SMC2560

olipudase alfa powder for concentrate for solution for infusion (Xenpozyme®)

Sanofi

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The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: As an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.

Key points:

- ASMD is a chronic disorder with highly variable symptoms ranging from severe, life-threatening complications early in life, to mild ones. Morbidities include splenomegaly, hepatomegaly, liver dysfunction, pulmonary impairment, thrombocytopenia and neurologic manifestations. Growth restriction during childhood and bone disease are also common features of chronic ASMD. Mortality in ASMD is most frequently due to respiratory failure or liver failure; many patients do not survive into adulthood. There are currently no treatments available and patients are managed with supportive care.
- In a double-blind, phase II/III study in adult patients with ASMD type A/B or type B, olipudase alfa significantly improved lung function and reduced spleen and liver volumes compared with placebo after 52 weeks. Data from an open-label, single-arm, phase I/II study in paediatric patients with ASMD type A/B or type B treated with olipudase alfa suggest similar improvements from baseline at week 52.
- There are limited data available in small numbers of patients. Key data in paediatric patients are uncontrolled and efficacy was assessed as exploratory outcomes only. There are limited longer-term efficacy and safety data available for olipudase alfa and some uncertainty about maintenance of effects and long-term safety, and there are no data to support a mortality benefit with olipudase alfa.
- The cost of olipudase alfa in relation to its benefit remains exceptionally high and there are outstanding uncertainties relating to clinical and quality of life data used in the economic model.

Chair
Scottish Medicines Consortium

SMC ultra-orphan designation

Olipudase alfa has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of ASMD is estimated to be ≤1 in 50,000 (or around 100 people in Scotland).
- Olipudase alfa has GB orphan designation for the treatment of ASMD and this was maintained at the time of marketing authorisation.
- ASMD is chronic and severely disabling due to its progressive and debilitating effects on multiple organs, which may shorten life expectancy.
- This condition requires highly specialised management.

1. Clinical context

1.1. Background

Olipudase alfa is a recombinant human acid sphingomyelinase that reduces sphingomyelin accumulation in organs of patients with ASMD, by converting sphingomyelin into ceramide. It is the first enzyme replacement therapy to be licensed for the treatment of non-CNS manifestations in patients with ASMD type A/B or type B. Olipudase alfa is not expected to cross the blood brain barrier, so is not expected to have an effect on neurological symptoms of ASMD. [1, 2]

The recommended maintenance dose is 3mg/kg by intravenous infusion every 2 weeks for adult and paediatric patients, following dose escalation from a starting dose of 0.1mg/kg for adult patients and 0.03mg/kg for paediatric patients (<18 years) as detailed in the Summary of Product Characteristics (SPC).[1]

1.2. Nature of condition

ASMD, formerly known as Niemann Pick disease type A and type B, is a rare lysosomal storage disorder caused by a deficiency of the lysosomal enzyme acid sphingomyelinase (ASM) due to biallelic mutations in the sphingomyelin phosphodiesterase 1 gene, *SMPD1*. This results in progressive accumulation of sphingomyelin within the mononuclear phagocytic system and hepatocytes and manifests as a multisystem disease involving the spleen, lung, liver, bone marrow and lymph nodes. In severe forms of the disease, the CNS and peripheral nervous system are also affected.[2, 3]

The phenotypic variability of ASMD has led to the categorisation of subtypes according to severity and extent of neurological involvement. Type A is the most severe and is characterised by rapidly progressive systemic manifestations, including neurodegeneration, and typically death by 3 years of age. Type B has a variable age of onset ranging from infancy to adulthood and is characterised by slowly progressive multisystem disease manifestations, including pulmonary disease (mainly interstitial lung disease), growth restriction, dyslipidaemia, cardiac disease, liver disease, osteoporosis and thrombocytopenia, with little or no neurological involvement. Patients may have a normal lifespan or die prematurely from complications including pulmonary disease, liver failure and haemorrhage. Type A/B is an intermediate

severity type with onset in childhood and is characterised by slowly progressive neurodegeneration, including mild hypotonia and hyporeflexia, loss of motor function, ataxia and cognitive decline. In all types of ASMD, hepatosplenomegaly is common.[2-5]

The disease burden in patients with ASMD type B or type A/B is primarily driven by the degree of impairment of lung and liver function and complications due to excessive organ enlargement, with respiratory complications, liver failure and bleeding events being key drivers of early mortality, development delays and failure to thrive prominent in children.[2]

Clinical manifestations of ASMD can have a severe impact on patients' quality of life. They can affect a patient's ability to care for themselves or for others, attend work or school, perform common daily activities and take part in social activities. They can also have an impact on a patient's self-esteem and can lead to anxiety and depression.

