



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 May 2022
EMA/571472/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xenpozyme

International non-proprietary name: olipudase alfa

Procedure No. EMEA/H/C/004850/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ADA:	anti-drug antibody
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
APR:	acute phase reaction
ASM:	acid sphingomyelinase
ASMD:	acid sphingomyelinase deficiency
ASMKO:	acid sphingomyelinase knock out
AST:	aspartate aminotransferase
AUC _{0-τ} :	area under the concentration-time curve over a dosing interval
BUN:	blood urea nitrogen
C _{max} :	maximum concentration
CMQ:	company medical query
COVID-19:	coronavirus disease 2019
CRS:	cytokine release syndrome
CSR:	clinical study report
CV%:	percent coefficient of variation
DBS	Dried blood spots
DLTs:	dose-limiting toxicities
EAIR:	exposure adjusted incidence rate
ECG:	electrocardiogram
ECHO:	echocardiogram
eIND:	emergency investigational new drug
ETP:	extension treatment period
EU:	European Union
GGT:	gamma glutamyl-transferase
HLT:	high-level term
hsCRP:	high sensitivity C reactive protein
IAR:	infusion-associated reaction

ID:	identification
Ig:	immunoglobulin
IL:	interleukin
ISI:	Integrated Summary of Immunogenicity
ISS:	Integrated Summary of Safety
LFT:	liver function test
LLN:	lower limit of normal
LVEF:	left ventricular ejection fraction
MedDRA:	Medical Dictionary for Regulatory Activities
NOAEL:	no observable adverse effect level
NPD:	Niemann-Pick Disease
NZW:	New Zealand White
PAP:	primary analysis period
PCSA:	potentially clinically significant abnormalities
PT:	preferred term
PY:	patient-years
rhASM:	recombinant human acid sphingomyelinase
SAE:	serious adverse event
SCS:	Summary of Clinical Safety
SM:	sphingomyelin
SMPD1:	sphingomyelin phosphodiesterase 1
SMQ:	standard MedDRA query
SOC:	system organ class
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
US:	United States
WBC:	white blood cell
WHO-DD:	World Health Organization-Drug Dictionary

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Genzyme Europe BV submitted on 26 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Xenpozyme, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 May 2017.

Xenpozyme, was designated as an orphan medicinal product EU/3/01/056 on 19 September 2001 in the following condition:

'Treatment of Niemann-Pick disease type B'

On 20 July 2016, Sanofi Genzyme submitted an application to broaden the orphan designation initially granted from the treatment of Niemann-Pick disease type B (NPD B) to the treatment of Acid Sphingomyelinase Deficiency (ASMD). The Committee for Orphan Medicinal Products (COMP) accepted broadening the orphan designation to "treatment of Niemann-Pick Disease", i.e., Niemann-Pick Disease including subtypes A, B, and C. The COMP opinion acknowledged that NPD Type C is a different disease than NPD Types A and B and cannot be treated with olipudase alfa.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Xenpozyme as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

<https://www.ema.europa.eu/en/medicines/human/EPAR/Xenpozyme>

The applicant initially applied for the following indication:

Xenpozyme (olipudase alfa) is indicated as a disease-modifying enzyme replacement therapy for long-term treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients.

The final applied indication was as follows:

Xenpozyme is indicated 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0459/2020, on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0459/2020 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active Substance status

The applicant requested the active substance olipudase alfa contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Olipudase alfa was granted eligibility to PRIME on 18 May 2017 in the following indication: treatment of non-neurological manifestations of acid sphingomyelinase deficiency (ASMD).

Eligibility to PRIME was granted at the time in view of the following:

- ASMD is a rare disease with high morbidity and mortality rates. No authorized, aetiology-specific treatment that modifies aspects of the disease or alters the rate of disease progression exists. Available treatment focuses on symptomatic management with palliative and supportive care. In line with the non-CNS distribution of the product, the highest potential of clinical benefit can be expected for patients with chronic visceral forms of ASMD.
- Olipudase alfa is a biologically plausible enzyme replacement therapy (ERT). Data derived in an ASMKO mouse model provide proof of principle in a relevant animal model.
- The preliminary clinical data presented support the assumption of biochemical and clinically relevant activity and therefore the ability to address the unmet medical need.
- Increased breakdown and reduced storage of sphingomyelin has been shown for up to 30 months.
- Consistent long-term reductions in spleen and liver volumes, transaminases, improvement in pulmonary function (DLCO) and pulmonary morphology, improvement of lung infiltration and a less atherogenic lipid profile suggesting potential clinical benefit in patients with ASMD.

Upon granting of eligibility to PRIME, Johann Lodewijk Hillege was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 23 October 2017. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- process validation, follow-up on critical quality attributes, and post-approval change management protocols;
- rationale for not conducting juvenile toxicity studies;
- paediatric investigation plan (PIP) including the extrapolation study component, the supplementary pharmacokinetic/pharmacodynamics model and the quantitative systems pharmacology;
- adequacy of the data package at the time of filing to support a paediatric indication;
- data quality and governance of the International Niemann Pick Disease Registry intended for post-marketing evidence generation, including for HTA purposes.

1.7. Protocol assistance

The applicant received the following Scientific Advice or Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference
23 October 2003	EMA/H/SA/438/1/2003/PA/III
23 October 2014	EMA/H/SAH/029/1/2014/II
23 April 2015	EMA/H/SA/3061/1/2015/PA/I
25 January 2018	EMA/H/SA/3061/2/2017/PA/PR/II
26 April 2019	EMA/H/SA/3061/2/FU/1/2019/PA/PED/PR/II
27 June 2019	EMA/H/SA/3061/1/FU/1/2019/PA/PED/PR/I
29 January 2021	EMA/SA/0000046707

The applicant received Scientific Advice or Protocol Assistance on seven occasions as mentioned in the table above for the development of Xenpzyme for treatment of non-neurological manifestations of Acid Sphingomyelinase Deficiency (ASMD). The Protocol Assistance pertained to the following Quality, Pre-Clinical and Clinical aspects:

- High-molecular weight forms of DS – characterisation and exclusion of untoward effects, identification and declaration of molecular form
- Manufacturing process change: validation including viral clearance, specifications, change in analytical methods, process related impurities, host cell protein control, comparability demonstration vs. previous process
- Use of DP from different manufacturing processes during different phases of clinical development and commercially
- Analytical control strategy for commercial material: release, characterisation, stability, in process tests, impurity characterisation
- Acceptance criteria for commercial release
- Tests to demonstrate bioreactor interchangeability, strategy for DS intermediate hold studies, demonstration of process consistency across lyophilizers used
- DP stability characterisation to inform shelf-life information

- Viral clearance studies validation
- Non-clinical comparability of DS lots for clinical and non-clinical use
- Phase 1/2 study design: study population, inclusion of paediatrics, dosing regimen, study duration, efficacy endpoints, performance of liver biopsies, PK characterisation
- Target indication in the light of planned evidence generation
- Phase 3 programme: primary and secondary efficacy endpoints,
- PRO development
- CMA: acceptability and evidence to support B/R assessment
- Disease progression in adults and children and evidence requirements to support broad indication in all age groups
- Plans for modelling and simulation studies to provide supplementary evidence for B/R assessment in children (PopPK, exposure/response, QSP)
- Safety database, overall and in children

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	26 October 2021
Accelerated Assessment procedure was agreed-upon by CHMP on	21 July 2021
The procedure started on	25 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	25 January 2022
The CHMP Co-Rapporteur's critique Assessment Report was circulated to all CHMP and PRAC members on	2 February 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	7 April 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 April 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	5 May 2022

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xenpozyme on	19 May 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	19 May 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication initially applied for is:

Xenpozyme (olipudase alfa) is indicated as a disease-modifying enzyme replacement therapy for long-term treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients.

The final applied indication was as follows:

Xenpozyme is indicated 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.

