. I would have home-schooled him, but he was absolutely determined to go to school. He was always trying to be seen as 'normal' even though he was so tiny in comparison to his developing pubescent peers (he was half the size of some). He had to run to keep up with their walking and was unable to join in with their activities because of fatigue, no muscle development and bone pain, as well as the severely enlarged spleen and liver. At that time, he loved lessons, as then he felt a bit normal, sitting down and working the same as them. By 14-16yrs it was very sad because his fatigue meant he had no real 'out-of-school' life as when home, he was just recovering from the effort of school. There was no sign of puberty or growth, whilst his friends were changing; going out, interested in girls, summer jobs, etc. I would often have to feed him on the sofa and help him to function really (like he would be too tired to wash). Fatigue was also affecting his academic work which upset him as he was so determined. He had previously been in top sets but was really struggling with his immediate memory, *"1st centile for recall - working memory"*. This was assessed by a neurologist and Education psychologist and found to be due to *"severe fatigue"*. He was spending more time off school at home resting which also made him more isolated from the other children. At this point, the pressure on us as a family felt much worse. I was struggling to ever do any work, get him to all the appointments, as well as care for him daily. He was waking up exhausted every day, with a list of things that hurt, and anxieties about school and peers. I constantly felt worried and tense. By 16, his bowel difficulties, feeling sick and hunger were often stopping him leaving the house until the afternoon, but then bone pain and fatigue would limit his activity. When he went out, he would walk with his camera as he loved photography. But a walk on one day would mean he'd be exhausted on the sofa the next, with hardly the energy to eat, which he needed to do

	little and often or he would get worse. This was a difficult cycle for me to manage. He had become even more dependent on me and panicked if I left him if we were somewhere he didn't know well. In hospital I couldn't go to the toilet without him wanting to come and drag his IV pump with him. Another source of stress was talking to professionals like councils and DWP. Trying to explain ASMD and his needs/symptoms to non-medical strangers was time consuming, emotionally draining and rarely successful. I think this was because their interpretation of *'fatigue'*, '*hunger'* and *'feeling sick'* was nothing like the severe, life-affecting symptoms that he was experiencing. We kept positive when with him, but as parents, found coping with his illness, anxiety and the obvious degradation (lung function was now 49%) stressful and very lonely. The time caring meant we didn't really have a social life and didn't have a support network either (my Mum and Dad got so distressed so I stopped telling them things, and extended family and friends couldn't really understand and had naturally moved on with their busy lives). I developed auto-immune health problems: Psoriasis patches, Lichen Planus and Atrophic Gastritis. Ironically, Covid came as the break we needed. Our son was shielded – which he said didn't feel much different to his normal winter months really. School closed, his GCSEs were cancelled, and we closed our business temporarily to protect him. He wasn't pushing himself in the same way and could manage his bowels (as always at home), slept and rested more. People said they could *"relate to your life better, having been through lockdowns".* We spent Covid and the next years (16-18yrs) with him studying only at home on photography and art A-levels. He contributed ideas, art and a voice to *'Invisible Manners'* a 5min animation by NPUK (https://www.youtube.com/watch?v=A1QmA_HK7e4) which showed the difficulties of having ASMD. This inspired him to apply to Norwich Arts University (as had always been his ambition) to study animation. His photography work got him an unconditional place. Determined to attend Uni and start getting back into the world, he asked a local business for a job, sitting serving ice-cream. However, he couldn't keep up. It was horrible to see that he had

	forgotten how limited he was by fatigue, after being at home all the time during and after Covid. Frustrated, he wrote to the company with a mind map of his symptoms asking to be considered for compassionate use of Olipudase Alfa. They were not able to consider his letter, as his consultant had to apply with clinical data only. However, I attach the mind map as an appendix, as it shows a useful snapshot of his symptoms and quality of life issues at 18yrs. His consultant encouraged him to do the Uni foundation year 0, even if not to the best of his ability, to occupy him whilst waiting to hear back from the compassionate use program. He worked at home and attended short lectures. He was offered DSA paid taxi trips, but declined, as he was too anxious about toilet accidents to go in a taxi. So, I drove him to the Uni door and back around his bowel movements and waited for him in Norwich. It was really hard to manage his health, as after a day out, he'd need a rest day. It was stimulating for him to have creative projects to work on in the afternoons when he was able, and meet people his own age, if only in the classroom. I was exhausted, struggling to get up in the morning, laying there thinking about future disease progression if we didn't get compassionate use. Would he be able to continue Uni, need oxygen, a liver transplant? I knew this was a possible outcome and it haunted me that a young lady I had met with ASMD had sadly passed away at just 21 from liver disease. This was very unlike me to allow these thoughts in. I tried to shake it off for my husband's sake, as his attitude was, *"we've just got to get on with it".* At 19 years old, he met the clinical criteria for compassionate use, with Hepatosplenomegaly, Interstitial lung disease, Osteoporosis, Neutropenia and all the symptoms I have described. Before it sunk in, the first thing he said was, *"So if I get hit, I won't die now."* I asked him why he said that, and he explained that it was because he had been told by the consultant that the enlarged spleen should be protected and couldn't be fully removed, as without it, storage would increase in the other organs like the lungs. Next was, *"I won't need to go to hospital when I'm ill now*".

	I thought his daily exhaustion, bone pain, bowel problems and isolation seemed to me to be the biggest difficulties I was helping him to manage, but obviously deep down he had these worries about his safety and going to hospital. However, once it sunk in, he was very excited. He began treatment in April 2023 at the Royal Free. At the time of writing, he has finished the 14-week dose escalation and has had 2 further full doses.
7a. What do you think of the current treatments and care available for acid sphingomyelinase deficiency) on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	There is no treatment for ASMD on the NHS. Care has been best in specialised centres (but travelling to appointments is costly in time and money). The only available care is to support the diverse range of symptoms, requiring many different professionals, in different departments and hospitals (lungs, blood, gastro, skin, liver, physio, diet, eyes, heart, orthotics, mental health). Often, they haven't seen a ASMD patient before, so ask a lot of questions which makes us feel insecure. Sometimes appointments have felt *"pointless"* as the consultants can't offer much help. The GP system has caused slow (and sometimes no) responses, immediate redirection, so a lot of chasing and going round in circles, which is very stressful for him and me. Sadly, these comments and experiences are very similar to what I've heard from other ASMD patients and their families.
8. If there are disadvantages for patients of current NHS treatments for acid sphingomyelinase deficiency) (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Often consultants are trying their best to relieve symptoms with medications that *"might help*" yet have side effects, rather than be able to treat the disease at source to prevent the progression. An example of this was for his bowel difficulties. The gastroenterologist prescribed a low dose of Domperidone. After only a week this caused such severe heart palpitations, our son was admitted to hospital which set off a chain of heart monitoring. He said he'd rather feel sick and stay home until he'd been in the toilet long enough for it all to pass, usually after lunch. A big impact on QoL. Another example of treatment affecting QoL was for his infections. The enlarged spleen had caused low neutrophils so febrile neutropenia protocol meant hospitalisation instead of getting better at home. We were anxious and limited our lifestyle to avoid infections. Last Autumn, the 2 hospitals where he has 'open-access' via Haematology, told us to avoid infection, *"as at this time we had no beds"*. I found this very stressful after 15yrs of Paediatricians saying he must go in within an hour.

9a. If there are advantages of olipudase alfa over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does olipudase alfa help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Only 4.5 months into treatment with Olipudase Alfa, He and we feel so much better emotionally – it feels like there is hope for a better life. He has started doing short walks most days – recently without pain! but still gets breathless if too far. I've noticed he is having less sofa days and has started pacing round the house, like he used to when he was young. Also, he doesn't keep saying he feels sick anymore – and he is eating larger portions. He asked me to show him how to cook eggs and make turkey burgers. He asked to go out to try Indian food. He isn't in the toilet as long and can leave the house earlier. Last week, he took photos of a local pub to give to them as a gift, so can introduce himself for a lunchtime job next summer. He is doing his digital artwork every day to prepare for Uni Yr 1 and starting work before lunch. He's emailed them for the timetable so he can arrange for his infusion to be on a free day. He has contacted the Uni badminton club. He has been to Norwich to check he can walk from Uni to the bus stop and told me he thinks that soon we can *"give the Blue Badge back!"*. He has been to the cinema and says he isn't worried about catching things because he has noticed his neutrophils have steadily gone up to the highest ever seen, *"I'm not neutropenic now Mum"*. He hit his leg hard on the car door 2 weeks ago – we were all surprised that there were no bruises (normally would be big and black) and his many Petechiae spots have all gone. It is too early to do the scans but already his abdomen appears different, it is flatter, instead of curving out. His pallor is rosier and eyes brighter. He is able to put his own shoes on now and has started wearing jeans (button fly instead of elastic). He has some energy in the evening now, so we three have started going out to dinner together regularly, have been making plans and are laughing together again. I honestly feel like *"we are recovering as a family."* I told him I was proud of his determination and positive attitude after all he has been through, and he looked confused and said, *"but if the spleen and liver go down most of it all goes away Mum"*. I see why he would think like that, on his mind map of symptoms most of the QoL issues are due to; the enlarged spleen, the low immunity (caused by the enlarged spleen), the fatigue (caused in part by the large spleen causing anaemia and difficulty sleeping) and other symptoms like sickness/bowel problems (also caused by the large spleen).