Due to the heterogeneity in clinical presentation and severity, patients with ASMD require individualised specialist management by multidisciplinary clinical teams. Currently this includes palliative care and supportive care to manage symptoms, such as statins, bronchodilators, antibiotics, fresh plasma (for thrombocytopenia) and calcium (for osteoporosis). Supplemental oxygen may be required in patients with severe pulmonary complications. Liver transplantation may also be offered to some patients with end-stage liver disease. There is currently no disease-specific treatment for ASMD to modify or slow the progression of the disease.[2, 3, 5]

The submitting company considers that best supportive care (including monitoring patients, providing symptomatic relief and supportive care) is the only relevant comparator. This was confirmed by clinical experts consulted by SMC.

Clinical experts consulted by SMC considered that olipudase alfa fills an unmet need in this therapeutic area, as patients are currently managed only with supportive care.

2. Impact of new technology

Comparative efficacy

Key evidence to support the efficacy and safety of olipudase alfa in adults with ASMD type A/B or B comes from ASCEND. Details are summarised in Table 2.1.

Table 2.1 Overview of relevant study[2, 6-8]

Criteria	ASCEND (DFI12712)
Study design	International, randomised, double-blind, phase II/III study.
Eligible patients	• Male or female, aged ≥18 years. • Documented deficiency of acid sphingomyelinase (ASM) as measured in peripheral leukocytes, cultured fibroblasts or lymphocytes; and a clinical diagnosis consistent with Niemann Pick disease type B. • Lung diffusing capacity for carbon monoxide (DL_{CO}) ≤70% of the predicted normal value. • Spleen volume ≥6 multiples of normal (MN) measured by magnetic resonance imaging (MRI); patients who have had partial splenectomy were included if the

	procedure was performed ≥1 year before screening and the residual spleen volume is ≥6 MN. • Splenomegaly-related score (SRS) ≥5.
Treatments	During the 52-week primary analysis period (PAP), patients were randomised equally to receive olipudase alfa at the target maintenance dose of 3.0mg/kg (a dose escalation scheme was followed starting at 0.1mg/kg with scheduled increases every 2 weeks to the target maintenance dose or maximum tolerated dose; n=18) or placebo (0.9% sodium chloride, n=18), administered by intravenous infusion (IV) every 2 weeks (±3 days). Medications that may decrease olipudase alfa activity were prohibited.
Primary outcomes	• Percentage change in DL_{CO} (in % predicted of normal) from baseline to week 52. • Percentage change in spleen volume (in MN) from baseline to week 52.
Secondary outcomes	• Percentage change in liver volume from baseline to week 52. • Percentage change in platelet count from baseline to week 52. • Change in Brief Fatigue Inventory (BFI) scale, item 3 from baseline to week 52. • Change in Brief Pain Inventory (BPI) scale, item 3 from baseline to week 52. • Change in Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnoea symptom score from baseline to week 52. • Change in SRS from baseline to week 52.
Statistical analysis	A hierarchical testing procedure was applied to the primary and secondary outcomes (in the order as listed above) with no formal testing after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes after the first non-significant outcome are descriptive only and not inferential (no p-values reported).