2.1.2. Epidemiology

Acid sphingomyelinase deficiency (ASMD), formerly known as Niemann Pick disease type A (NPD A) and type B (NPD B), is a rare lysosomal storage disorder resulting from deficiency of the lysosomal enzyme acid sphingomyelinase (ASM) due to bi-allelic mutations in the sphingomyelin phosphodiesterase 1 gene, *smpd1* (Schuchman *et al.*, 2013; Schuchman and Desnick, 2017). ASMD is an autosomal recessive single gene-disease. Niemann Pick C Disease (NPD C) is distinct from ASMD type A and B as it has a different molecular pathway. NPD C cannot be treated with olipudase alfa and the indication is not applied.

In a systematic review of birth prevalence studies, based on data from ASMD types A and B patients referred to biochemical testing facilities, the birth prevalence per 100.000 life-births was reported as 0.4 in Australia, 0.53 in the Netherlands, 0.6 in Northern Portugal, 0.33 in Czech republic, and 0.25 in the United Arab Emirates (Kingma *et al.*, 2015); placing the birth incidence of ASMD at about 0.4 to 0.6 per 100.000 births.

There are more than 180 mutations of the ASM gene (*smpd1*) described (Mc Govern *et al.*, 2017). In the Ashkenazi Jewish population, the only population that performs DNA-based screening, the carrier frequency of the 3 common pathogenic variants (L302P, R496L, fsP330) known to cause ASMD type A is 1 in 90 individuals, corresponding to a birth prevalence of about 3 per 100.000 (Schuchman and Miranda, 1997; Schuchman *et al.*, 2015). In non-Jewish populations, the prevalence of ASMD type A is unknown (Acuna *et al.*, 2016). Estimates extrapolated from the results of carrier screening suggest that the true incidence may be higher in select populations, with a higher incidence of ASMD type A phenotype among persons with Ashkenazi Jewish ancestry. The birth prevalence for type A patients is 0.25 per 100 000 (Schuchman and Wasserstein, 2015; McGovern *et al.*, 2017; Simonaro *et al.*, 2002; Orphanet series).

For chronic forms of ASMD (type B), several factors contribute to the absence of accurate estimates of the prevalence, including under-diagnosis related to poor access to enzyme testing, misdiagnosis due to the high degree of variability in presenting symptoms, and/or lack of knowledge about chronic forms of ASMD in the clinical community (Schuchman and Wasserstein, 2015; Kingman *et al.*, 2015; Simonara *et al.*, 2002). The Orphanet survey estimated the prevalence of chronic forms of ASMD (type B) as 0.4 per 100.000 individuals (Orphanet series). The highest frequencies of chronic forms of ASMD

have been reported in individuals of Turkish, Arabic, and North African descent, although the disorder affects many other distinct populations (Simonara *et al.*, 2002).

2.1.3. Aetiology and pathogenesis

ASMD results primarily in the progressive accumulation of sphingomyelin within the mononuclear phagocytic system and hepatocytes and manifests as a multi-system disease involving the spleen, liver, lung, bone marrow, and lymph nodes. In severe forms of the disease (ASMD type A), the CNS and peripheral nervous system are affected as well. While the same metabolic defect is common to all ASMD patients, disease severity is determined by the presence or absence of neurological involvement, the extent of systemic disease, and the rate of disease progression, resulting in a wide spectrum of clinical manifestations. Infantile neurovisceral ASMD [Niemann-Pick disease type A (NPD A)] is the most severe form and is rapidly progressive and uniformly fatal in early childhood (McGovern *et al.*, 2006). More slowly, progressive, chronic, neurovisceral ASMD (intermediate, NPD A/B, NPD B variant) and chronic visceral ASMD (NPD B) have onset of symptoms in childhood through adulthood and are associated with significant morbidity (McGovern *et al.*, 2017), and reduced life expectancy due to respiratory and/or liver disease (Cassiman *et al.*, 2016; McGovern *et al.*, 2013).

ASM catalyses the hydrolysis of sphingomyelin to ceramide and phosphocholine. Reduced ASM activity results in the progressive lysosomal accumulation of sphingomyelin mostly within cells of the monocyte/macrophage lineage that reside in reticuloendothelial tissues, namely in the spleen, liver, lung, bone marrow, and lymph nodes. With severe disease, neurons may also be affected. The deacylated form of sphingomyelin, lyso-sphingomyelin (LSM), is a potential biomarker for this disease. The framework of using lyso-sphingolipids as a biomarker has been successfully applied to other sphingolipidoses, such as Fabry disease (lysoGB3) and Gaucher disease (LysoGL1) (Polo *et al.*, 2017).

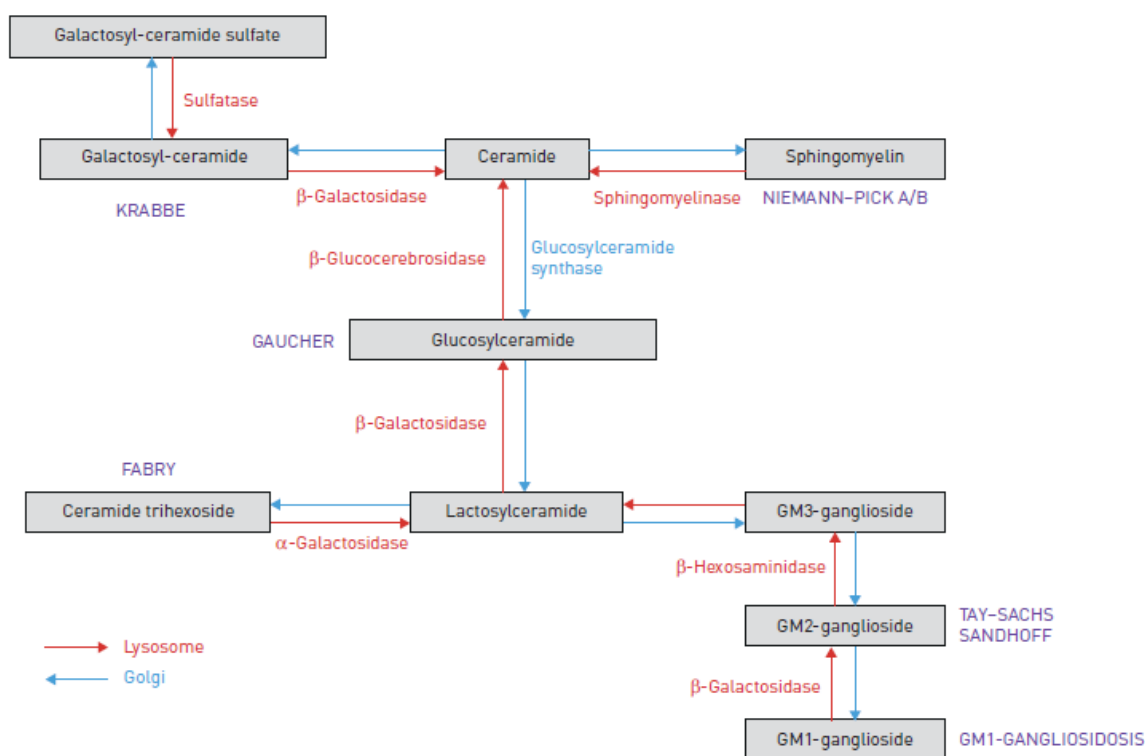


Figure 1. Biochemical pathway of sphingomyelin synthesis (adapted from Borie *et al.*, 2021).

Sphingolipids diffuse and switch between the membranes of lysosomes and the Golgi. Diseases corresponding to the accumulation of the adjacent substrate are reported in purple.

2.1.4. Clinical presentation, diagnosis and prognosis

Presentation

Pulmonary involvement

Pulmonary involvement, mainly interstitial lung disease (ILD), occurs in all three types of ASMD but most frequently in type B. It is also associated with recurrent respiratory tract infections (Cox *et al.*, 2018) and progressive decline in pulmonary function, which are major contributors to decreased QoL and disease burden in ASMD patients (von Ranke *et al.*, 2016; Freitas *et al.*, 2017; McGovern *et al.*, 2013; Iaselli *et al.*, 2017).