	In coming months, we hope his organ storage will reduce and energy levels will increase, as seen in the clinical trials so he can (as he said in his letter to the company), *"stop wasting my life, exhausted on the sofa and be able to live a better life starting with attending Uni and producing cool animation work I'll be proud of!"* If our son continues to respond to this treatment i.e., reduced spleen and liver volume, resulting in higher platelets, and neutrophils (seen already) less fatigue, bowel difficulties/sickness and anxiety about being knocked into, then I predict these outcomes for my QoL as his carer (in order of my importance, best one first): 1.Freedom/Independence: as he gains daily independence from needing care and support (e.g. from constant fatigue, needing food) and anxiety (e.g. from feeling unwell, from worry that enlarged, so vulnerable, organs being knocked, etc). I too would gain independence again (feeling able to leave him) allowing; some time with my husband - doing as we choose, enjoy exercise, have hobbies and spend time with my elderly Mum (which I regret not being able to do with my Dad). Really, to have some life of my own without constant considerations, limitations and anxiety. 2.Reduction in anxiety and stress: nearly all of my stress is caused by his daily difficulties (pain/feeling unwell, limitations and frustrations) and trying to enable him to study, be a little independent and manage what he considers risk. A reduced spleen volume and less fatigue and easier eating would reduce that and as a result my stress related conditions: panic attacks, psoriasis and other auto immune conditions (even in this short time since beginning the enzyme replacement treatment my psoriasis has already improved and my days feel much calmer). 3.Be able to have goals, refresh skills and return to some sort of career: not feel any more like my education, and previous career success has been wasted. I feel this would be possible if I did not feel constantly 'needed' and stressed, so had the ability to plan my time and focus once more. 4.Social relationships/activities: Both me and my husband were very sporty and social people so I think our physical and mental health would dramatically improve if we had time to get back to even a small social life. It would also be great to feel that I was 'good company' for friends again. Note: It would feel fine still helping our son -if he wanted me to! (Being there for his medical appointments and fortnightly infusions) as they are planned and not everyday care.

	So, disease modifying Olipudase Alfa, absolutely addresses the disadvantages of trying to care for diverse symptoms (symptoms which are a consequence of storage enlarging and damaging organs).
10. If there are disadvantages of olipudase alfa over current treatments on the NHS please describe these. For example, are there any risks with olipudase alfa? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No because the treatment is a regular and straightforward routine and doesn't feel stressful. Initially, during dose escalation in hospital, he had slightly raised temperatures and headaches a day after infusion which went away with paracetamol and one loratadine tablet. He didn't need to slow down or reduce the dose. He finds having the infusion no problem and happily does his photo editing during the infusion (he is very used to cannulas). We have all said it is nice to have medical interventions which feel positive.
11. Are there any groups of patients who might benefit more from olipudase alfa or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Infusions at home feel very easy. People with mobility and cognitive issues may need support to attend hospital for the initial 14-week escalation. Although they must already have some support in place to attend the many medical appointments anyway. Children and adults will both benefit greatly for different reasons. Children won't have to go through the unpredictable, stressful childhood of constant infections, low platelets, possible neutropenia, anxiety and isolation, ruining their (and their family's) quality of life. Adults will get back some of the health and quality of life they have lost, at a time when they are likely to be much more unwell, with greater and more complex health needs than the children (as progressive).
12. Are there any potential equality issues that should be taken into account when considering acid sphingomyelinase deficiency) and olipudase alfa? Please explain if you think any groups of people with this condition are particularly disadvantaged	None that I can see.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case	No comment
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	I know its difficult with such a small sample size, but this data should continuously improve over time. The people I have known involved in trials since they first started have shown startling improvement, both in the initial 2-3 years (reduced spleen & liver size, normalising of bloods, bowels, less bone pain, anxiety, fatigue and more muscle development and energy) but longer term (5 years +) seeing much more improvement in lung function, muscle development and energy.
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL	The company's assumption that QoL improves on treatment is linked to how many of the QoL issues are a result of an enlarged spleen and storage. I think more data will be collected to validate this assumption on 'carer quality of life after treatment' as treatment is given. Caring for an ASMD patient has a daily, severely negative effect on carers' quality of life in order of most difficult:

Patient expert statement

• *How does acid sphingomyelinase deficiency affect the quality of life of carers?* • *On average, how many people are involved in caring for someone with acid sphingomyelinase deficiency? Does this differ by age?* • *Would you expect carer quality of life to improve in people whose disease responded to treatment? If so, how?*	1.Stress/anxiety: Watching my son get more unwell, suffer symptoms (I can't help with) and feel his embarrassment, humiliation and frustration, know it is progressive and life limiting, having to explain it is life limiting and all the diverse symptoms to family and professionals (schools, councils, disability allowance, employers, medics), fear of the future, managing appointments, financial pressures, not getting out of the house nor exercise, being isolated, not being relatable to friends and family, being in hospital, all cause stress. 2.Career/ Self-fulfilment: The stress, demands on time and unpredictability of his health prevented me having my career. Caring for our son's ASMD symptoms has not allowed me to have personal goals. 3.Relationship with partner: We have managed to pull through all the stress together, with the focus on our son. We don't have time 'as a couple' as others do with children over 18yrs. I think if we'd had had another child or I had a part-time job with an employer (rather than our own business), we would really have struggled to stay together as a unit. Divorce seems really common. 4.Social Isolation: I've felt physically isolated, without the time to mix, and the care is home-based on the sofa as he is too tired (so can't mix as carer and patient). I've felt emotionally isolated as others don't understand our situation and can sometimes unintentionally make you feel worse! 5.Self-care: I don't feel able to leave my son, pursue hobbies, sports or exercise. Some days in the morning I don't have time to wash or eat properly through the day, as my day is led by him. You don't have room for other difficulties: eg I was distraught that I wasn't able to spend as much time as I wanted with father when he was end of life. 6.Family planning: I would have loved more children, but I dare not feeling it would compromise my ability to look after my son (not knowing how ill he would be) and I didn't want 1 in 4 chance of having another ill child (I would not have been able to terminate a pregnancy). In childhood, me and my husband cared for our son (husband needed, but to a lesser extent in terms of time). I would say without Olipudase Alfa, it would be the same at 18yrs but over time getting worse (with him needing more care) in adulthood. This is because as a child he had the energy to attend school giving me a break. From 16yrs, as he was getting so much more fatigued school was at

	home, so going forward, if he didn't have the energy to work and always needed me there, I would need breaks. Reference to how carers QoL improves with response to Olipudase Alfa, in a relatively short time period, mine and my husband's QoL has improved significantly both emotionally and physically. For example, already I have not got to spend all morning; preparing food, encouraging him to eat little amounts very often (to pick up his energy) and help him with self-care. This is because he doesn't feel sick anymore, not in the toilet so much and can eat more giving him more energy and time to do things himself. I do not have the stress of listening to a list of painful ailments or anxiety about what he can and can't manage (as the headaches, bruising and bone pain are already reduced and he feels more positive about his day). Please may I draw the committee's attention to **my response to all of question 9 above (a list of changes and QoL improvements)**.
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	No comment.
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	For your information, I think the enlarged spleen and liver contributed to my son's weight. He was always on the 0.4-2 centile for height, yet around 25 centile for weight, even though very little muscle development with extremely thin arms and legs, no visible fat at all and a protruding rib cage. He had an enlarged abdomen. At 19yrs he was 53kg.
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations	No comment
Are there any important issues that have been missed in EAR?	No comment

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Untreated by Olipudase Alfa (a disease modifying therapy), ASMD is an increasingly multi-symptomatic, painful, and psychologically damaging disease, which reduces length and quality-of-life.
- For both the patient and the carers, it is stressful, isolating, distressingly progressive and severely impacts their ability to work, have relationships and self-care.
- The spleen enlargement causes other complex physiological and psychological symptoms, which have a debilitating effect on the patient's health and quality-of-life, (and as a direct consequence, that of the carers).
- Treatment by enzyme replacement is proven to prevent and even reverse storage in the affected vital organs; spleen, liver and lungs. This not only stops the disease progression that causes early morbidity but removes most of the quality-of-life issues, enabling a life with the energy, health and state of mind to make choices, achieve goals and plan for the future.

Thank you for your time.