At week 52, at the end of the PAP, patients treated with olipudase alfa had a significantly greater improvement in the percentage change in predicted DL_{CO} and the percentage change in spleen volume (in MN) from baseline, compared with placebo. The percentage change in liver volume from baseline and the percentage change in platelet counts from baseline were also both significantly improved in the olipudase alfa group compared with the placebo group. However, the change from baseline in fatigue severity (as assessed by BFI item 3) was not statistically significant and therefore the hierarchical testing was stopped. Results are summarised in Table 2.2 below.[2, 6]

Table 2.2 Results for primary and selected secondary outcomes in ASCEND[2, 6,9]

	Olipudase alfa (n=18)[a]	Placebo (n=18)[a]
Primary outcomes		
% predicted DL_{CO}		
Mean at baseline	49	48
Percentage change from baseline to week 52, LSM	22	3.0
Difference versus placebo (95% CI), p-value	19 (9.3 to 29), p<0.001	
Spleen volume (MN)		
Mean at baseline	11.7	11.2
Percentage change from baseline to week 52, LSM	-39	0.5
Difference versus placebo (95% CI), p-value	-40 (-47 to -33), p<0.001	

Selected secondary outcomes		
Liver volume (MN)		
Mean at baseline	1.4	1.6
Percentage change from baseline to week 52, LSM	-28	-1.5
Difference versus placebo (95% CI), p-value	-27 (-34 to -19), p<0.001	
Platelet count (10^9/L)		
Mean at baseline	107.2	115.6
Percentage change from baseline to week 52, LSM	17	2.5
Difference versus placebo (95% CI), p-value	14 (2.6 to 26), p=0.02	

Abbreviations: CI=confidence interval; DL_{CO}=diffusing capacity for carbon monoxide; LSM=least squares mean; MN=multiples of normal; NS=not significant.
[a] For olipudase alfa: n=17 for DL_{CO}. For placebo: n=17 for spleen and liver volume, and DL_{CO}, n=16 for platelet count.

Health-Related Quality of Life (HRQoL) was assessed using nine questionnaires (BFI, BPI Short form, FACIT-Dyspnoea Short form, EuroQol-5 dimension-5 level, Short Form Health Survey-36 item v2, Niemann Pick B-Health Assessment Questionnaire, health-related productivity questionnaire, Patient Global Impression of Change [PGIC] scale and Patient Global Impression of Symptom Severity scale).[8] At week 52, with the exception of one item on the PGIC (shortness of breath), the results suggest there was no difference in HRQoL between treatment groups.[2, 6]

Patients who completed the double-blind PAP could enter a 52-week open-label, extension treatment period (ETP) to receive olipudase alfa. After week 104, patients could remain in the study for long-term follow-up. Thirty-five patients (all except one patient from the placebo group) continued in the ETP and 33 patients completed to week 104 of the ETP. At week 104, the percentage change from baseline in % predicted DL_{CO} improved by 28% in both the crossover (placebo/olipudase alfa) group (n=10) and the group originally assigned to olipudase alfa (olipudase alfa/olipudase alfa; n=10). The percentage change in spleen volume from baseline was also reduced by 36% in the placebo/olipudase alfa group (n=11) compared with 47% in the olipudase alfa/olipudase alfa group (n=14). A further reduction in spleen volume was also observed in both groups at week 132 (43% in the placebo/olipudase alfa group [n=11] versus 52% in the olipudase alfa/olipudase alfa group [n=13]). At week 104, the percentage change in liver volume and the percentage change in platelet count also improved by -31% and +22% in the placebo/olipudase alfa group, respectively, compared with -33% and +25% respectively in the olipudase alfa/olipudase alfa group. Further reductions in liver volume were also observed in the placebo/olipudase alfa group at week 132 (31%) and at week 156 (35%), compared with 34% and 34% respectively in the olipudase alfa/olipudase alfa group.[2, 7]

Key evidence to support the efficacy and safety of olipudase alfa in paediatric patients with ASMD type A/B or B comes from ASCEND-Peds. Details are summarised in Table 2.3.