ILD may be diagnosed in newborns to adults in their late 40s, may precede ASMD diagnosis or may develop during follow-up (Guillemot *et al.*, 2007; Capron *et al.*, 2019). Up to 42% of patients report shortness of breath at ASMD diagnosis (Acuna *et al.*, 2016). The clinical ILD presentation varies from asymptomatic involvement to respiratory failure with no association with organomegaly (Hollak *et al.*, 2012); however, the accumulation of Niemann–Pick cells in the alveolar septa and bronchial walls potentially leads to progressive respiratory insufficiency (Guillemot *et al.*, 2007). Foam cell infiltrates of the pulmonary alveoli block oxygen uptake through the alveolar wall into the blood vessels. This abnormal diffusing capacity is consistent with ILD (Mendelson *et al.*, 2006), which may manifest with coughing, shortness of breath, and recurrent respiratory infections. With low partial pressure of oxygen (PO₂) values, patients are affected by dyspnoea upon exertion.

Almost 90% of patients with ASMD-B exhibit ILD on CT scan (Mendelson *et al.*, 2006).

There is a poor correlation between the extent of radiological abnormalities and pulmonary function test changes; however, both tests are needed for diagnosis (Mendelson *et al.*, 2006). In a cohort of 55 patients with ASMD-B, half presented a restrictive pattern on pulmonary function testing (mean FVC 82% predicted). Almost 75% of patients with ASMD-B present impaired DLCO (mean DLCO 60% predicted). In addition, mean values for FVC and DLCO are lower in patients who are <18 than >18 years old (McGovern *et al.*, 2008). Hypoxaemia is frequent and may be observed in up to 85% of patients (Guillemot *et al.*, 2007).

A retrospective study of 29 paediatric and adult patients with ASMD-B with a mean follow-up of 4.3 years documented the slow progression of pulmonary disease. The mean decline per year of forced expiratory volume in 1 s (FEV₁), FVC and DLCO was –1.6%, –0.1% and –0.4% predicted, respectively (McGovern *et al.*, 2008). In another series of 10 paediatric patients with ASMD-B, all showed respiratory symptoms and three required long-term oxygen therapy (Guillemot *et al.*, 2007).

Liver fibrosis and, finally, cirrhosis occur in the natural course of ASMD (Pinto *et al.*, 2004; McGovern *et al.*, 2013; Cassiman *et al.*, 2016). Therefore, elevated serum transaminases may be noted. Serum bilirubin concentrations are commonly normal, except for children who could present with cholestatic liver disease (Pinto *et al.*, 2004).

Linear growth and weight gain are progressively impaired over time in patients with chronic disease, with linear growth below normal for greater than 50% of patients with chronic visceral disease at age 5 years and older (Cox *et al.*, 2018). *et al.*

Dyslipidaemia is a common feature of patients with ASMD, even at a very early age.^{3,15,17} (McGovern *et al.*, 2017).

Developmental delay, developmental regression, and learning disabilities are reported for 40% of patients with chronic neurovisceral ASMD and are less common in patients with chronic visceral ASMD (21%, 2%, and 13%, respectively) (Cox *et al.*, 2018).

Diagnosis

Patients with ASMD present with a large phenotypic spectrum of nonspecific disease manifestations that can lead to considerable diagnostic delay and missed cases. Demonstration of missing or significantly diminished enzyme activity remains the proof of the presence of the disease, especially in view of the many unique mutations or genetic variants of unknown significance. Results from other clinical and laboratory assessments, such as the presence of characteristic lipid-laden foam cells present in the liver, spleen, airways, and bone marrow, together with low platelet levels and mixed dyslipidaemia (low HDL cholesterol with high levels of LDL cholesterol and triglycerides), although highly suggestive of ASMD, are not substitutes for the need to obtain confirmatory enzyme test results (McGovern *et al.*, 2017).

Following biochemical and molecular analyses to confirm the diagnosis of ASMD, predictions of phenotypic outcomes will permit more appropriate patient care and family counselling. Physicians will rely on clinical assessments to predict the phenotype and clinical course for paediatric patients when *smpd1* mutations of unknown pathogenicity are identified (McGovern *et al.*, 2017).

Prognosis

Several natural history studies and case report series consistently demonstrate that ASMD is associated with significant pulmonary morbidity and mortality.

The median life expectancy for the chronic visceral end of the ASMD spectrum has been reported as 17 years with a range of 1 to 72 years (McGovern *et al.*, 2013; Cassiman *et al.*, 2016). Patients infantile neurovisceral end of the ASMD spectrum (type A) do not survive beyond the third year of life (Schuchman and Wasserstein, 2015). In these patients, both rapidly fatal lung disease and progressive pulmonary disease leading to lung failure have been reported (Guillemot *et al.*, 2007).

The primary causes of death in patients with chronic visceral ASMD (type B) were respiratory (32.1%) and liver (26.4%) disease, which together accounted for the majority of deaths. By definition, there were no deaths due to neurodegenerative disease in patients with chronic visceral ASMD. For patients with chronic neurovisceral ASMD (type A), respiratory disease (23.1%), neurodegeneration (23.1%), and liver disease (19.2%) were the primary causes of death (Cassiman *et al.*, 2016, McGovern *et al.*, 2013).

2.1.5. Management

There is no aetiology-specific treatment that can modify the disease or slow the rate of progression. Patients can only be provided palliative and supportive care for managing symptomology.

Reduction of hepatosplenomegaly and consequentially correcting haematological and lipid abnormalities and improving respiratory status may improve patient outcome.

For the treatment of the underlying disease symptoms, the following interventions are used: for neutropenia: antibiotic (typically penicillin or azithromycin), with GI track disturbances and risk of

resistance; for lung capacity: inhalators (cortisone, broncho-dilatators); for bone density: calcium; for thrombocytopenia: fresh plasma; for high cholesterol: very high doses statins and low-fat diet (EMA patient consultation). Although statins are used, they do not fully correct the abnormal lipid profile (i.e., low concentration of HDL). Additionally, lipid-lowering drugs are usually not used in children as they may delay growth. Supplemental oxygen may be needed when pulmonary complications are severe. Use of growth hormone has also been reported. Further, loperamide is used to treat diarrhoea and pain medication (avoiding NSAIDs and paracetamol).

Several attempts have been made to use cell and solid organ transplantation as an indirect source of ASM replacement therapy. Transplantation of either amniotic cell sheets or purified amniotic epithelial cells has been performed in several patients at the chronic visceral end of the ASMD spectrum. Most patients did not experience a noticeable change in hepatosplenomegaly. This approach was limited by the short-term viability of amniotic cells, which necessitates repeat transplantation procedures every 2 to 4 months to maintain corrective ASM activity.

While the experience to date with cell and organ transplantation has been limited, observations from these cases have shown that some improvement in somatic features may occur in patients at the chronic visceral end of the ASMD spectrum. However, little to no improvement has been observed in slowing disease progression in patients at the infantile neurovisceral end.

Therefore, there remains an unmet medical need for medicinal products to treat or slow disease progression.

2.2. About the product

Xenozyme (olipudase alfa), developed as an enzyme replacement therapy to supplement deficient ASM in ASMD patients, converts sphingomyelin into ceramide in ASMD patients. Olipudase alfa (in the report abbreviated as olipudase alfa) is a recombinant human acid sphingomyelinase expressed in Chinese hamster ovary cells. The resulting gene product retains the enzymatic activity and lysosomal targeting of the native protein.

The indication is: *Xenozyme is indicated 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.*

The proposed target dose regimen, with within-patient dose escalation, is 3.0 mg/kg every two weeks (Q2W) administered as a ~3.67 hours (220 minutes) intravenous (IV) infusion. Full details on the within-patients dose escalation and infusion time are available in the proposed SmPC which is separately attached. For a discussion on the indication, refer to the clinical efficacy discussion.