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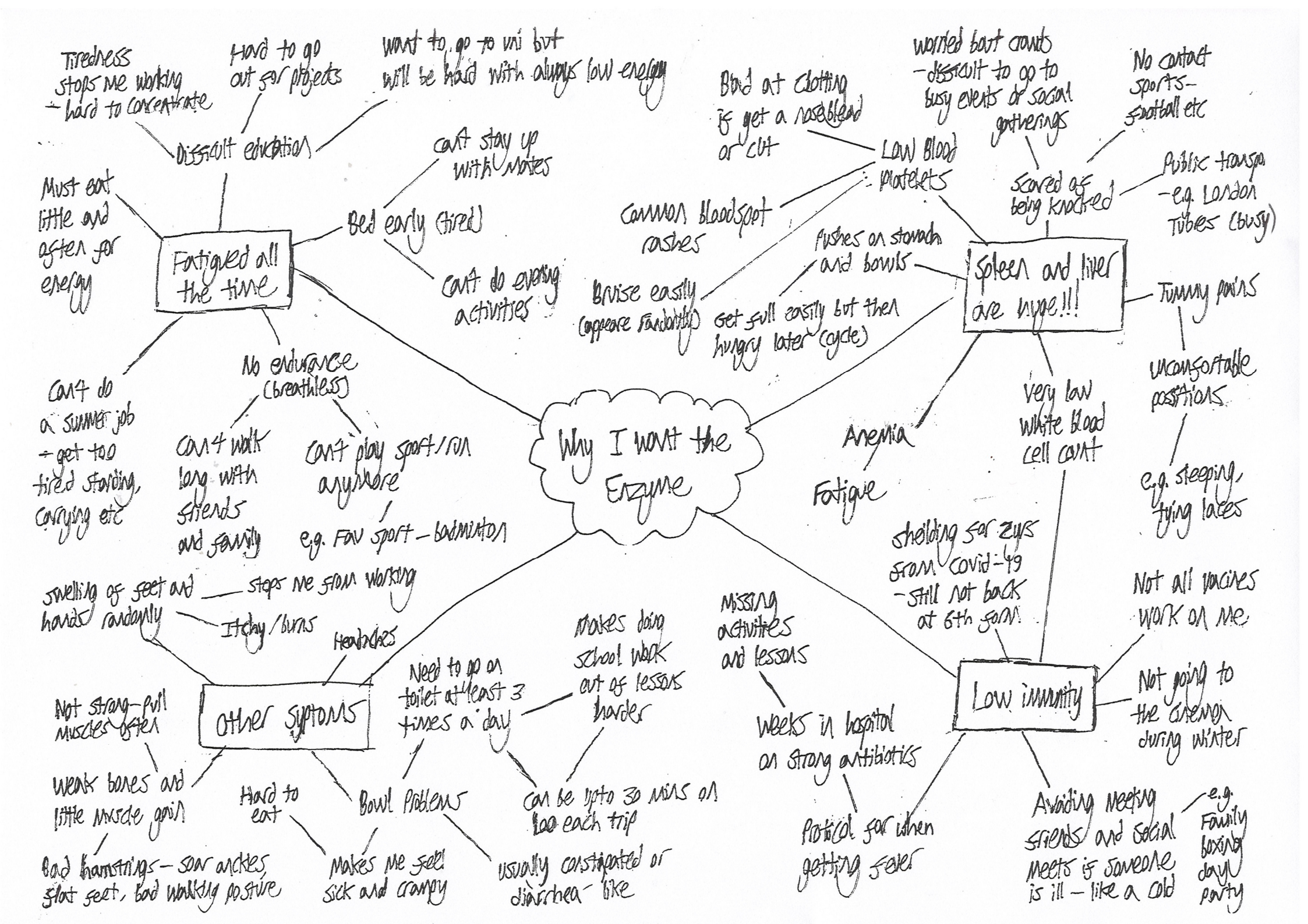
Why I want the Enzyme
Fatigued all the time
Tiredness stops me working - hard to concentrate
Hard to go out for projects
Want to go to uni but will be hard with always low energy
difficult education
Must eat little and often for energy
Bed early (tired)
Can't stay up with mates
Can't do evening activities
Can't do a summer job - get too tired standing, carrying etc
No endurance (breathless)
Can't walk long with friends and family
Can't play sport/run anywhere
e.g. Fav sport - badminton
Other Syptoms
Swelling of feet and hands randomly
Stops me from working
Itchy/burns
Headaches
Not strong - pull muscles often
Weak bones and little muscle gain
Bad hamstrings - sore ankles, flat feet, bad walking posture
Bowl Problems
Need to go on toilet at least 3 times a day
Makes doing school work out of lessons harder
Can be upto 30 mins on loo each trip
Hard to eat
Makes me feel sick and cramp
Usually constipated or diarrhea - like
Low Blood platelets
Bad at clotting if get a nosebleed or cut
Common bloodspot rashes
Bruise easily (appears randomly)
Worried bout counts - difficult to go to busy events or social gatherings
No contact sports - football etc
Scared of being knocked
Public transp - e.g. London Tubes (busy)
Spleen and liver are huge!!!
Rushes on stomach and bowels
Get full easily but then hungry later (cycle)
Tummy pains
Uncomfortable positions
e.g. sleeping, tying laces
Anemia
Fatigue
Very low White blood cell count
Low immunity
Shielding for 2yrs from covid-19 - still not back at 6th form
Missing activities and lessons
Weeks in hospital on strong antibiotics
Protocol for when getting fever
Not all vaccines work on me
Not going to the cinema during winter
Avoiding meeting friends and social meets if someone is ill - like a cold
e.g. Family boxing day party

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

A Highly Specialised Technology Appraisal

EAG Review of Company's Response to Technical Engagement

Produced by

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1. INTRODUCTION

This document provides the External Assessment Group's (EAG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID3913]. In this document, the company's response to key issues raised in the draft guidance is presented alongside the EAG's response. The company presented results for a revised base case alongside additional scenario analyses to explore uncertainty in key assumptions. The EAG has not changed its base case following technical engagement, and the results from its preferred analyses are presented in its original assessment report.

2. EAG review of company response to key issues raised in the draft guidance

In response to the technical engagement report, the company provided a response to the key issues raised by the NICE committee in the draft guidance. This section contains both the company response and the EAG review of this.

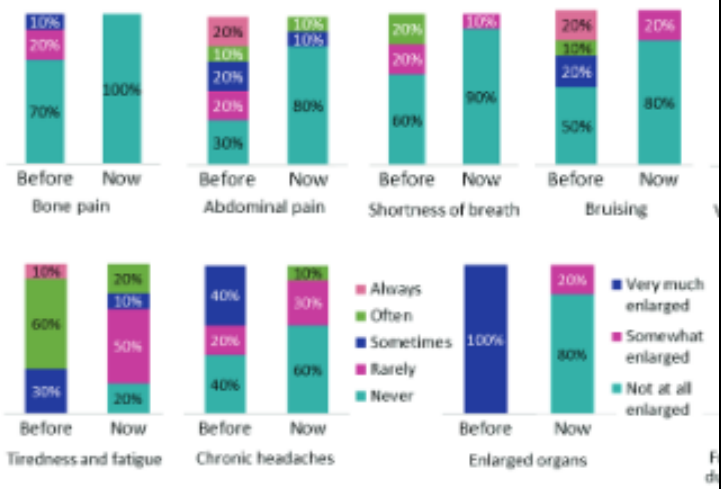
Table 1: Company and EAG response to key issues

Key issue	Company response	EAG response
EAG key issue #1: The company used differential discounting, which is not consistent with the NICE reference case	Sanofi believe that costs and benefits should be discounted using different rates in line with the HM Treasury's Green Book. Although we acknowledge that the differential discounting is not consistent with the NICE reference case, based on the guidance provided in the NICE health technology evaluations manual, there is a strong case to apply a discount of 1.5% to both costs and benefits, if a differential rate is not accepted. In consideration of the comments in the external assessment group's (EAG's) report, a case for using a 1.5% discount rate for both costs and health effects is presented, based on the criteria provided in Section 4.5 of the NICE health technology evaluations manual. Results using 1.5% discounting for both costs and outcomes are provided in Section 3.10.3.1 of the company submission and are provided as the company's revised base case in Table 3 below. <u>The technology is for people who would otherwise die or have a very severely impaired quality of life</u> Severe and progressive somatic multi-systemic manifestations, including splenomegaly (present in >90% of patients), hepatomegaly (present in >70% of patients), lung disease (present in >80% of patients), and gastrointestinal (GI) issues (present in >75% of	The EAG did not agree with use of differential discounting as it is inconsistent with the NICE reference case. The company has revised their base case and discounted both costs and benefits by 1.5%. There are three criteria to satisfy for the use of non-reference case discounting: • The technology is for people who would otherwise die or have a very severely impaired life • It is likely to restore them to full or near-full health • The benefits are likely to be sustained over a very long period. The EAG do not consider that these criteria have been met for this appraisal. While the EAG agree that people with ASMD have an increased mortality risk compared to the general population, the evidence for the mortality benefit of olipudase remains uncertain, due to limited numbers and follow-up in the evidence base. The EAG further noted that the precise mortality risk of ASMD types B and A/B is an ongoing uncertainty in this appraisal.

Key issue	Company response	EAG response
	patients), are indicative of acid sphingomyelinase deficiency (ASMD) type A/B and type B, which worsen in the absence of disease-modifying treatment. These manifestations cause irreversible organ damage and result in substantial morbidity and mortality, leading to reduced life expectancy in patients with ASMD. Early onset of the disease is also associated with an increased risk of early mortality. There are no patients over 60 years of age currently living with ASMD in the UK, with most patients dying in or before their 50s. Reduced life expectancy is particularly apparent with paediatric onset ASMD. There are three studies highlighted in Document B that reported worldwide mortality outcomes in adult and paediatric patients with ASMD along with a chart review and pooled data analysis of patients with ASMD (n=270) in Germany, France, the USA and Brazil (1-4). These studies consistently show shorter life expectancy in patients with ASMD (1-4). The standardised mortality ratio (SMR) from the pooled chart data analysis was [redacted]) (using 2018 as reference) (4). There is a substantial burden with ASMD. Patients must make changes to their lifestyle, including nutritional, social, employment, and activity adaptations due to an enlarged spleen and/or liver, pulmonary impairment, excessive bleeding, and growth deficits. Patients with ASMD experience a substantial impact on their mental health including depression, anxiety, and psychosis due to the severe limitations imposed by their disease. Additionally, ASMD negatively impacts physical, self-esteem, emotional, personal care, and	Moreover, the EAG did not consider the evidence base to have demonstrated that the technology restores people with ASMD types B and A/B to full or near full health, and whether the benefits are sustained over a very long period. Regarding the restoration of full or near full health, the company states that olipudase alfa has met this criterion based on the significant improvements in clinical outcomes (respiratory function, spleen volume, liver volume) in both the ASCEND and ASCEND-Peds trials. The EAG acknowledges the therapeutic benefit of olipudase alfa with respect to these clinical outcomes, however it is uncertain whether such improvements could be considered the equivalent of returning people to full of near-full health. Based on the clinical evidence reported in the original company submission, organs following treatment remain enlarged at multiples greater than the norm, and benefits for respiratory function and platelet count were visible but lesser in magnitude. With regards to change in DLco, the primary outcome of the trial, data in the ASCEND clinical study report shows that mean DLco values for those in the ASCEND arm at 52 weeks were [redacted] heterogeneity in response (only 27.8% of participants had shown a response in DLco by 52 weeks). Clinical advisors to the EAG noted that, due to the heterogeneous nature of ASMD, the magnitude of benefits experienced by patients may vary across outcomes. While the trials showed no benefit of olipudase alfa on quality of life and functional outcomes, overall, clinical advisors to the EAG considered that the benefits of