Table 2.3 Overview of relevant study [2, 10-12]

Criteria	ASCEND-Peds (DFI13803)
Study design	International, open-label, single arm, phase I/II safety study.
Eligible patients	• Male or female <18 years of age. • Documented deficiency of acid sphingomyelinase (ASM) consistent with Niemann Pick disease, as measured in peripheral leukocytes, cultured fibroblasts or lymphocytes without acute or rapidly progressive neurological abnormalities. • Spleen volume ≥5 multiples of normal (MN) measured by magnetic resonance imaging (MRI); patients who have had partial splenectomy were allowed if the procedure was performed ≥1 year before screening and the residual spleen volume was ≥5 MN. • Patient's height was -1 Z-score or lower.
Treatments	Olipudase alfa IV infusions were administered once every 2 weeks (±3 days) for 64 weeks, starting at 0.03mg/kg with dose escalation up to the final target maintenance dose of 3mg/kg (n=20). Medications that may decrease olipudase alfa activity were prohibited.
Selected exploratory efficacy outcomes	• Mean percent change in % predicted diffusing capacity for carbon monoxide (DL_{CO}) to week 52. • Mean percent change in spleen volume and liver volume (in MN), as measured by abdominal MRI to week 52. • Mean percent change in platelet counts to week 52. • Linear patient growth as measured by height Z-score to week 52.
Statistical analysis	Efficacy outcomes were exploratory only. No multiplicity adjustments were conducted.

ASCEND-Peds data are suggestive of improvements, including on the outcomes of DL_{CO}, spleen and liver volumes, platelet count and height Z-scores with olipudase alfa at week 52 compared to baseline in paediatric patients and were seen across all paediatric age cohorts.[1, 2, 10, 11] Descriptive results for selected exploratory outcomes are summarised in Table 2.4.

Table 2.4 Results for selected exploratory outcomes in ASCEND-Peds[1, 2, 10, 11]

	Olipudase alfa (n=20)
% predicted DL_{CO}	
Mean at baseline[a]	55%
Mean at week 52[a]	72%
% change from baseline to week 52 (95% CI)	33% (13 to 52)
Spleen volume (MN)	
Mean at baseline	19
Mean at week 52	9.3
% change from baseline to week 52 (95% CI)	-49% (-53 to -45)
Liver volume (MN)	
Mean at baseline	2.7
Mean at week 52	1.5
% change from baseline to week 52 (95% CI)	-41% (-44 to -37)
Platelet count (10^9/L)	
Mean at baseline	137.7
Mean at week 52	173.6
% change from baseline to week 52 (95% CI)	34% (18 to 50)

Height Z-scores	
Mean at baseline[b]	-2.1
Mean at week 52[b]	-1.6
change in height Z-scores from baseline to week 52 (95% CI)	0.6 (0.4 to 0.7)

Abbreviations: CI=confidence interval; DL_{CO}=diffusing capacity for carbon monoxide; MN=multiples of normal.
[a] evaluated in nine paediatric patients aged ≥5 years who were able to perform the test. [b] evaluated in 19 paediatric patients.

Questionnaires designed to measure general quality of life (PedsQL Generic Core Scale), fatigue (PedsQL Multidimensional Fatigue Scale) and pain (PedsQL Paediatric Pain Questionnaire) were used. PedsQL Generic Core Scale and Multidimensional Fatigue Scale showed some improvements at week 52 compared to baseline.[2, 13]

LTS13632 is an ongoing open-label, long-term, phase II study, designed to assess the safety of olipudase alfa in adult and paediatric patients with ASMD type B or type A/B, who completed the treatment period of ASCEND-Peds or DFI13412 (a 26-week open-label, single group, ascending dose, phase Ib study in five adult patients). All 20 patients from ASCEND-Peds and all five patients from DFI13412 were enrolled in the study. Patients started at the same dose they were receiving in their original study provided they had not missed more than one biweekly dose before entry, with dose escalation as per the original studies; patients would receive their olipudase alfa dose IV every 2 weeks for up to 9 years or until marketing authorisation. At the data cut-off 1 March 2021 (second interim analysis), all patients demonstrated a reduction in spleen volume (in MN) starting at month 6 and continuing up to month 78 in the overall population (-60% in adults from baseline to month 78, and -69% in paediatric patients from baseline to month 48). A reduction in liver volume (in MN) was also observed in all patients, starting at month 6 and sustained up to month 78 in adult patients (-44% from baseline to month 78) and month 48 in paediatric patients (-55% from baseline to month 48). Improvements in predicted DL_{CO} were also observed over time; adult patients had a 55% improvement on average by month 78 and paediatric patients had a 60% improvement on average by month 48.[1, 2, 14, 15,]