2.3. Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that

"Based on the clinical data submitted within this request it is anticipated that olipudase alfa will fulfil the existing unmet medical need in the treatment of disease symptoms of ASMD. Treatment with olipudase alfa is likely to have an effect on the visceral symptoms of ASMD. Considering that the protein will not cross the BBB, no effect on the neurological symptoms of ASMD, that mainly occur in ASMD type A and ASMD type A/B, is expected.

Given the rarity of ASMD, the number of patients treated in the clinical program (e.g. 59 patients) is the best at this moment. It is anticipated that the benefits of treatment outweigh the potential safety issues and risk of not treating these ASMD patients”.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a sterile lyophilised powder for concentrate for solution for infusion containing 20 mg olipudase alfa per vial as the active substance.

Other ingredients are sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sucrose, and L-methionine.

The product is available in Type I glass vial with a siliconised chlorobutyl-elastomer lyophilization stopper, and an aluminium seal with a plastic flip-off cap. Each pack contains 1, 5, 10 or 25 vials.

2.4.2. Active Substance

2.4.2.1. General Information

Olipudase alfa is a recombinant human acid sphingomyelinase. The enzyme is expressed in Chinese hamster ovary (CHO) cells. The physical and chemical characteristics of olipudase alfa active substance are presented in Table 1. The active substance is presented in the final formulation. No dilution or formulation takes place at the finished product stage.

Table 1. Physical and chemical characteristics of olipudase alfa active substance

Property	Results
Appearance	Clear, colorless liquid essentially free from foreign matter
Isoelectric Point (pI)	6.9
Molecular Weight	~ 76,000 Daltons ¹
Solution pH	6.1 – 6.9
Extinction Coefficient	2.41 mL / (mg*cm)
Post Translational Modifications	N-glycosylation at N-27, N-116, N-276, N-336, N-444 and N-461 and a free cysteine at C-terminal that can undergo differential modifications

¹ The molecular weight determined by LC/MS includes the molecular weight from oligosaccharides

2.4.2.2. Manufacture, process controls and characterisation

Manufacturer

Active Substance manufacturing is performed by Patheon Biologics LLC, Saint Louis, MO, USA. During the procedure a major objection (MO) was raised to request proof of GMP compliance of the Patheon Biologics site. Relevant documentation was provided and the MO was considered resolved.

Manufacturing process

The olipudase alfa active substance manufacturing process has been adequately described. Main steps are expansion of viable cells from WCB, fermentation, harvest, purification, formulation, filtration and

filling. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxins, are described for each step. The active substance manufacturing process is considered acceptable.

One WCB vial is used to produce one batch of olipudase alfa active substance. Each harvest is clarified and loaded onto the purification column. The resulting eluates are pooled prior to the next purification operation, and the pool is then processed to generate the active substance.

No reprocessing or reworking is performed.

The overview of the active substance manufacturing process in S.2.2 is sufficiently detailed. For each process step, a narrative description and flow diagram with information on non-critical IPCs and their action limits, critical IPCs and their acceptance criteria, and process parameters and their criticality and operational ranges is provided. The operational ranges provided in S.2.2 are sufficiently supported by process characterisation studies.

Control of Materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. A Certificate of Analysis and Certificate of Suitability are provided and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

The olipudase alfa transgene used to generate the manufacturing cell line was derived from a cDNA obtained from the IMAGE Consortium.

Generation and isolation of the product clone expressing olipudase alfa included transfection with the expression vector, selection, single cell cloning of selected pools, scale-up and productivity and clone selection.

The applicant has provided sufficient information on the construction of the olipudase alfa expression vector, host cell line, and generation of the manufacturing cell line. Monoclonality of the cell bank is based on one single-cell cloning step and supported by a probability calculation and characterisation of end of production cells (EOP), confirming transgene sequence, transgene integrity and comparability between MCB, WCB, and EOP (Southern Blot), and gene copy number analysis of MCB, WCB, and EOP.

A two-tiered cell bank system was prepared from the seed bank according to cGMP requirements and ICH guidelines. In addition, EOP from the bioreactor were characterised to establish the limit of *in vitro* cell age. The applicant has provided sufficient information on the two-tiered cell banking system. Testing of the MCB, WCB and EOP for adventitious agents was performed in line with ICH Q5A. No viruses other than the retrovirus-particles that are known to be present in CHO cells were detected. Stability of the cell banks will be monitored by % viability on thaw. The limit of *in vitro* cell age is determined and controlled.

Control of critical step and intermediates

The applicant has provided a summary of the control strategy, including definitions, an overview of key and critical process parameters, in process intermediate hold times, in-process controls, and method descriptions and validations. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

The olipudase alfa active substance manufacturing process has been validated adequately. Consistency in production has been shown on multiple full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces olipudase alfa active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Process consistency validation has been completed for the olipudase alfa active substance commercial manufacturing process.

Impurity clearance was evaluated at full scale. This is acceptable. For most impurities, adequate removal is demonstrated and/or ensured by active substance release tests. The applicant is recommended to include a control for an impurity in the active substance release specification (**REC 3**).

Transport validation of active substance was performed from the active substance facility to the facility for fill finish processing. Three substance batches were used for the transport validation protocol. The results demonstrate that temperature could be controlled within 2-8°C, and that product quality was not impacted.

Membrane lifetime validation is performed at the manufacturing scale, concurrently with the process validation campaign and then with commercial production. Chromatography column resin lifetimes were established through small scale studies and are being confirmed at manufacturing scale as part of the validation campaign and concurrent with commercial manufacturing campaigns.

The olipudase alfa purification process intermediates were validated for routine hold times (Normal Operating Range) and for the maximum allowable hold times (Proven Acceptable Range). The routine hold time study was conducted at a commercial scale. The extended hold times for maximum hold times (PAR) study was conducted at a small scale using commercial-scale material and tested for chemical/ biochemical stability, while the PAR study for microbial control was conducted at a commercial scale using the bioreactor production medium.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development program. Several important changes have been introduced during the development of the manufacturing process.

For each change in manufacturing process, a comparability study has been carried out demonstrating that, apart from some expected differences, the change did not have a significant influence on the quality of the product.

Control strategy development

For all process steps, the applicant performed a risk assessment to select parameters for further characterisation in development or small scale studies. Equivalence between the small scale/development process steps and the commercial process steps is sufficiently demonstrated. A high-level summary of the results of the characterisation studies is provided, including for each process step, a tabular overview of the proven acceptable ranges for the studied process parameters. In addition, an overview of the final control strategy, including the conclusion on parameter criticality, NORs, and, if applicable, PARs is provided. The approach is acceptable.

Characterisation

The olipudase alfa active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a recombinant human acid sphingomyelinase. The analytical results are consistent with the proposed structure.

The applicant has in general appropriately characterised the physicochemical properties of olipudase alfa, including its primary structure, secondary and higher-order structure, glycosylation and post-translational modifications. A sufficient number of PPQ batches were included in the characterisation study.

Furthermore, heterogeneity of the active substance was adequately characterised by analysing the presence of impurities in the active substance. A summary of the levels of product-related impurities observed historically and in the clinical batches is provided.

Biological activity was characterised by evaluating enzyme kinetics and relative potency. Potency is determined using a cell-based assay. The information provided on biological activity and potency control is in general sufficient.

The applicant has provided an overview of the levels of process-related impurities in active substance batches and performed a safety assessment for the process-related impurities. The residual levels of impurities are acceptable.

In summary, the characterisation is considered appropriate for this type of molecule.

2.4.2.3. Specification

Specifications

The active substance specifications for olipudase alfa includes tests for appearance (colour, clarity, degree of opalescence), osmolality (Ph. Eur.), pH (Ph. Eur.), identity (peptide map by UPLC-UV), protein concentration (A₂₈₀), enzymatic (Specific) Activity (HAD-PC), aggregation (SEC), dimer content (SEC), purity (RP-UPLC), free thiol content (spectrophotometric), oligosaccharide profiling (HPLC-FLD), charged isoforms pattern (cIEF), residual CHO DNA (qPCR), pyrogen test (Ph. Eur.), bioburden (Ph. Eur.).