Key issue	Company response	EAG response
	social function and relationship quality of life (QoL) domains. In addition to the burden to the patient, there is a substantial impact on the QoL of caregivers of patients with ASMD. More detail on caregiver burden is provided in Key Issue 3. <u>It is likely to restore them to full or near full health</u> The clinical results from the ASCEND and ASCEND-Peds trial demonstrate that olipudase alfa is associated with significant improvements in multisystemic clinical manifestations of ASMD (including respiratory function, spleen volume, and liver volume) in both adults and children, with increased growth and musculoskeletal development in children. In the ASCEND trial, treatment with olipudase alfa resulted in a significant improvement in diffusing capacity of the lung, as measured by percent predicted lung diffusion of carbon monoxide (DLCO), compared with placebo at Week 52 (least squares [LS] mean difference of 19.01%, p=0.0004). Additionally, olipudase alfa treatment resulted in a significant reduction in liver volume (LS mean difference of –26.60%; p<0.0001) and a significant increase in platelet count (LS mean difference of 14.33%; p=0.0185) at Week 52 compared with placebo. In the ASCEND-Peds trial, treatment with olipudase alfa resulted in a statistically significant improvement in diffusing capacity of the lung, as measured by percent predicted DLCO, compared with baseline at Week 52 (32.94%; p=0.0053) and a statistically significant reduction in spleen volume (SV) and liver volume at	olipudase alfa would be clinically meaningful to patients, though again the EAG is uncertain that this corresponds to a restoration of near or full health. The supportive online survey data provided by the company, outlining frequency of ASMD symptoms before and after olipudase alfa treatment, is useful and shows reductions in a number of symptoms following treatment with olipudase alfa. This includes a meaningful number of people reporting that they never experience some symptoms following treatment. However, the EAG note that there are limitations surrounding these data also, i.e. data were from a poster abstract, there was uncertainty about the selection of participants, and responses were elicited from a small cohort (ten patients or carers). Overall, the EAG consider there to be a lack of robust evidence to support the claim that olipudase alfa returns patients to near or full health following treatment. Regarding the final NICE criterion, i.e. whether benefits are likely to be sustained over a 'very long period', the EAG did not consider that the current clinical evidence base was sufficient to demonstrate this. The company stated that the sustained long-term effects of olipudase alfa are likely to resemble that of Enzyme Replacement Therapy (ERT), for the treatment of Gaucher disease, which indicated a maintained response of 20 years. The EAG acknowledge that there is evidence to support a maintained effect of ERTs in Gaucher disease, however it is unclear whether this effect is generalisable to olipudase alfa for the treatment of ASMD. As per the NICE methods guide (2022), *'when considering analyses using a 1.5% discount rate, the committee must take account of plausible long-term health benefits in its discussions. The*

Key issue	Company response	EAG response
	Week 52 compared with baseline (-49.21% and 40.56%, respectively; p<0.0001). A recent international study conducted on behalf of National Niemann-Pick disease Foundation (NNPDF), Niemann-Pick UK (NPUK), and the International Niemann-Pick Disease Registry (INPDR), which involved an online survey and semi-structured interviews with 10 patients or their caregivers, reported that olipudase alfa was associated with improvements in all non-neurologic manifestations of ASMD (Figure 1) (5). Results from this study highlighted the impact of olipudase alfa on the range of symptoms experienced by paediatric patients with ASMD. **Figure 1: Frequency of ASMD symptoms before (n=10) and after (n=10) treatment with olipudase alfa**	*committee will need to be confident that there is a highly plausible case for the maintenance of benefits over time when using a 1.5% discount rate.'* Due to the relatively short-term trial data available within the ASCEND and ASCEND-Peds and the length of the extrapolation period within the economic model, the EAG consider that there is considerable uncertainty surrounding the extrapolation of a maintained olipudase alfa treatment effect. Due to these limitations, the EAG did not agree with the company's decision to use 1.5% discounting for both costs and benefits in their revised base case. Furthermore, the EAG do not consider the company's sensitivity analysis to be appropriate (which uses differential discounting) given that the approach deviates from the NICE reference case.

Key issue	Company response	EAG response
	 Abbreviations: ASMD, acid sphingomyelinase deficiency. Clinical opinion was sought after the initial submission on the long-term efficacy of olipudase alfa. Clinicians indicated that patients continue to improve in clinical parameters during treatment and approach normal range over time. In particular, they noted that DL_{CO} shows improvement and normalises over time. Liver and spleen volume approach normal range over time and patients are expected to stabilise at a lower spleen and liver volume compared to prior to treatment. <u>The benefits are likely to be sustained over a very long period</u> At the latest data cut off ASCEND (01 March 2021), data were available for up to 6.5 years of follow-up for adult patients and 4 years of follow-up for paediatric patients (6). The company believes that effects will be sustained long-term, in line with what has been observed in Gaucher disease where there is evidence	

Key issue	Company response	EAG response
	showing patients continue to maintain response 20 years after initiation of treatment (7). This is further supported by clinical opinion provided to both the company and EAG that there is nothing that suggests loss of long-term efficacy in observed patients, with normalisation/improvement in key clinical outcomes over extended treatment, and no indication of antibody response. An updated base case analysis is provided for a discount rate of 1.5% for both costs and benefits in Table 3. Sensitivity analyses for differential discount rates and 3.5% discount rate for costs and benefits are shown in Table 5 and Table 6 respectively.	
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	At the latest data cut of ASCEND (01 March 2021), data were available for up to 6.5 years of follow-up for adult patients and 4 years of follow-up for paediatric patients. Results from the clinical trials indicate that patients are 'normalised' (i.e. restored to full or near full health) at the latest data cut. The company has no reason to believe that treatment effects will not be sustained long-term. This is further supported by clinical expert opinion obtained both by the company and EAG and similar results have been shown with long-term enzyme replacement therapy (ERT) in Gaucher disease, another lysosomal storage disorder. Therefore, in the absence of longer-term data, our base case assumption is appropriate. However, following the technical engagement meeting where the reservations regarding a transition to a normalised health state after two years were discussed, the	The EAG noted that data in the CS for the March 2021 data cut includes 6.5 years' of follow-up for five adult participants, and 4 years' of follow-up for spleen and liver volume in seven paediatric participants. As noted in the EAG report, the EAG did not consider this data to be reliable due to high levels of attrition and considered that data at one year from the double-blind period of ASCEND was the most probative to decision-making. This is partially due to concerns that response to treatment may vary across the population, and that this may not be captured in follow-up timepoints with high levels of missing participants. The company did not submit further evidence for this data cut as part of their response to technical engagement, and so the EAG assumed that no further data has become available for this timepoint since their original submission.

Key issue	Company response	EAG response
	company would like to provide alternative methodology and additional scenario analyses that address the long-term treatment effect in the model. In the original company base case, patients receiving olipudase alfa can only transition to an alternative health state for up to 2 years, after which (from year 3 onwards) they all transition to the SV <6 / DL_{CO} >80 state and remain there until the end of the time horizon or death. We have revised our base case so that patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which all patients transition to the SV <6 / DLCO >80 state from year 10 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients' probability to transition to the 'SV <6 / DLCO >80' state from the other health states between year 2 and year 10. In scenario analysis transition probabilities at year 2 are applied each year until the end of the time horizon or death. In other words, patients are no longer all assigned to the 'SV <6 / DL_{CO} >80' state from year 3 onwards. The probability of patients reaching this state over time is driven by the transition probabilities that applied during year 2 and are assumed to be constant afterwards. Sensitivity analyses are provided to demonstrate the effect of modelling long-term treatment effect on the	The EAG dispute the use of the term 'normalised' in the company's response and, as noted above, consider there to be no clear evidence that participants who receive olipudase alfa return to near or full health following treatment. Clinical outcomes demonstrated that participants who received olipudase alfa continued to experience clinical symptoms of their condition, with clinical signs (e.g. of splenomegaly and impaired respiratory function) still outside of the normal range. The EAG note that the company's revised base case approach, which assumes that patients receiving olipudase alfa transition to the SV <6 / DL_{CO} >80 state at year 10, could be considered a more conservative approach than their original base case assumption wherein all patients were assumed to transition to SV <6 / DL_{CO} >80 state after year 2. However, given that there is no clinical evidence to support the company's revised efficacy assumption, the EAG retain its previous preference to the extrapolation of olipudase treatment efficacy in its base case (as outlined in the EAG report, whereby the observed treatment benefit for olipudase is frozen after 2 years i.e. there are no further transitions after 2 years).

Key issue	Company response	EAG response
	model results. Please see **Error! Reference source not found.** and **Error! Reference source not found.** for results.	
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL	ASMD has a profound impact on not only patients, but also on their families. Due to the severe and progressive somatic multi-systemic manifestations and the high morbidity and mortality, particularly associated with the paediatric population, it is assumed that there is a meaningful detrimental impact on the QoL of caregivers of patients with ASMD. Caregivers face the grief of losing a loved one prematurely, and this is especially true for those caring for children. In addition to facing grief, caregivers have difficulty maintaining their emotional and mental state, along with preserving social activities and relationships. The caregiving burden directly impacts the QoL of the caregiver. Caregiving responsibilities including the requirement to attend medical appointments, changing daily routines, and maintaining the overall wellbeing of their loved one are associated with a substantial caregiver burden, and in turn this impacts QoL. Physical exhaustion and pain from the caregiving process decreases the ability of caregivers to socialise resulting in further emotional impact. The extreme financial burden resulting from caregiving duties and the associated inability to work can also contribute to feelings of low self-worth, further increasing the caregiving burden and decreasing the caregiver's QoL. Physical symptoms associated with ASMD include respiratory symptoms (shortness of breath, requirement for supplemental oxygen), abdominal symptoms (pain and discomfort [resulting in sleep	The EAG acknowledges the severity of ASMD and the impact that the condition has on both patients and families. The EAG is not advocating for the complete removal of caregiver disutility from the model, but rather the adoption of a more conservative approach in the face of an absence of evidence and NICE preferred methods (for full details please see the EAG's assessment report). The EAG draws the committee's attention to the fact that including the HRQoL impact of a treatment on more and more individuals results in increased incremental QALYs and thus lower estimated ICERs. In order to ensure efficient allocation of finite NHS resources, a decision to widen the perspective of an analysis would necessitate a commensurate (and likely substantial) reduction in the acceptable threshold. *Carer disutility* The EAG acknowledges that the lack of published disutility estimates for carers of people with ASMD introduces uncertainty into the analysis. However, based on clinical input to the EAG, Pompe disease was not considered to be an analogous condition to ASMD in that Pompe was considered to be a more severe disease. Given the HRQol assumptions used in the company's model i.e. the application of carer disutility to the BSC arm only, the impact of applying a large disutility (derived from Pompe disease) leads to a severe reduction in QALYs within the

<table>
<tr><th>Key issue</th><th>Company response</th><th>EAG response</th></tr>
<tr><td></td><td>disturbances], enlarged and distended abdomen), musculoskeletal symptoms (muscle weakness, bone pain, and joint pain), fatigue, excessive bleeding and bruising, gastrointestinal symptoms and headaches, which are all indicative of the substantial clinical burden that requires the involvement of caregiver(s).