Comparative safety

Comparative safety data are only available in adults from ASCEND. In the 52-week placebo-controlled period of ASCEND, any treatment-emergent adverse event (AE) was reported by all patients in the olipudase alfa group (n=18) and in the placebo group (n=18); these were considered potentially related to study treatment in 67% and 33%, respectively. In the olipudase alfa and placebo groups respectively, patients reporting a severe AE were 5.6% versus 33% and patients with a reported serious AE were 17% versus 22% (no serious AEs were related to treatment). One patient in the olipudase alfa group and none in the placebo group had an AE leading to dose reduction. The proportion with study treatment interruption due to treatment-emergent AEs was 17% in both groups. No patients withdrew or discontinued the study due to an AE. In the 52-week placebo-controlled period, the most frequently reported AEs potentially related to treatment in the olipudase alfa group versus the placebo group

(reported in more than 10% of patients in any group) were: headache (44% versus 17%); nausea (11% versus 17%); abdominal pain (11% versus 0); musculoskeletal chest pain (11% versus 0); myalgia (11% versus 0); pyrexia (11% versus 0); vomiting (5.6% versus 11%); increased blood bilirubin (5.6% versus 11%); fatigue (5.6% versus 11%); and feeling hot (0 versus 11%).[6]

No comparative safety data are available in paediatric patients. Data suggest a higher proportion of paediatric patients than adults experienced the most frequently reported AEs.[2] Refer to SPC for safety details. [1]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- Statistically significant and clinically relevant improvement in the co-primary outcomes (the use of which has been agreed upon by regulators) of % predicted DL_{CO} (pulmonary function test, considered capable to objectively show treatment effect on lung function and reduction of local inflammation) and spleen volume reduction were seen with olipudase alfa in a double-blind, phase II/III study, at week 52 when compared with placebo in adult patients. Liver volume reduction and improvement in platelet counts observed with olipudase alfa, when compared with placebo in adults, were also statistically significant and considered supportive of its benefits for patients with ASMD type A/B and B.[2]
- Exploratory efficacy data from an open-label, single arm, phase I/II study in paediatric patients are also suggestive of improvements (including on the outcomes of DL_{CO}, and spleen and liver volumes) from baseline to week 52 in children who received olipudase alfa. In addition, regulators considered it was reasonable to extrapolate efficacy results from adults to children. In paediatric patients, there was a trend towards improvement in quality of life and fatigue and height Z-scores (suggestive of growth catch-up).[2]
- Although limited, uncontrolled, open-label extension data suggest maintenance of the improvements seen in the key studies with olipudase alfa in the long term.[2]
- Clinical experts consulted by SMC considered that olipudase alfa is a therapeutic advancement as it is the only available specific treatment for this disease, which is currently managed with supportive care.

Key uncertainties:

- Key data in paediatric patients are from a small open-label, single group, phase I/II study. Regulators considered, because of the small sample size (n=20) and uncontrolled, open-label nature of the study, that no firm conclusions could be drawn from the paediatric

data. In addition, in the paediatric study, efficacy outcomes were exploratory; therefore, these results should be interpreted with caution. [2]