Analytical procedures and reference standard

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Appropriate information on reference standards was provided.

The applicant has provided descriptions of all methods, including, if relevant, information on the method principle, critical reagents and equipment, sample preparation and dilutions, reference standards and controls, procedural details, system suitability and sample acceptance criteria, and data analysis and reportable results. The provided information is sufficiently detailed.

Method validation was performed in line with ICH Q2(R1). Brief summaries are provided. The applicant states that method validation was executed at the active substance manufacturing site under approved validation protocols, the following cGMP and using qualified instrumentation. Compendial methods were verified for their intended use. All validation criteria were met.

Batch analysis

An overview of the release testing results of the batches is provided, including information on the date of manufacture and purpose. The results support batch-to-batch consistency, although some

differences in specific activity are noted when comparing batches manufactured according to the different active substance manufacturing processes (see the section on comparability).

Justification of specification

The proposed active substance release test panel is agreed, with a recommendation to include a test for an impurity **(REC 3)**.

Part of the tests is performed on unformulated bulk. This can be accepted.

The pyrogen test replaced the bacterial endotoxin test due to low endotoxin recovery. This can be accepted.

The correlation between relative potency and specific activity is limited. However, as the active substance release test panel also includes controls for other quality attributes it can be accepted that the cell-based potency test is only performed at the finished product stage. The applicant is recommended to further identifying the root cause of the difference between the results in the specific activity assay and the relative potency assay **(REC 1)**.

Container closure

The applicant has provided a brief description of the container closure system, including drawings and CoAs and acceptable specifications were provided.

2.4.2.4. Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

The applicant performed long-term (refrigerated, $5 \pm 3^\circ\text{C}$), accelerated ($25 \pm 5^\circ\text{C}/60\pm 5\%\text{RH}$), and forced degradation studies (30°C at pH 5.0, 35°C at pH 8.0, photostability, agitation, oxidation). Based on the forced degradation studies, the applicant identified degradation pathways. In addition, an impact of the stress conditions is observed. The applicant states that potency decreased under all conditions.

Five batches were included in the long term and accelerated stability study. Data are available for 12 (accelerated) and 24 (long-term) weeks. The stability test panel includes appearance, activity, SE-HPLC (aggregates and dimer), concentration, deamidation, pH, purity by CE-SDS (reduced), purity by RP-HPLC, specific activity, bacterial endotoxin, and bioburden. A control for free thiols will be included in the test panel for future stability studies. The absence of the cell-based potency test in the stability test panel is acceptable for routine stability testing. The applicant is recommended to include the cell-based potency assay in the stability test panel for stability studies that are performed to demonstrate comparability in case of process changes, unless this is covered by finished product stability data.

The stability data all complied with the acceptance criteria, but some trends have been identified by the applicant. The changes are generally modest, and results support the proposed shelf life of 24 weeks at $2-8^\circ\text{C}$.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

The olipudase alfa finished product (Xenpozyme) is a sterile lyophilised powder for solution for intravenous infusion. It is supplied in an aseptically filled single-use vial with a nominal strength of 20

mg/vial. Prior to lyophilization, the nominal fill volume is 5.0 mL. The finished product is reconstituted with nominal 5.1 mL sterile water for injection (WFI) prior to use. The composition of the olipudase alfa finished product is identical to the olipudase alfa active substance.

The finished product is filled in a 20 mL Ph. Eur. Type 1 colourless clear glass vial closed with 20 mm siliconised gray chlorobutyl elastomeric stopper. The stoppered vials are crimped with an aluminium seal with a Flip-Off button. The primary packaging material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

No overage is used.

The excipients in olipudase alfa active substance and finished product are well known pharmaceutical ingredients and are widely used in commercial biopharmaceutical formulations for intravenous administration. Their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. No excipients of human or animal origin are used.

The provided data including comparative data of the biological activity on finished product batches manufactured from the different active substance processes and optimised finished product processes do not appear to show any relevant differences.

Finished product development studies included optimisation of the lyophilization cycle. Real-time stability has been performed to confirm the suitability of the lyophilisation cycle for implementation.

Extractable and leachable (E&L) assessments of the primary packaging components and the key product-contact materials associated with the filling lines were performed. The levels of any potential leachable or extractable compound were considerably lower than the Analytical Evaluation Threshold and do not pose a toxicological safety concern for olipudase alfa finished product. No elemental impurity above the ICH Q3D limits for parenteral compounds was detected in the course of the leachable study.

2.4.3.2. Manufacture of the product and process controls

The manufacture of olipudase alfa finished product is a standard process in which active substance, without further formulation, is lyophilised. It consists of 7 process steps : 1) active substance receipt and storage 2) Transfer and hook-up 3) Sterile filtration and filling 4) Lyophilization 5) Capping and inspection 6) Labelling and Packaging 7) finished product storage and shipping.

The process has been described in sufficient detail. Critical steps have been identified. Reprocessing is not allowed in finished product manufacturing. Setpoints and PAR (proven acceptable ranges) have been provided for the CPP. Sufficient details have been provided for the CPP of each step. Hold times and time out of refrigeration have been validated.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate. The manufacture of the PPQ lots included all steps of the manufacturing process. All four PPQ lots were lyophilised successfully and confirmed the Process parameter ranges as set in the control strategy; CPPs were verified for each PPQ lot. A simulated shipping validation study has been performed to support stability during transport.

2.4.3.3. Product specification

The finished product specifications for Xenpozyme, include tests for appearance powder (visual), appearance reconstituted (visual, colour, clarity/degree of opalescence) (Ph. Eur.), osmolality (Ph. Eur.), particulates (Ph. Eur.), pH (Ph. Eur.), reconstitution time (visual), residual moisture (Ph. Eur.), identity (dot blot), protein concentration (A280), enzymatic (specific) activity (HAD-PC), relative potency (cellular uptake), impurities (aggregation, dimer content (SEC)), purity (RP-UPLC), free thiol content (spectrophotometric), pyrogen test (Ph. Eur.), sterility (USP), container closure integrity (headspace analysis).

The proposed set of critical quality attributes selected as release criteria covers all relevant aspects of the finished product. The relative potency test will be added to the shelf life specification for the post-approval stability studies. The applicant is recommended to provide data for three post-approval stability batches including the potency results **(REC 4)**.

During the procedure, a MO was raised on the control of potency at both active substance and finished product level and further details were requested to ensure there is adequate control. In response the applicant has provided additional data and discussion and has sufficiently justified that the release testing strategy for potency, including the relative potency test, specific activity test, and the free thiols is appropriate to control the relevant biological activities including uptake. In combination with the relative potency assay the biological activity is sufficiently controlled and the MO was considered resolved. However, the Applicant is recommended to further investigate the apparent discrepancy between the specific activity assay and the relative potency assay **(REC 1)**.

The assays for identity testing, residual moisture, Protein content (A280), Purity (RP-UPLC), Container Closure Integrity test (headspace test) and reconstitution time are sufficiently validated/verified. The same reference standard is used as in the active substance testing. The endotoxin test (LAL) showed a low endotoxin recovery, and as a replacement, a rabbit Pyrogen test is being implemented. The pyrogen assay was sufficiently qualified. The applicant is committed to developing a non-animal test that will replace the rabbit assay **(REC 6)**.

The proposed acceptance criteria for aggregation, concentration and free thiol content can be accepted. As the release specification for reconstitution time is considered rather wide, the applicant is recommended to review it after an additional 30 batches have been manufactured **(REC 5)**.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

During the procedure, a MO was raised as only a QP statement, on the risk of presence of nitrosamines was provided. In response, risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Batch analysis

Batch release data have been provided for all batches manufactured (preclinical, clinical and PPQ). The different (developmental and characterisation) biological activity assays have not been performed on all batches. For the cellular uptake potency test results for the PPQ batches have been provided as well

as justified bridging data for cellular uptake assay of the clinical batches finished product. This is sufficient to support the potency testing strategy.