<u>Carer disutility</u>
We agree with the EAG that modelling carer disutility is an area where insufficient methodological guidance currently exists. Furthermore, there are no published estimates of disutility for caregivers of patients with ASMD or analogue conditions such as Gaucher disease.
As discussed in response to Key Issue #1, results from the clinical trials indicate that patients treated with olipudase alfa are ‘normalised’ (i.e. restored to full or near full health). Additionally, clinicians indicated that the clinical parameters of patients in trials continue to improve over time and approach a normal range.
As patients quickly approach full or near full health with olipudase alfa treatment, it is also anticipated that the impact on caregivers diminishes to a very low level and therefore in the absence of data disutilities are applied to the BSC arm only.
As highlighted above, no caregiver disutilities were identified for ASMD or Gaucher disease, which could be considered an analogue. Therefore, other disease areas were used to obtain disutility values for scenario testing. We acknowledge that there are limitations to the use of caregiver disutilities from Pompe disease (company analysis), as well as those used by the EAG,</td><td>BSC arm, thereby biasing the analysis in favour of olipudase alfa.

In the absence of robust published carer disutility values, the EAG’s preference, as outlined in the EAG report, was to take a more conservative approach to the overall modelling of carer disutility, which included using proxy values from other conditions including MS and meningitis and attaching the disutility to severity of health state rather than treatment (see Table below). The EAG maintain that it is logically inconsistent for the carer burden to be equivalent across all health states.

The EAG accepts that its preferred approach uses several simplifying assumptions, however given the underlying uncertainty, these assumptions provide a more balanced/conservative approach than the approach taken by the company.

EAG preferred carer disutility assumptions
<table>
<tr><th>Population</th><th>Mild/moderate health states (all health states other than severe)</th><th>Severe health state (SV ≥ 15MN)</th></tr>
<tr><td>Paediatrics</td><td>-0.023</td><td>-0.080</td></tr>
<tr><td>Adults</td><td>-0.010</td><td>-0.045</td></tr>
</table>

Furthermore, the EAG maintains that application of carer disutility to the BSC arm only remains inappropriate, as carer disutility should logically be based on disease severity (irrespective of treatment), i.e. a patient in the</td></tr>
</table>

Key issue	Company response	EAG response
	which were derived from conditions such as multiple sclerosis and meningitis. *1.78 carers for children* Providing care for patients with ASMD is a time-consuming task and often involves and affects the entire family. As has been considered appropriate in other appraisals (e.g. highly specialised technology [HST] guidance HST 3, HST 9, HST 10, HST 11), the inclusion of utilities for multiple caregivers has been considered appropriate. In this ASMD model, we account for an average of 1.78 caregiving parents per child with ASMD, in line with HST 11 (8). This is likely an underestimate of the true impact of the condition, as does not take into account the real impact on the extended family and friends of ASMD patients. Although very limited evidence exists in ASMD, publications in Duchenne muscular dystrophy indicate that both parents are involved in caregiving duties (9, 10). There is further a substantial impact on the QoL of siblings of patients with chronic disease. While siblings' emotional experiences are characterised by diverse and contradictory feelings (11), the QoL of siblings of patients with chronic conditions is lower than that of patients whose siblings had no chronic conditions (12, 13). Healthy siblings of children with chronic disease are affected physically and psychosocially (12), and	worst health state will have an impact on the HRQoL carer even if the patient is receiving olipudase alfa. Applying disutility to the BSC arm only biases the analysis in favour of the olipudase alfa. <u>*Number of carers for children*</u> In its report, the EAG considered that incorporating 1.78 carers in the company's economic analysis was unjustified and chose to use 1 carer in its preferred base case. The EAG do not consider the company's revised approach, to further increase the number of carers per patient from 1.78 to 2.6, to be appropriate. The EAG acknowledges that paediatric patients with ASMD are likely to require care (whether informal or formal). The uncertainty however lies in the number of carers required and whether the inclusion of siblings within the economic evaluation as carers is appropriate. As noted in the EAG's original report, the company's decision to use the number of carers in HST 11 (voretigene neparvovec for inherited retinal blindness) was not appropriate, given that children in that appraisal had significant visual impairment and were expected to require a higher burden of care to complete activities of daily living. Whilst the EAG acknowledges that ASMD will have an impact on the wellbeing of family members, the EAG considers that revising the number of carers to 2.6, based on the average number of siblings in the UK, is inappropriate and introduces further uncertainty. The EAG report contains further discussion of this issue, including why the inclusion of siblings as carers in the economic appraisal is problematic. In addition, the EAG notes the following concerns with the company's approach:

Key issue	Company response	EAG response
	their health-related QoL is lower in well-being, social support, and financial dimensions compared with their peers (13). A web-based survey of Duchenne muscular dystrophy caregivers showed that siblings are perceived to have to give up time with friends, sports and/or extracurricular activities, and holiday-related activities (14). Further, caregivers report that there may be insufficient finances for siblings' educational or other activities (14). According to a report on the impact of a rare disease on sibling experience conducted by Alexion, the QoL of a sibling of a person with a rare disease is negatively affected due to the presence of the rare disease in the family unit (15). Although siblings are generally not the primary carer, they do provide care and support, and this increases with age and maturity, as does the impact on their mental health (15). Siblings are unable to experience the same QoL as that of their peers; this can be due to feeling overlooked as their parents devote a large amount of time to caring for their sibling, constant feelings of worry for their family, or the stress of feeling the need to protect their sibling (15). We therefore believe this should be reflected in the economic model by the inclusion of siblings in the mean number of caregivers. The mean number of siblings in the UK in 2021 was 1.77 (16). This gives an overall average of 2.6 carers affected per patient. *Impact of patient death on carer disutility*	• By including siblings as carers, this implies that sibling disutility should also be included in the model. However, this is not aligned with NICE guidance. The expansion of siblings as carers introduces additional uncertainty as it potentially allows for the disutility of extended family members and friends to be modelled. Whilst this is an area of current academic debate and ongoing research, the direct impact on cost effectiveness would be to reduce the company's ICER. • The EAG note that for HST 9 (inotersen for treating hereditary transthyretin amyloidosis) and HST 10 (patisiran for treating hereditary transthyretin amyloidosis), the committee accepted 1 carer for patients with a PND Score of 1, II, IIIA, and IIB and two carers for patients with a PND Score of IV. There is no precedent for accepting >2 carers. As demonstrated in the EAG's initial report, assuming 1 carer per paediatric patient did not have a major upward impact on the results and was not a key driver of the ICER. <u>*Impact of patient death on carer disutility*</u> The EAG acknowledge that the death of a patient will impact on the HRQoL of the carer. However, the exact disutility and duration of application within the model is extremely uncertain given the absence of robust evidence and the inclusion of HRQoL impacts in economic

Key issue	Company response	EAG response
	The exclusion of disutility due to bereavement from the model leads to spurious results suggesting that parent QoL increases following the death of their child. In fact, publications highlight the substantial impact on QoL experienced by carers of patients with chronic and severe disease approaching death. Carers experience reduced mental QoL when caring for ill family members (17-24). More specifically, patients with a high level of anticipatory grief had a lower QoL (17). Carers of patients with advanced cancer, or disorder of consciousness reported poorer physical and mental health than the general population (18, 20, 22, 24). In a survey focusing on symptoms of grief and depression to determine the extent of overall functional impairment in caregivers of terminally ill patients in Denmark, 51% of caregivers reported overall functional impairment before the death of the patient (22). Depressive symptoms were a common characteristic observed in caregivers of patients with chronic or severe disease approaching death (20, 22). The importance of bereavement in rare diseases is reflected by its inclusion in over 30% of HST appraisals. In a study of 23 HST appraisals, eight included considerations involving bereavement. Grief and bereavement were included in company submissions (n=2), patient advocacy group submissions (n=3), and company and patient advocacy group submissions (n=3). The impact of grief and bereavement on caregivers and the carer disutility due to bereavement was included in two appraisals (25). HST 7 (an economic evaluation of a meningitis vaccine) modelled family quality-adjusted life year (QALY) loss resulting in an incremental cost-	evaluations following the death of a patient is not established practice. The EAG maintain that the company's approach of applying a large carer disutility (-0.50) for the duration of the entire modelled time horizon is inappropriate and biases the analysis in favour of olipudase alfa. Additionally, the company has not adequately tested uncertainty surrounding this model assumption. There is a detailed critique of this issue within the original EAG assessment report. Based on the EAG's scenario analysis (and preferred base case analysis), removing the carer disutility associated with patient death had a large upwards impact on the ICER, indicating that this is a key driver of results.