- The prospective natural history study, SPHINGO-100, which included 30 paediatric patients, was used to inform the economic case for best supportive care in paediatric patients. Upon request, the submitting company presented a comparison of the data from ASCEND-Peds for olipudase alfa (n=20) and the paediatric subgroup from SPHINGO-100 (n=30). This was a naive side-by-side comparison of baseline characteristics and selected efficacy results (up to week 52) and no measures of relative efficacy were presented. There are several limitations associated with this comparison including the methods used, and the significant clinical and methodological differences between the two studies (including in terms of study design and baseline characteristics).[16] An adjusted comparison, using the same two studies, was presented in a regulatory public assessment report. This compared efficacy outcomes reported at week 52, adjusting for baseline value, baseline age and baseline neurological manifestation. In line with the naïve comparison, the results of the adjusted comparison suggest there were relevant improvements seen in spleen volume (-46%) and liver volume (-48%), platelet count (+46%) and height Z-score (+0.64), but not in percent predicted $DL_{CO,}$ in patients treated with olipudase alfa in the ASCEND-Peds study, compared with patients from the SPHINGO-100 study. This adjustment reduced the patient numbers available for analysis (n=15 and n=14 respectively).[2]
- ASMD is a chronic lifelong condition. The primary outcomes were surrogate outcomes and there are no long-term controlled data beyond 52 weeks. The available longer term data, although supportive of maintenance of effects, are very limited; thus, there is uncertainty about maintenance of efficacy and long-term safety of olipudase alfa, a potentially lifelong treatment. There are no data on longer term effects on morbidity or mortality.
- In the ASCEND study in adults, change from baseline in fatigue severity (as assessed by BFI item 3) was not statistically significant, which stopped the hierarchical testing and the results for subsequent key secondary outcomes were only descriptively assessed.[6]
- Improvements in quality of life measurements would be relevant in patients with ASMD, whose day-to-day functioning may be affected by their disease. In adults, with the exception of the shortness of breath item on the PGIC, results suggest there was no difference between olipudase alfa and placebo groups. In paediatric patients, where data suggest improvements in quality of life and fatigue compared to baseline, no firm conclusions can be drawn, given the data limitations (including the small sample size and uncontrolled nature of data).
- ASCEND study eligibility criteria were that patients had a clinical diagnosis with Niemann Pick disease type B. ASCEND-Peds study eligibility criteria were that patients had a clinical diagnosis with Niemann Pick disease without acute or rapidly progressive neurological abnormalities. The studies did not differentiate between patients with ASMD type B or A/B. Neurologic manifestations at baseline, consistent with a clinical diagnosis of ASMD

type A/B, were seen in 25% of patients in ASCEND and in 40% of patients in ASCEND-Peds. The remaining patients had a clinical diagnosis consistent with ASMD type B. There were no results available by subtype.[1, 2, 6, 10, 11]

3. Impact beyond direct health benefits and on specialist services

The reduction in ASMD manifestations may allow patients to better participate in activities of daily living, self-care (and care for others), education and employment, with fewer absences due to illness and medical appointments. This may lead to improved economic situations and quality of life for both the patients and their families and carers, whose care burden may be reduced. Family functioning may be improved.

Although patient numbers are expected to be small, there may be service implications related to treatment initiation and supervision and necessary monitoring. Olipudase alfa is expected to be delivered by homecare services following a period of hospital use.

4. Patient and carer involvement

- The following information reflects the views of the specified Patient Group. We received a patient group submission from Niemann-Pick UK, which is a registered charity.
- Niemann-Pick UK has received 12.6% pharmaceutical company funding in the past two years, with none from the submitting company.
- ASMD is a systemic disease with a wide array of manifestations causing a high physical and psychological burden (for patients, carers and siblings) and significantly impacting quality of life. The psychosocial impact 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. For patients, this includes a sense of 'feeling different' due to delayed puberty, short stature and significantly enlarged abdominal organs.
- There are currently no treatment options for ASMD except supportive care. Best supportive care is complex and costly, due to the progressive and multi-systemic nature of ASMD and involvement of many different specialities.
- 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. Following treatment with olipudase alfa, families and carers consulted by the patient group observed life-changing effects, reporting that their child was no longer exhausted, could attend school for a full day, eat normal size meals, walk greater distances without breathlessness and have the energy to enjoy social activities. The emotional and mental health impacts of ASMD on both patients and families is profound, and they reported that olipudase alfa mitigated those impacts in a meaningful way. The impact of this technology may go 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.