2.4.3.4. Stability of the product

Based on available stability data, the finished product shelf life of 48 months and storage conditions at 2-8°C, as stated in the SmPC are acceptable.

The requested shelf life is generally supported by 60 months primary stability results of an Engineering lot of the commercial process with the optimised lyophilisation process stored at 2-8°C and 6 months accelerated stability data stored at 25±2°C. In addition, the supporting stability includes up to 60 months of long-term stability data from two finished product lots manufactured using the original lyophilization cycle stored at 2-8°C. All Quality Attributes tested were within specification, and no trends were observed. However, the stability test panel did not include an appropriate potency test. The applicant has agreed to add the relative potency test to the post-approval stability protocol and committed to provide data for three of these batches (**REC 4**). The currently provided data showing no trend in the biological activity and gives sufficient reassurance concerning the stability during shelf life.

The stability studies of the PPQ batches are ongoing, and the company is committed to completing the stability studies.

Photostability testing was performed on finished product packaged in immediate (primary) and marketing (secondary) packs. Samples were exposed to light (as per ICH Q1B option 2) for 5 days. All test results for samples exposed to light are comparable to dark control samples.

In-use stability

(SmPC): "After reconstitution, 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). After dilution, 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)." The provided in use stability data show no OOS results or trends and support the stability at these conditions.

2.4.3.5. Post approval change management protocol(s)

n/a

2.4.3.6. Adventitious agents

Cell bank testing is performed in accordance with ICH guidance, and the unprocessed bulk harvest is tested for adventitious viral agents and minute mouse virus. The only material of animal or human origin used in the production of olipudase alfa is gamma irradiated bovine serum. A Certificate of Analysis and Certificate of Suitability are provided.

Virus validation studies are in line with expectations. The suitability of the scaled-down models has been sufficiently demonstrated. Both new and aged resins were used in the studies and yielded comparable results. The model viruses used in the studies include Xenotropic Murine Leukemia Virus (XMuLV), Murine Minute Virus (MMV), Feline Calicivirus (FCV), and Pseudorabies Virus (PRV). This is acceptable.

2.4.3.7. GMO

Not applicable

2.4.4. Discussion on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure MOs were raised on the GMP status of the active substance manufacturer, on the control of potency at both active substance and finished product level, and on the missing nitrosamines risk assessment. All MOs were sufficiently answered and resolved by the applicant by the provision of additional documentation and data.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to commitments made by the applicant to complete various characterisation, development and stability studies. These points listed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should perform additional work to understand the root cause of the difference between the specific activity and potency assays by further evaluating the role of (and potential interaction between) the key attributes associated with activity and potency . This work may include characterizing olipudase alfa samples.
2. The applicant should submit the final report concerning the mixing studies as soon as the validation activities are completed in a Post-Authorisation Measure.
3. The applicant should implement the ELISA-based determination of cathepsin D to the active substance release test panel upon successful method transfer, completed validation work and establishment of acceptance criterion with 20 active substance lots and submit as an appropriate post-approval variation.
4. The first three stability studies in which relative potency is included in the specification will be the 2021, 2022 and 2023 annual finished product stability lots. The applicant should submit two (2) Post-Authorization Measures with stability data for these three lots when 24 months and 60 months of long-term stability data is available from the 2023 annual finished product stability lot, and to report any confirmed out of specification results or significant adverse trends observed during the stability studies.

5. The applicant should review the Reconstitution Time for dosing with a view to tightening the acceptance criteria upon completion of the manufacture of 30 finished product batches.
6. The applicant should submit a Type II variation to replace the pyrogen with a validated non-animal test.

2.5. Non-clinical aspects

2.5.1. Introduction

Olipudase alfa is a recombinant human acid sphingomyelinase produced in Chinese hamster ovary (CHO) cells. Xenpozyme (olipudase alfa) is indicated as an enzyme replacement therapy for long-term 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.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Animal model used in pharmacology

The applicant made use of a disease model for NPD, ASMKO mice. In this mice model, the ASM enzyme is removed. In the publication from *Horinouchi et al.*, the model is described. The enzyme was shown not to be active in brains, heart, liver, spleen, kidney and lung. The characteristic foam cells were mainly observed in bone marrow and spleen. In a moribund state, the animals had lower weight, and the main organs were smaller. The hepatosplenomegaly, characteristic of the disease in human, was thus not observed. In the brains, loss of Purkinje cells and atrophy of the cerebellum and midbrain was observed as well. In the animals, an increase in plasma cholesterol was also observed, but this was not used as a marker of disease in the studies presented in this dossier. The absence of ASM activity is also present in human. However, the observation that organs get smaller due to the disease and the absence of hepatosplenomegaly is not common to human disease.

Primary Pharmacology

In vitro

The enzyme appears to be optimally effective at acidic pH between 5.2 and 5.5. While pH in early endosome is ~6.5, late endosome ~5.5 and lysosome ~4.5, it could be suggested that this enzyme is most active in the late endosome. Bach et al., 1999* seem to suggest that the pH in lysosomes of cells from Nieman Pick Syndrome Type C or Type A is in the range of 4.3-4.5. As the in vivo data clearly show activity of the enzyme, olipudase alfa might rather become activated in the late endosome. Indeed, in their recently appeared review[†], Breiden and Sandhoff refer to ASM as an endo/lysosomal enzyme. This would explain the in vivo observed effects considering the in vitro data on activity.

* G Bach 1, C S Chen, R E Pagano, Elevated lysosomal pH in Mucopolysaccharidosis type IV cells, *Clin Chim Acta*. 1999 Feb; 280(1-2):173-9. doi: 10.1016/s0009-8981(98)00183-1.

† Bernadette Breiden1 and Konrad Sandhoff Acid Sphingomyelinase, a Lysosomal and Secretory Phospholipase C, Is Key for Cellular Phospholipid Catabolism, *Int. J. Mol. Sci.* 2021, 22(16), 9001; <https://doi.org/10.3390/ijms22169001>

Sphingomyelin depletion due to Olipudase Alfa administration

ASMKO mice were IV administered a single dose of 1, 3 or 5 mg/kg olipudase alfa to evaluate its effect on sphingomyelin (SPM) depletion in liver, spleen, lung and kidney. In study 02-0428Pnp, a single dose of 1 mg/kg olipudase alfa reduced sphingomyelin levels in all tissues. In the liver 62-75% SPM reduction starting at Day 3 and continuing to Week 2 was observed. In the spleen and lung, 46-48% SPM reduction at day 7 and in the kidney 23% SPM reduction at day 3 was observed. All tissues showed sphingomyelin re-accumulation back to pre-dose level at week 4. In study 05-1223Pnp, following a single 3 mg/kg intravenous administration of olipudase alfa in ASMKO mice, maximal depletion of SPM was observed in the liver at approximately 5 days post-dose, while for the spleen, this occurs at approximately 7 days post-dose. Re-accumulation of SPM starts between 7 and 14 days post-dose. Three weeks post-dose, sphingomyelin levels were still depleted with 48% in the liver and with 30% in the spleen. In study 01-0110Pnp, upon administration of a single IV dose of 5 mg/kg olipudase alfa to ASMKO mice, SPM reduction from Day 1 to Day 7 post-dose was observed in all tissues. In liver 74-95%, in spleen 65-80%, in kidney 70% and in lung 26-43% SPM reduction (compared to untreated animals) was observed. All tissues showed starting of sphingomyelin re-accumulation between 7 and 21 days post-dose. Predose plasma sphingomyelin levels were just above the level of detection. Plasma sphingomyelin levels remained unchanged throughout the duration of the study. From this study it is suggested that the dose level of 5 mg/kg is most effective.