Key issue	Company response	EAG response
	effectiveness ratio (ICER) decrease of 9%; the additional QALY loss experienced by a bereaved family was assumed to be 9% of the child's QALY loss (26). Appraisal ID800 included a caregiver disutility in the base case which corresponded to the most severe health state; the Extended Disability Status Scale illustrated that the caregiver disutility increased as the disease becomes more severe (27). Although the publications documenting disutilities associated with grief and bereavement are scarce, there is evidence that grief and bereavement profoundly influence caregiver QoL. We therefore believe it is appropriate to include a carer disutility associated with death of the patient in the economic model. Sensitivity analyses are provided for health state-specific carer disutilities applied from a proxy disease area, Pompe (28). Please see **Error! Reference source not found.** for the utility values used and **Error! Reference source not found.** for results.	
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	ASMD is a disease that shortens overall survival. There is consistent evidence of this from the SPHINGO-100 study, and from the pooled data analysis of patients with ASMD included in the Addendum. This was further confirmed in advice received from clinical experts. Regarding low paediatric mortality rates proposed by the EAG, clinical opinion suggests the assumption that paediatric patients with ASMD type B would die sooner	In April 2023, the company submitted updated economic results using a revised approach to estimating mortality/overall survival. In the revised analysis, overall survival was estimated using a parametric modelling approach for BSC (based on a chart review and subsequent pooled data analysis of ASMD patients (n=270) in Germany, France, the USA and Brazil) and the application of a hazard ratio of 0.1 to general population mortality for patients receiving olipudase alfa. The company submitted a document containing the results of

Key issue	Company response	EAG response
	than the general population is correct, but noted the incidence of these deaths would likely be underreported, given these patients transition to adult care services at 16 years and thus any deaths after this point would not be recorded. Advice from clinical experts supported the use of parametric fits based on the pooled analysis forming the basis of the Addendum, as these reflected the underlying data. It was also considered that the population included in the study was generalisable to patients with ASMD in the UK, as the treatment paradigm is similar across the world due to the lack of disease modifying treatments.	this chart review but did not submit details of the methods used. This created uncertainty in the evidence presented, in particular the selection of an adjusted estimate of mortality without explanation of the adjustment performed. While the adjustment may have been appropriate to the data, as the adjustment reduced the life expectancy of the population (and therefore favours olipudase alfa in the analysis), the EAG highlights this as a potential concern. Baseline characteristics of participants in the chart review study were included in the provided document and were reviewed by the EAG. It was noted that the study included a lower proportion of people with ASMD type A/B than were included in the trials of olipudase (type A/B is associated with a higher risk of mortality) and a higher proportion of people who had undergone splenectomy than would be expected in NHS practice (splenectomy is associated with an increased risk of mortality). There was extensive missing data for baseline outcome/severity markers (~80% missing data; spleen volume, liver volume, and DLco). The EAG therefore was unable to judge if the study population was representative of the target NHS population, and considered all analyses including these outcomes to be severely limited. The EAG further noted several limitations surrounding the company's revised approach to estimating mortality in their economic model. These included the following. • The mortality HR for olipudase alfa, which was derived from a poster presentation by Kapetanakis et al, is subject to uncertainty due to the lack of detail about the methodology and the high

Key issue	Company response	EAG response
		imprecision in the result: the HR was estimated to be 9.99 (95%CI: 1.03-97.14). Both the abstract authors and the EAG note that this estimate should be interpreted with caution, as outlined by the wide confidence interval. • For BSC, the company used two different extrapolation approaches to model OS for the paediatric and adult populations. For the paediatric population, mortality was modelled using a single Weibull curve, whilst for the adult population a piecewise approach was used whereby a Gompertz curve was used up to 40-years and a Weibull used post-40-years. The EAG noted several limitations surrounding the company's approach. Firstly, AIC/BIC statistics were not provided individually for the two distinct populations, that is, AIC/BIC statistics were only provided for the pooled adult and paediatric overall population. As such it was not possible to determine best fitting curve (based on AIC/BIC statistics) individually for each population. During clarification (response A.5), the company noted that *'All analyses were carried out using the full dataset (for both adult and paediatric patients) and therefore there are no separate AIC/BIC statistics for the paediatric population'.* Given that the EAG's preference was for results to be presented according to subgroup (paediatric or adult), this introduces considerable uncertainty. Secondly, the company did not adequately discuss the validity of each curve based on visual fit. The company provided a single graph in the Addendum (Figure

Key issue	Company response	EAG response
		2), which displayed Kaplan Meier data for the overall population and the piece wise fits considered for use in the adult population (Gompertz-Gompertz and Gompertz-Weibull). However, a complete assessment of alternative curves based on visual fit was not discussed. Given the number of curves available, comparison of curves based on visual fit helps to validate curve selection and prevents selection bias. Thirdly, it is unclear why the company did not explore the use of restricted cubic spline models as a means of estimating overall survival. As per NICE TSD 21, restricted cubic spline models represent an alternative flexible modelling approach. • In addition to the revised mortality approach, the EAG noted that there were a number of changes to the company's revised model that were not highlighted to the EAG and clearly documented with a rationale, including the dose calculation for children which resulted in a change in mean dose i.e. in the treatment costs sheet, the weekly dose escalation for children at weeks 6, 10, 12 and 14 has changed from 0.30mg, 0.60mg, 1mg and 2 mg to 0.60mg, 1mg, 2mg and 3mg respectively. Furthermore, the EAG noted a change to the baseline health state distribution estimates for DIco in the adult population i.e. DIco (>80, 40-80, <40) has changed from 0%, 0% and 100% to 0%, 80.6% and 19.4% The EAG are concerned that there may be further revisions that have not been highlighted. However, due to time constraints it was not possible to scrutinise the entirety of the company's model in detail.

Key issue	Company response	EAG response
		Overall, the EAG considered that the company's revised approach to modelling mortality was lacking in important details and introduced additional uncertainty. Due to the aforementioned limitations, the EAG do not consider the company's revised mortality estimation approach to be appropriate for consideration as part of the base case.
EAG key issue #5: There was uncertainty surrounding the company's approach to modelling patient weight. As the dose of olipudase alfa is based on patient weight, these assumptions affected drug costs in the model.	On average, patients with ASMD are lighter than the general population, as shown by trial data, clinical expert interviews, and compassionate use requests received by the company. The EAG preferred assumption of using the mean UK population weight is not representative of patients with ASMD. Data from the pivotal ASCEND and ASCEND-Peds trials shows that weight for both children and adults was low relative to the general population due to the nature of the disease. In addition, according to a retrospective chart review of 100 patients with ASMD (Cox et al., 2018), growth was subnormal throughout childhood for all patients with chronic neurovisceral disease and for 50% of patients with chronic visceral disease; weight gain was impaired over time in patients with ASMD (2). A publication by Diaz et al. (2022), indicated that the short stature and low weight associated with patients with ASMD is correlated with large organ volumes, delayed bone age, and low serum insulin-like growth factor 1 concentrations (29). These additional publications support the rationale for the patient weight used in the model.	The EAG acknowledges that patients with ASMD are likely to have lower weight than the general population. The EAG's preference was to derive patient mean weight data from the Health Survey for England report 2019, as this source was considered more generalisable to the UK (compared to patient characteristic data from the multi-centered ASCEND study). To account for lower patient weight due to ASMD, in its original report the EAG applied the z-score for 18-year olds (as estimated by the company) to data from Health Survey for England report 2019. The EAG conducted scenario analyses surrounding patient weight for both the paediatric and adult populations. The use of data from the Health Survey for England report 2019, was not considered to be a key driver of the ICER.

Key issue	Company response	EAG response
	Following compassionate use requests, Sanofi have provided olipudase alfa to [redacted] UK patients who were severely affected by ASMD type B and A/B. The maximum weight of these patients recorded at baseline was [redacted]. This information further substantiates the rationale that patients with ASMD have a lower weight than the general population.	
EAG key issue #6: The company's economic model was accompanied with a subgroup analysis in people with severe disease, but this analysis had significant limitations	We acknowledge that there are limitations in carrying out a subgroup analysis based on the small sample size in ASCEND. The severe subgroup analysis was provided for illustrative purposes, to explore the cost-effectiveness of olipudase alfa in particularly severe patients. In addition, this analysis is likely conservative, as it uses transition probabilities from the broad patient population.	The EAG thank the company for acknowledging the limitations of this subgroup. The EAG advise caution when interpreting the results of this subgroup, due to the underlying assumptions used.

Abbreviations: AIC, Akaike information criterion; ASMD; acid sphingomyelinase deficiency; BIC, Bayesian information criterion; BSC, best supportive care; CI, confidence interval; DL_{CO}, lung diffusion of carbon monoxide; DSU, Decision Support Unit; EAG, external assessment group; ERT, enzyme replacement therapy;

HST, highly specialised technology; ICER, incremental cost-effectiveness ratio; INPDR, International Niemann-Pick Disease Registry; KOL, key opinion leader; LS, least squares; NICE, National Institute for Health and Care Excellence; NNPDF, National Niemann-Pick disease Foundation; NPUK, Niemann-Pick UK; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; QoL, quality of life; RARE sibling, sibling of a person with a rare disease; SMR, standardised mortality ratio; SV, spleen volume.

3. ADDITIONAL ISSUES

The company further responded to issues raised by the EAG in its report (EAR) that were not considered key issues in the draft guidance. The company and EAG response to these issues is provided in this section.

Table 2: Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Response	EAG response
Potential impact of antibody resistance mentioned by clinical advisers to EAG in Section 4.2.7 of the EAG report	Section 4.2.7 of the EAG report	Immunogenicity data In response to the potential impact of antibody resistance mentioned by clinical advisers to EAG in Section 4.2.7 of the EAG report, Sanofi would like to submit a report on the immunogenicity of olipudase alfa which supports the maintenance of response with long-term olipudase alfa treatment of patients with ASMD, demonstrating that olipudase alfa has a low risk of immunogenicity impacting clinical outcomes (30). [redacted]	The EAG thanks the company for the provision of these data and the associated report. The EAG reviewed the data provided and noted that there may be some limitations in the available follow-up for the immunogenicity data due to the number of participants with data beyond 1 year in the clinical trials, and the wide variation in time to ADA response (time to treatment induced ADA ranged between 2 – 198 weeks). The EAG was also unable to discuss the findings of these analyses with its clinical experts during the timeline for technical engagement. However, the EAG considered the report to show no evidence of antibody resistance in the available evidence. While a significant number of participants developed ADA during the follow-up period, results showed that overall clinical outcomes were comparable with those who did not. While there is still uncertainty surrounding longer-term outcomes of olipudase alfa, the EAG considered these data to provide reassurance around

		[redacted]	concerns that a waning of treatment effect may occur due to antibody resistance, at least within the length of trial follow-up available.

		[redacted]	

Abbreviations: EAR, external assessment report; NA, not applicable.

4. SUMMARY OF CHANGES TO THE COMPANY'S COST-EFFECTIVENESS ESTIMATE(S)

The company made several changes to its basecase analysis; the changes and the EAG response is provided in this section. The company also provided results from a series of sensitivity analyses, including variations to the application of discounting, the long-term treatment effect, and implementation of utility estimates. However, due to concerns about the assumptions made in the company base case as a whole, the EAG did not consider these to be probative to decision-making and these are not presented herein.