5. Value for money

5.1. Economic case

The submitting company provided an economic case as described in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (up to 100 years of age; 66 years in the adult population and 92 years in the paediatric population)
Population	Adult and paediatric patients with non-CNS manifestations of ASMD type B or A/B.
Comparators	Best supportive care (BSC)
Model description	Markov cohort model with 10 health states according to: spleen volume <6 MN (mild splenomegaly), 6 to 15 MN (moderate splenomegaly) and >15 MN (severe splenomegaly) and lung function (DLco - ≥80% [mild reduction], 40-80% [moderate reduction] and <40% [severe reduction]) and an all-absorbing dead state. Cycle length was 6 months for the first two cycles and annual thereafter.
Clinical data	Clinical data on spleen volume and lung function for intervention and comparator were obtained from various sources. For the analysis in the adult population, data for the first year came from ASCEND [6,9] and DFI13412[17], and from ASCEND and LTS13632[14, 15] and the observational SPHINGO-100[18] study thereafter. Data for the paediatric population came from the ASCEND-Peds[10, 11] and LTS13632 for olipudase alfa and from SPHINGO-100 in the comparator arm. Mortality was modelled using estimated standardised mortality ratios (dependent on the presence of severe splenomegaly) from SPHINGO-100 and US Life tables and applied to Scottish general population mortality. Annual health state-specific respiratory and bleeding complications were derived using data from two observational studies (SPHINGO-100 and SPHINGO-302). Additionally, annual treatment-specific rates were assumed for liver, spleen and cardiovascular complications.
Extrapolation	Treatment-specific transition probabilities were estimated using a multi-state modelling approach. Patients in the olipudase arm were assumed to move between states in the first 2 years only and remain in the best possible health state – SV < 6 MN and DLco >80% thereafter, for the duration of the model.
Quality of life	Health state-specific utility weights were obtained from a time-trade-off utility elicitation exercise conducted by the manufacturer. Health-states were described in terms of spleen volume and lung capacity with preferences elicited from the general population. Utility decrements associated with complications were obtained from the literature. Caregiver disutilities (-0.15 in each health state) were assumed in the comparator arm only. A one-off care giver disutility associated with death was applied in both arms (-0.5). In the paediatric population, 1.8 carers were assumed reducing to 1 in the adult population. No utility decrements associated with treatment-related adverse events were included.
Costs and resource use	Apart from medicine acquisition (90% compliance) and administration costs, other cost included in the analysis were medical management of ASMD, treatment of adverse events, and complications.

PAS	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of olipudase alfa.

5.2. Results

The SMC-preferred base case results are presented in Table 5.2 below with the company base case in Table 5.3 (scenario 2). The QALY gain is primarily driven by the modelled improvement in splenomegaly and lung capacity, and no carer utility decrements in the olipudase arm but also by the reduced rate of ASMD-related complications and the modelled improvement in survival. The main driver of incremental costs is the acquisition cost of olipudase alfa.

Table 5.2: SMC-preferred base case results (with PAS and no caregiver utility decrements)

Population	**ICER (£/QALY)**
Paediatric	£1,145,879
Adult	£1,340,531
Combined	£1,230,407

5.3. Sensitivity analyses

A limited number of sensitivity analyses were provided by the company with the majority of main scenarios additionally requested by SMC. Key scenarios are summarised in Table 5.3.

Table 5.3: Selected scenario analyses (ICERs with PAS)

	Scenario	**Base case**	**Paediatric**	**Adult**	**Combined**
0	**Base case (SMC-preferred)**	**-**	**£1,145,879**	**£1,340,531**	**£1,230,407**
1	Compliance: 100%	Compliance: 90%	£1,272,348	£1,486,171	£1,365,201
2	Carer disutilities: per-cycle included in the BSC arm only; one-off disutility associated with death in both arms **(company-presented base case)**	No care giver disutilities included	£679,604	£813,116	£736,846
3	Spleen-volume dependent SMR calculated using lower end of the confidence interval from SPHINGO-100 OR for splenomegaly mortality risk	Spleen-volume dependent SMR calculated using SPHINGO-100 OR for splenomegaly mortality risk	£1,210,430	£1,545,314	£1,377,872

4	Spleen-volume dependent SMR calculated using upper end of the confidence interval from SPHINGO-100 OR for splenomegaly mortality risk	Spleen-volume dependent SMR calculated using SPHINGO-100 OR for splenomegaly mortality risk	£1,136,262	£1,368,996	£1,252,629
Abbreviations: ICER, incremental cost-effectiveness ratio; OR, odds ratio					

5.4. Key strengths:

Key strengths of the analysis include the use of an appropriate comparator and somewhat adequate use of the available scarce clinical efficacy data.