The C_{max} in humans cannot be compared to that in the non-clinical species since the infusion rate is much longer in humans (220 minutes) compared to the non-clinical species (<30 minutes). The exposure (AUC) in the non-clinical species at a dose of 3 mg/kg is lower than in humans.

Comparison of different lots

Three different lots of olipudase alfa after a single dose of 3 mg/kg were compared in a time-dependent manner. No significant differences in sphingomyelin reduction in the liver, spleen and lung were observed between the three lots. Hereby, the efficacy of all three lots is shown, and their use in toxicology studies is supported. Likewise, the influence of the two manufacturing processes of 0, 1, and 3 mg/kg olipudase alfa on reducing sphingomyelin in the liver, kidney, and spleen was evaluated. Again, no statistical differences in sphingomyelin reduction or ceramide production were observed.

Effect of different levels of HMWS

High Molecular Weight Species (HMWS) have been observed during the production of olipudase alfa. To evaluate the effect these HMWS may have on the efficacy of olipudase alfa, ASMKO mice were administered a single dose of 1.0 mg/kg ([Study 02-0790Pnp]) or 5.0 mg/kg ([Study 02-0495Pnp]) olipudase alfa or HMWS-olipudase alfa and tissues were collected 24 or 72 hours post-dose for biochemical sphingomyelin analysis. Upon a dose of 1.0 mg/kg, the presence of HMWS seemingly reduced the efficacy of olipudase alfa in the liver (24 and 72 hr) and the kidney (24 hr only), but not in the lung and spleen. However, in a subsequent study [Study 13-04646] with three lots of olipudase alfa (3.0 mg/kg) containing low (target 15%), medium (target 30 %) or high (target 65 %) amounts of HMWS, no statistically significant differences in sphingomyelin content were noted between olipudase alfa and all HMWS-olipudase alfa treatment groups in liver, spleen, and kidney. Based on these data, it does not appear that HMWS olipudase alfa (low, mid, or high) impacts efficacy or safety in the ASMKO mouse compared to olipudase alfa under the conditions of this study.

Effect of variations in the dose regimen

Two studies were performed to evaluate the pharmacodynamics of olipudase alfa following a repeat dosing regimen of every other week for 12 weeks in ASMKO mice. In study 02-1084Pnp (0, 0.1, 0.3, or 1 mg/kg olipudase alfa QOW (every other week), the biochemical analysis showed a dose-responsive reduction of sphingomyelin in the liver, spleen, and kidney at 1 and 2 weeks post-dose followed by re-

accumulation of SPM at Week 2 post-dose. Histo-morphometric analysis showed a dose-responsive reduction of sphingomyelin in the liver and spleen, with the kidney following a similar trend. There was no evidence of sphingomyelin reduction in the lung by biochemical or histo-morphometric analysis across doses. In study 04-0813 (0, 0.3, 1.0, 3.0 mg/kg olipudase alfa QOW), the biochemical analysis showed a dose-responsive reduction of sphingomyelin in the lung and spleen. Sphingomyelin reduction in the lung of the 1 and 3 mg/kg groups were 61% and 58%, respectively. Sphingomyelin levels were reduced to near background levels in the liver in all dose groups (0.3, 1.0, and 3.0 mg/kg) and had re-accumulated to pre-dose levels at 28 days post final dose.

2.5.2.2. Secondary pharmacodynamic studies

Two-phase degradation

A single administration of olipudase alfa at 20 mg/kg results in a rapid increase in ceramide, sphingosine and sphingosine-1-phosphate in the serum of ASMKO mice. There appear to be two distinct phases to the generation of ceramide characterized by an early, rapid rise (2-45 min) followed by a second rise at 240 and 540 minutes postdose. SPH and S1P were significantly elevated at 240 minutes postdose and SPH remained elevated at 540 minutes postdose. Sphingosine-1-phosphate levels returned to baseline at 540 minutes postdose. The two phases of degradation products may indicate separate SPM breakdown events due to different sources of SPM. The applicant provided a discussion on the activity of the enzyme at different pH and locations of SPM and of the enzyme. The initial production of ceramide in ASMKO mice (5-45 min. postdose) is the result of olipudase alfa mediated hydrolysis of sphingomyelin that is not present in lysosomes but rather in an "easy to access" pool. It is unknown where this pool may reside but may include sphingomyelin found in the outer leaflet of the plasma membrane or in blood lipid particles. The early high peak of ceramide, following SPM degradation by olipudase alfa in ASM KO mice, was apparently not observed in ASM patients. This is reassuring for the safety. The second and later peak of ceramide is likely reflecting SPM degradation in the endolysosomal compartment.

Degradation products and pro-inflammatory cytokines

Five studies were performed to investigate the toxic effects of a single high dose of olipudase alfa in ASMKO mice and in C57BL/6 mice dosed up to 20 mg/kg. In study 05-1008Pnp (20 mg/kg), significant elevations of ceramide were noted from 2 minutes through 45 minutes postdose, but no elevation of pro-inflammatory cytokines was noted within 45 minutes postdose. In study 05-0127Pnp (20 mg/kg) and 05-0374Pnp (0.3, 3.0, and 10 mg/kg), large dose-responsive increases in interleukin- (IL) 6 and G-CSF were observed at 3 and 4 hours postdose and continuing up to 9 hours postdose at doses of 3, 10, and 20 mg/kg. Smaller increases were seen in IL-1 α , IL-1 β , and MIP-1 α 3, 4, and 6 hours postdose at these doses. No notable increase in TNF- α was observed at any time point for any dose. In this second phase also, the elevation of pro-inflammatory cytokines is noted. No cytokine response was seen in C57BL/6 (wild type) mice [Study 05-0436Pnp] following a single dose of 20 mg/kg olipudase alfa. Results suggest that elevations in cytokines seen in ASMKO mice at this dose (previous studies) are related to the breakdown of substrate present in ASMKO mice.

Dose escalation strategy to minimize the toxic effect of degradation products

To mitigate the toxic response of olipudase alfa in ASMKO mice, a dose-escalation strategy was evaluated as part of the nonclinical program. Cytokine levels were assayed following a variety of dose escalation regimens in four studies in ASMKO mice [Studies 05-1009Pnp, 05-1010Pnp, 05-1240Pnp and 05-0437Pnp], each employing a different dosing regimen. Serum was collected four and eight or nine hours post last dose in all studies for the measurement of cytokine levels using the Bio-Plex Mouse Cytokine 18-Plex Panel assay. In study 05-1009Pnp, it was shown that administration of 3 mg/kg olipudase alfa (D1) and 20 mg/kg (D3) to ASMKO mice significantly altered circulating levels of pro-inflammatory cytokines compared to samples from untreated mice from Genzyme Study 05-0374Pnp. Compared to samples from ASMKO mice receiving a single dose of 20 mg/kg in Study 05-0127, elevations were considerably lower. These data support a controlled debulking strategy to minimize the cytokine response. In study 05-1010Pnp 3 mg/kg olipudase alfa on (D1) and on (D6) to ASMKO mice resulted in an increase in proinflammatory cytokine levels following the first 3 mg/kg dose only. In contrast, the second dose (D6) did not result in cytokine release of the same magnitude, supporting a controlled debulking strategy as a means to reduce or eliminate the cytokine release. In study 05-1240Pnp, administration of olipudase alfa doses of 3 mg/kg on (D1) and 20 mg/kg on (D6) resulted in a reduction of circulating levels of selected cytokines at 4 and 9 hours post olipudase alfa administration relative to a single 20 mg/kg olipudase alfa. In study [05-0437Pnp] an initial 3 mg/kg olipudase alfa dose prevented increases in proinflammatory cytokines following subsequent doses of 3 mg/kg and followed by a final 20 mg/kg dose and ASMKO mice surviving toxic dose (20 mg/kg) of olipudase alfa. These data support the implementation of a dose-escalation regimen in the treatment of patients with olipudase alfa.