Table 3: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
EAG key issue #4: There was uncertainty surrounding the company's approach to modelling mortality	After provision of the initial evidence submission to NICE in August 2022, further data relevant to the decision problem have become available. A chart review and subsequent pooled data analysis of patients with ASMD (n=270) in Germany, France, the USA, and Brazil provides new survival estimates for adults and children with ASMD (31). Clinicians consulted by Sanofi confirmed	New survival data were used to generate survival curves and were incorporated into the model. Please see company addendum to the HST submission for further details.	The original submitted unweighted ICER (£/unweighted QALY gained) for the paediatric population was £[redacted] The original submitted unweighted ICER (£/unweighted QALY gained) for the adult population was £[redacted] The original submitted weighted ICER (£/weighted QALY gained) for the paediatric population was £[redacted] The original submitted weighted ICER (£/weighted	The EAG has highlighted a number of limitations surrounding the company's revised approach to modelling mortality and do not consider this approach to be appropriate (see EAG response to key issue 4 above).

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
	that the population included in this study was generalisable to patients with ASMD in the UK (32).		QALY gained) for the adult population was £[redacted] The original submitted unweighted ICER (£/unweighted QALY gained) for the paediatric population was £[redacted] The original submitted unweighted ICER (£/unweighted QALY gained) for the adult population was £[redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is £[redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is £[redacted]	
EAG key issue #1:The company used differential discounting, which is not consistent with	Sanofi believe that costs and benefits should be discounted using different rates in line with the HM Treasury's Green Book.	We acknowledge that differential discounting is not consistent with the NICE reference case, based on the guidance provided in the NICE health	When added to the change outlined above: The updated unweighted ICER (£/unweighted QALY	The EAG do not consider differential discounting or discounting costs and benefits at 1.5% to be appropriate (see EAG response to key issue 1 above).

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
the NICE reference case		technology evaluations manual, but that there is a strong case to apply a discount of 1.5% to both costs and benefits, if a differential rate is not accepted.	gained) for the paediatric population is [redacted] The updated unweighted ICER (£/unweighted QALY gained) for the adult population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is [redacted]	
EAG key issue #2: The company's long-term efficacy assumption was not supported by robust clinical data.	In the company base case, patients receiving olipudase alfa can only transition to an alternative health state for up to 2 years, after which (i.e., from year 3 onwards) they all transition to the SV <6 / DL_{CO} >80 state and remain there until the	We have revised our base case so that patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which all patients	When added to the change outlined above: The updated unweighted ICER (£/unweighted QALY gained) for the paediatric population is [redacted] The updated unweighted ICER (£/unweighted QALY	The EAG do not consider the company's revised approach to estimating the long-term treatment effect of olipudase to be appropriate (see EAG response to key issue 2 above).

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
	end of the time horizon or death.	transition to the SV <6 / DL_{CO} >80 state from year 10 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients' probability to transition to the 'SV <6 / DL_{CO} >80' state from the other health states between year 2 and year 10.	gained) for the adult population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is [redacted]	
EAG key issue #3: The EAG disagreed with several of the company's assumptions used to model carer HRQoL	In the company's base case model, we account for an average of 1.78 caregiving parents per child with ASMD, in line with HST 11. This is likely to be an underestimate of the true impact of the	We therefore believe this should be reflected in the economic model by the inclusion of siblings in the mean number of caregivers. The mean number of siblings in the UK in 2021 was 1.77 (16). This gives an overall	When added to the change outlined above: The updated unweighted ICER (£/unweighted QALY gained) for the paediatric population is [redacted]	The EAG do not agree with the company's revised approach to estimating number of carers per patient (see EAG response to key issue 3 above).

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
	condition, as it does not take into account the real impact on the extended family and friends of ASMD patients.	average of 2.6 carers per patient.	The updated unweighted ICER (£/unweighted QALY gained) for the adult population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is £[redacted]	
Company's base case following technical engagement (or revised base case)	Paediatric population Incremental weighted QALYs: 112.13 Adult population Incremental weighted QALYs: 61.85	Paediatric population Incremental costs: [redacted] Adult population Incremental costs: [redacted]	The cumulative result of the updates to the company's base case model as a result of the changes outlined in this table is as follows:	Due to the uncertainties discussed throughout this document, the EAG do not consider the company's revised base case to be appropriate for decision making. Furthermore, the company's scenario analyses should be

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
			The updated unweighted ICER (£/unweighted QALY gained) for the paediatric population is [redacted] The updated unweighted ICER (£/unweighted QALY gained) for the adult population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the paediatric population is [redacted] The updated weighted ICER (£/weighted QALY gained) for the adult population is [redacted]	interpreted with caution, as they contain assumptions deemed to be inappropriate by the EAG.

Abbreviations: EAR, external assessment report; ICER, incremental cost-effectiveness ratio; NICE, The National Institute for Health and Care Excellence; QALY, quality-adjusted life year.

5. REFERENCES

1. Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases. Mol Genet Metab. 2016 Jul;118(3):206-13.

2. Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of Illness in Acid Sphingomyelinase Deficiency: A Retrospective Chart Review of 100 Patients. JIMD Rep. 2018;41:119-29.

3. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis. 2021 May 10;16(1):212.

4. Sanofi Genzyme. ASMD chart review pooled data analysis. Data on file. 2022.

5. Hopkin J, Donnelly C, Poutney J, Crowe J, Mathieson T, Mbua S. Acid sphingomyelinase deficiency: Burden of disease and real-world impact of enzyme replacement therapy on pediatric patients and caregivers. Poster presented at 19th Annual WORLDSymposium. Orlando, Florida, USA. 2023.

6. Sanofi. Clinical Study Report: LTS13632. A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency. Data on file. 2021.

7. Weinreb NJ, Camelo JS, Charrow J, McClain MR, Mistry P, Belmatoug N. Gaucher disease type 1 patients from the ICGG Gaucher Registry sustain initial clinical improvements during twenty years of imiglucerase treatment. Molecular Genetics and Metabolism. 2021 2021/02/01/;132(2):100-11.

8. NICE. HST 11. Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. Available at https://www.nice.org.uk/guidance/hst11/resources/voretigene-neparvovec-for-treating-inherited-retinal-dystrophies-caused-by-rpe65-gene-mutations-pdf-50216253809605. Accessed 25 August 2023.

9. Chen J-Y, Clark M-J. Family Resources and Parental Health in Families of Children With Duchenne Muscular Dystrophy. Journal of Nursing Research. 2010;18(4):239-48.

10. Siden H, Steele R. Charting the Territory: Children and families living with progressive life-threatening conditions. Paediatrics & Child Health. 2015;20(3):139-44.

11. Haukeland YB, Fjermestad KW, Mossige S, Vatne TM. Emotional Experiences Among Siblings of Children With Rare Disorders. Journal of Pediatric Psychology. 2015;40(7):712-20.

12. Dinleyici M, Çarman KB, Özdemir C, Harmancı K, Eren M, Kirel B, et al. Quality-of-life Evaluation of Healthy Siblings of Children with Chronic Illness. Balkan Med J. 2019 Dec 20;37(1):34-42.

13. Velasco J, Ferraris V, Eymann A, Coccia PA, Ghezzi LR, Sánchez MC, et al. Quality of life among siblings of patients with chronic conditions. Arch Argent Pediatr. 2020 Aug;118(4):252-7.

14. Schwartz CE, Stark RB, Audhya IF, Gooch KL. Characterizing the quality-of-life impact of Duchenne muscular dystrophy on caregivers: a case-control investigation. J Patient Rep Outcomes. 2021 Nov 20;5(1):124.

15. Alexion. The impact of RARE disease on sibling experience. Impact report. Available at https://rare-revolution-wp-images.s3.eu-west-1.amazonaws.com/wp-content/uploads/2023/01/20092626/The-impact-on-RARE-disease-on-siblings-1.pdf. Accessed 24 August 2023.

16. Office for National Statistics. Average number of dependent children per family in England and Wales, 2020 and 2021. 2023. Accessed August 2023. Available online at: [https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/adhocs/15662averagenumberofdependentchildrenperfamilyinenglandandwales2020and2021].

17. Al-Gamal E. Quality of life and anticipatory grieving among parents living with a child with cerebral palsy. International Journal of Nursing Practice. 2013;19(3):288-94.

18. Duggleby WD, Williams A, Holstlander L, Thomas R, Cooper D, Hallstrom LK, et al. Hope of rural women caregivers of persons with advanced cancer: guilt, self-efficacy and mental health. Rural Remote Health. 2014;14:2561.

19. Götze H, Brähler E, Gansera L, Schnabel A, Gottschalk-Fleischer A, Köhler N. Anxiety, depression and quality of life in family caregivers of palliative cancer patients during home care and after the patient's death. European Journal of Cancer Care. 2018 2018/03/01;27(2):e12606.

20. Liew TM, Tai BC, Wee SL, Koh GC-H, Yap P. The Longitudinal Effects of Caregiver Grief in Dementia and the Modifying Effects of Social Services: A Prospective Cohort Study. Journal of the American Geriatrics Society. 2020;68(10):2348-53.

21. Moore KJ, Davis S, Gola A, Harrington J, Kupeli N, Vickerstaff V, et al. Experiences of end of life amongst family carers of people with advanced dementia: longitudinal cohort study with mixed methods. BMC Geriatrics. 2017 2017/07/03;17(1):135.

22. Nielsen MK, Christensen KS, Neergaard MA, Bidstrup PE, Guldin M-B. Exploring Functional Impairment in Light of Prolonged Grief Disorder: A Prospective, Population-Based Cohort Study. Frontiers in Psychiatry. 2020 2020-December-09;11.

23. Persson C, Östlund U, Wennman-Larsen A, Wengström Y, Gustavsson P. Health-related quality of life in significant others of patients dying from lung cancer. Palliative Medicine. 2008 2008/04/01;22(3):239-47.