5.5. Key uncertainties:

The analysis is associated with the following uncertainties:

- Lack of adequate direct comparative efficacy evidence due to the rarity of the disease. Although some direct comparative efficacy data are available in the adult population, no such data are available for the paediatric population. The company provided little detail regarding the multi-state modelling adopted for the derivation of treatment-specific transition probabilities. However, it does not appear that the available data for olipudase alfa and comparator were adjusted in any way to reflect possible differences between populations. Therefore, the modelled relative treatment efficacy of olipudase alfa is highly uncertain.
- No justification was provided for the choice of cut-off points for splenomegaly and DLco severity levels upon which the model health states were based. It is unclear if these cut-off points represent clinically meaningful differences in disease severity.
- The assumption of only mild disease after 2 years of treatment with olipudase alfa as patients transition to the best possible health states (mild splenomegaly (<6MN) and a mild reduction in lung capacity (DLco >80%)) for the entire duration of the economic model is considered optimistic. The evidence in support of durable treatment effect is limited. Furthermore, the clinical efficacy evidence for olipudase alfa was presented as the average change from baseline, which does not imply that all patients achieve those outcomes. It is therefore inappropriate to make such assumption in the economic model. This uncertainty has not been adequately explored.
- There is uncertainty around mortality benefit associated with the effect of olipudase alfa on spleen volume.
- The effect of olipudase alfa on HRQoL for patients with ASMD remains uncertain. The use of a vignette study to derive health state utilities instead of the available relevant EQ-5D data may not be appropriate. The preference elicitation study conducted by the company has little external validation. The utility weights for the best possible health states seemed higher than the general population age and sex-adjusted utility values. This raises concerns

regarding validity and possible bias in favour of olipudase alfa due to the treatment effect assumption discussed above.

- Additionally, the inclusion of unusually high carer disutilities only in the comparator arm may be creating a bias in favour of olipudase alfa. In line with SMC guidance, these have been removed in the preferred base case analysis.
- Lack of evidence presented regarding the source and the method behind the derivation of treatment arm-specific complication rates associated with ASMD.
- The context of administration of olipudase alfa in the economic evaluation is inconsistent with assumptions in the clinical evidence provided and may underestimate costs associated with administration.

The cost of olipudase alfa in relation to its benefit remains exceptionally high and there are outstanding uncertainties relating to clinical and quality of life data used in the economic model.

6. Costs to NHS and Personal Social Services

The submitting company estimated there would be 2 patients eligible for treatment with olipudase alfa in year 1 rising to 4 patients in year 5. The estimated uptake rate was 100% in all years.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

There are currently no Scottish or British guidelines for the management of patients with ASMD. Three publications reporting international guidelines for the treatment pathway of ASMD are currently available. These consensus recommendations predate the availability of olipudase alfa.

- The American College of Medical Genetics Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases published in 2011: Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals.[5]
- An international panel of experts in the clinical and laboratory evaluation, diagnosis, treatment and management, and genetic aspects of ASMD published in 2017: Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency.[4]

- An international group of ASMD experts in various research and clinical fields published in 2019: Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD).[3]

8. Additional information

8.1. Product availability date

04 July 2023

8.2. Summary of product characteristics

Olipudase alfa 20mg powder for concentrate for solution for infusion (Xenpozyme®). SPC is available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
olipudase alfa	**Recommended starting dose: 0.1mg/kg for adult patients and 0.03mg/kg for paediatric patients. Recommended maintenance dose (dose escalation regimens detailed in SPC): 3mg/kg every 2 weeks for adult and paediatric patients.**	**Year 1 (dose escalation + maintenance):** • **Paediatric patients: £227,556** • **Adult patients: £834,372** **Subsequent years (maintenance)** • **Paediatric patients: £281,736** • **Adult patients: £1,033,032**

Costs from eMC Dictionary of Medicines and Devices Browser (NHS Indicative Price) on 03 March 2023. Costs calculated based on a body weight of 20kg in paediatric patients and 70kg in adults, and using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 14 April 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.