24. Giovannetti AM, Covelli V, Sattin D, Leonardi M. Caregivers of patients with disorder of consciousness: burden, quality of life and social support. Acta Neurologica Scandinavica. 2015;132(4):259-69.

25. Wentzel H, Malottki K. Capturing the Impact of Grief and Bereavement on Caregivers in National Institute for Health and Care Excellence Highly Specialised Technology Appraisals. Poster presentation at ISPOR EU 2022 Vienna. 2022.

26. NICE. HST 7. Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. Available at https://www.nice.org.uk/guidance/hst7. Accessed 26 June 2023. 2018.

27. NICE. Velmanase alfa for treating alpha-mannosidosis [ID800]. .

28. Simon N-J, Richardson J, Ahmad A, Rose A, Wittenberg E, D'Cruz B, et al. Health utilities and parental quality of life effects for three rare conditions tested in newborns. Journal of Patient-Reported Outcomes. 2019 2019/01/22;3(1):4.

29. Diaz GA, Giugliani R, Guffon N, Jones SA, Mengel E, Scarpa M, et al. Long-term safety and clinical outcomes of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency: two-year results. Orphanet J Rare Dis. 2022 Dec 14;17(1):437.

30. Sanofi. Integrated Summary of Immunogenicity (Acid Sphingomyelinase Deficiency), Olipudase Alfa. Data on File. 2021.

31. Sanofi Genzyme. ASMD Chart review pooled data analysis. November 2022. Sanofi data on file. .

32. Sanofi Genzyme. Clinical opinion. March 2023. Sanofi data on file.

6. APPENDIX A: EAG COMMENTARY AND CLARIFICATION POST TECHNICAL ENGAGEMENT

The EAG noted that there was a lack of clarity surrounding the company's reported results i.e. it was unclear whether the company's use of the term 'weighted' in the TE response was referring to 'undiscounted' results. Based on review of the Company Updated Base Case Results Post TE, the EAG note that incremental QALYs for the paediatric and adult populations, reported to be 112.13 and 61.85 respectively (in the company's TE response document) reflect QALY weighted results not undiscounted results. These incremental QALYs were estimated by multiplying the discounted QALYs by the maximum QALY weight of 3. The company's respective 'weighted' ICERs of [redacted] and [redacted] for the paediatric and adult populations were estimated based on discounted costs at 1.5% and discounted QALYs at 1.5% (which were multiplied by the maximum QALY weight of 3).

6.1. EAG Accuracy Check of Company Updated Base Case Results Post TE

The EAG noted that the Company Updated Base Case (Post TE results), were not accurate. Concerns related to the following.

- The incremental results reported by the company in their TE response did not match the incremental results reported in the company's model (submitted at TE). For example, the company's 'weighted' ICERs in the paediatric and adult populations were reported to be [redacted] and [redacted] respectively. However, based on the company's model ('Settings' sheet), the ICERs for the paediatric and adult populations were estimated to be [redacted] and [redacted] respectively. The EAG note that the company's revised base case results reported in the TE response were not replicable and the results in the 'Settings' tab were manual entries (also not replicable). The company should have derived their revised results from the 'Base case results' case tab.
- When selecting results from the 'Base case results' tab, the company's 'weighted' ICER's reported for paediatric and adult populations were [redacted] and [redacted] (as per 'Settings' tab) respectively. See Table 2 below.

6.2. Updated Company Base Case Results Post TE (Corrected by the EAG)

For clarity, the EAG considered that it would be useful to provide undiscounted and discounted results separately, as well as provide the company's results which reflect QALY weighting. Table 1 presents the company's revised undiscounted base case results post TE. Note that these results assume 0% discounting of costs and benefits. These results are also unweighted i.e. QALY weighting has not been applied. Table 2 presents the company's revised discounted base case results post TE and also presents results which apply QALY weighting used by the company. For completeness, the EAG have provided further results using undiscounted QALYs and discounted costs (see Section 6.3). However, the EAG draws attention to the fact that there is no precedent for differential discounting of costs and benefits in NICE submissions and that this introduces ethical problems relating to the value placed on the lives of different groups of patients. The EAG strongly recommends an equal discount rate for both costs and benefits.

Table 4: Company Updated Base-Case Post TE (deterministic: undiscounted costs and QALYs)

	Incremental costs (£)	**Incremental QALYs**	**ICER**
Paediatric	[redacted]	55.31	[redacted]
Adult	[redacted]	33.08	[redacted]

Note: Discount rates for costs and QALYs both set to zero and QALYs are unweighted

Table 5: Company Updated Base-Case Post TE (deterministic: discounted base case results and QALY weighted results

	Cost and QALYs discounted at 1.5% (no QALY weighting applied)			**QALY weighting applied (As per company's approach)**	
	Incremental costs (£)	**Incremental QALYs**	**ICER (£/QALY)**	**Incremental QALYs**	**ICER (£/QALY)**
Paediatric	[redacted]	31.00	[redacted]	92.99	[redacted]
Adult	[redacted]	20.85	[redacted]	62.551	[redacted]

Note: for the QALY weighted results, a QALY weight of (x3) has been applied to discounted QALYs as per the company's approach

6.3. Company Updated Base-Case Post TE (using undiscounted QALYs and discounted costs)

The following tables present the company's Updated Base Case Post TE results (as per Table 1 above), but use undiscounted QALYs and discounted costs (at 1.5% to reflect the company's preference and also 3.5%). No QALY weighting has been applied.

Table 6: Company Updated Base-Case Post TE (deterministic: costs discounted at 1.5% and undiscounted QALYs)

	Incremental costs (£)	**Incremental QALYs**	**ICER**
Paediatric	[redacted]	55.31	[redacted]
Adult	[redacted]	33.08	[redacted]

Note: Discount rates for costs set to1.5% as per company base case

Table 7: Company Updated Base-Case Post TE (deterministic: costs discounted at 3.5% and undiscounted QALYs)

	Incremental costs (£)	**Incremental QALYs**	**ICER**

Paediatric	[redacted]	55.31	[redacted]
Adult	[redacted]	33.08	[redacted]

Note: Discount rates for costs set to 3.5%

Comments for the EAG on slide 9 [Part 2-Post PMB]

Comment from Yelan: *'EAG, after another check of the company's response to TE, our take is when company stated "weighted QALYs" or "weighted ICERs", what it meant was undiscounted incremental QALYs and ICERs calculated using these QALYs. Please could you confirm this is your understanding too and what's reported in this table correct as well, thanks.'*

EAG response: The EAG notes that there was a lack of clarity surrounding the company's reported results i.e. it was unclear whether the company's use of the term 'weighted' in the TE response was actually referring to 'undiscounted' results. Based on review of the Company Updated Base Case Results Post TE, the EAG note that incremental QALYs for the paediatric and adult populations, reported to be 112.13 and 61.85 respectively (at the bottom of slide 9 and in their TE response document) reflect QALY weighted results not undiscounted results. These incremental QALYs were estimated by multiplying the discounted QALYs by the maximum QALY weight of 3. The company's respective 'weighted' ICERs of [redacted] and [redacted] for the paediatric and adult populations were estimated based on discounted costs at 1.5% and discounted QALYs at 1.5% (which were multiplied by the maximum QALY weight of 3).

For completeness (and for NICE's consideration), the EAG has estimated the company's Updated Base Case Results Post TE using undiscounted costs and QALYs, and with no consideration of QALY weighting (see Table 1 below).

Furthermore, as described below, the EAG has noted that there were some additional concerns surrounding the company's reported results vs the modelled results. The EAG has therefore provided amended Updated Company Base Case Results Post TE below, which should be used for decision making and replace the estimates at the bottom of slide 9.

EAG Accuracy Check

(Company Updated Base Case Results Post TE)

The EAG noted that the Company Updated Base Case (Post TE results), as reported at the bottom of slide 9 of NICE's Part 2 slide deck were not accurate. The EAG noted the following.

- The incremental results reported by the company in their TE response (and at the bottom of slide 9) did not match the incremental results reported in the company's model (submitted at TE). For example, the company's 'weighted' ICERs in the paediatric and adult populations were reported to be [redacted] and [redacted] respectively. However, based on the company's model ('Settings' sheet), the ICERs for the paediatric and adult populations were estimated to be [redacted] and [redacted] respectively. The EAG note that the company's revised base case results reported in the TE response were not replicable and the results in the 'Settings' tab were manual entries (also not replicable). The company should have derived their revised results from the 'Base case results' case tab.
- When selecting results from the 'Base case results' tab, the company's 'weighted' ICER's reported for paediatric and adult populations were [redacted] and [redacted] (as per 'Settings' tab) respectively. See Table 2 below.

Updated Company Base Case Results Post TE (Corrected by the EAG)

For clarity, the EAG considered that it would be useful to provide undiscounted and discounted results separately, as well as provide the company's results which reflect QALY weighting.

Table 1 presents the company's revised undiscounted base case results post TE. Note that these results assume 0% discounting of costs and benefits. These results are also unweighted i.e. QALY weighting has not been applied.

Table 1: Company Updated Base-Case Post TE (deterministic: undiscounted costs and QALYs)

	Incremental costs (£)	**Incremental QALYs**	**ICER**

Paediatric	[redacted]	55.31	[redacted]
Adult	[redacted]	33.08	[redacted]

Note: Discount rates for costs and QALYs both set to zero and QALYs are unweighted

Table 2 presents the company's revised discounted base case results post TE and also presents results which apply QALY weighting.

Table 2: Company Updated Base-Case Post TE (deterministic: discounted base case results and QALY weighted results)

	Cost and QALYs discounted at 1.5% (no QALY weighting applied)			**QALY weighting applied**	
	Incremental costs (£)	**Incremental QALYs**	**ICER (£/QALY)**	**Incremental QALYs**	**ICER (£/QALY)**
Paediatric	[redacted]	31.00	[redacted]	92.99	[redacted]
Adult	[redacted]	20.85	[redacted]	62.551	[redacted]

Note: for the QALY weighted results, a QALY weight of (x3) has been applied to discounted QALYs