Relationship degradation products and toxicity of olipudase alfa in ASMKO mice

The relationship between ceramide levels (blood ceramide and ceramide isoforms measured by LC/MS/MS) and the toxicity observed in ASMKO mice was investigated. In study 06-0778, transient increases in total and C16 circulating ceramide in C57BL/6 and ASMKO+/- HET mice without statistically significant differences in CRP levels between ASMKO and C57BL/6 mice receiving 20 mg/kg olipudase alfa. In study 07-1346, increased levels of plasma ceramide (total) and C16-ceramide were observed that correlated with increased lethality and poor clinical outcome in ASMKO, mostly at the 10 mg/kg olipudase alfa. Male mice treated with 10 or 20 mg/kg olipudase alfa had statistically significant increases in total ceramide and C16-ceramide compared to female mice treated with corresponding doses. The reason for this apparent difference in ceramide levels between genders is unknown. However, no apparent difference in safety findings was noted in the toxicity studies between male and female ASMKO mice. In study 07-1511, a single dose of 10 mg/kg olipudase alfa in C57BL/6

mice resulted in a significant increase of total circulating ceramide (C16, C22 and C24) concentrations at 60 minutes postdose and C16 isoform was transiently increased up to 120 minutes postdose, compared to untreated animals. However, by 540 minutes postdose, circulating levels were returning to untreated concentrations. No toxicity was observed at the time points evaluated (consistent with previous studies). In study 07-1578 ASMKO mice following a debulking regimen (3 mg/kg QOD) all survived the final 20 mg/kg olipudase alfa dose. The debulking regimen eliminated the toxic response to olipudase alfa, and elevations of ceramide, SPH, and S1P seen with high doses of olipudase alfa. Plasma ceramide, SPH, and S1P levels were significantly lower than those seen in historical controls up to 540 minutes. In summary, the increased levels of ceramide (C16) observed after single dose of 20 mg/kg olipudase alfa to ASMKO mice that are correlated with increased lethality and poor clinical outcome are not observed in C57BL/6 mice and can be eliminated by applying a debulking regimen.

2.5.2.3. Safety pharmacology programme

Heart effects upon olipudase alfa treatments in ASMKO mice

In study 05-0533Pnp, telemetry in conscious ASMKO mice was used to evaluate the effect of olipudase alfa on heart function. Single IV doses of 20 mg/kg olipudase alfa resulted in *decreased heart rate, blood pressure, and activity* leading to death or the need for moribund euthanasia in all animals within 43 hours at 20 mg/kg and in 3 of 4 animals within 75 hours of dosing at 10 mg/kg. The 3 mg/kg olipudase alfa dose elicited mild decreases in heart rate and activity; however, both single and repeated dosing with 3 mg/kg was well tolerated. In study 06-0302Pnp ECGenie for conscious, non-invasive measurement of cardiac function was used to evaluate the effects of olipudase alfa. Baseline data gathered from these twenty ASMKO mice indicated a normal resting heart rate of 755 +/- 41 beats per minute on average without arrhythmias. Administration of 20 mg/kg in olipudase alfa to ASMKO mice caused significant bradycardia ($p < 0.01$). This was composed of an initial drop in heart rate approximately 50 min post-dose, followed by a compensation and continued with a further drop in heart rate around 3 hours post-dose. The bradycardia was accompanied by a statistical significant QT prolongation. This was composed of an initial increase in the QT interval 80 min post-dose, followed by a period where the QT appeared to decline to a normal interval, and then a steady increase beginning 4 hours post-dose. The applicant provided additional QTc data. Also QTc was significantly increased 5,6,7, and 8 hours after administration of 20 mg/kg olipudase alfa. This is possibly linked to the toxic effects of a single high dose of olipudase alfa. Patients will not receive such a high dose. In addition, no QTc prolongation has been observed in the clinical study. In study 06-0292Pnp, electrocardiograms (ECGs) collected from C57BL/6 mice indicated no significant drop in heart rate throughout the 6 hours of monitored electrocardiograms, suggesting 20 mg/kg dose of rhASM is non-toxic to C57BL/6 mice. It is presumed that because the C57BL/6 strain has acid sphingomyelinase enzyme activity, there is a little build-up of sphingomyelin substrate which further supports that ASMKO toxicity is substrate-dependent. However, as a dose of 20 mg/kg is lethal to the ASMKO mice, the relevance of the studies using ECGenie is questioned. A dose of 3 mg/kg only elicited a mild decrease in heart rate and activity. The clinical relevance of this observation is unknown as an increase in heart rate was observed upon administration of olipudase alfa to patients.

Pivotal single dose study in Cynomolgus monkey

In study 08002 the effects of IV doses of olipudase alfa on hemodynamic and respiratory parameters and electrocardiographic activity were examined in conscious, telemetered cynomolgus monkeys. The IV administration of olipudase alfa at 30 mg/kg was well tolerated in all study animals. No dose-related, biologically significant, or adverse effects were observed on blood pressure, heart rate, body temperature, ECG intervals, respiratory rate, tidal volume, or blood gas parameters. NOAEL was considered to be 30 mg/kg olipudase alfa.

Single dose study in Beagle dogs

The potential toxicity of olipudase alfa upon single IV administration of 0, 3, 10, and 30 mg/kg to Beagle dogs followed by a 2-week recovery period [Study 02026]. In addition, samples were collected for toxicokinetic evaluation. No significant pathological findings were noted. Hypersensitivity reactions were observed in control animals, which were treated with diphenhydramine and all remaining test article animals. All animals recovered over the 2-week recovery period. After Day 1, no effects were observed on blood pressure, rectal body temperature, or respiration rate. NOAEL was >30 mg/kg.

It should be noted that this study was conducted on healthy animals, and therefore any effect of high levels of sphingomyelin degradation products on hemodynamic and respiratory parameters is uncertain. However, the absence of such effects in toxicology studies precludes the need for further studies.

2.5.2.4. Pharmacodynamic drug interactions

The potential pharmacodynamic drug interactions of olipudase alfa with two potential functional inhibitors of acid sphingomyelinase (FIASMA), citalopram and fluoxetine, were evaluated in ASMKO mice. FIASMAs are a large group of cationic amphiphilic molecules that may disrupt the interaction of ASM with the lysosomal membrane. These drugs could have a negative effect on the activity of olipudase alfa. ASMKO mice were administered 1 mg/kg (olipudase alfa with or without 192 µg/day (citalopram) or 300 µg/day (fluoxetine)). The latter two were also administered alone. Sphingomyelin was significantly reduced in the liver and spleen 3 days post-administration of 1 mg/kg olipudase alfa to ASM. Co-administration of fluoxetine did not alter olipudase alfa-mediated sphingomyelin reduction in liver or spleen. Co-administration of citalopram did not alter olipudase alfa-mediated sphingomyelin reduction in the liver, but an effect on the spleen could not be excluded.

2.5.3. Pharmacokinetics

Olipudase alfa is a recombinant form of the human enzyme acid sphingomyelinase and is administered in humans every 2 weeks as IV infusion over a dose range of 0.03 mg/kg to 3 mg/kg over a period of 18 minutes to 220 minutes, respectively. The non-clinical kinetics of olipudase alfa were investigated in non-clinical species following single or repeated intravenous (IV) administration over a dose range of 0.3 mg/kg up to 30 mg/kg. Since it is a human enzyme, it is agreed that the kinetics of olipudase alfa have only been investigated in a limited number of non-clinical kinetic studies. No plasma protein binding, blood-to-plasma ratio, metabolism or excretion studies are warranted. IV infusion over a prolonged period is not feasible in non-clinical species except for Cynomolgus monkey. Therefore, olipudase alfa is administered as bolus dose or an infusion in 10 minutes in mice, rat, rabbit and dog and a 30 minute infusion in monkey. This approach is acceptable.

The non-clinical kinetics of olipudase alfa were investigated in the non-clinical species CD-1, C57BL/6 and acid sphingomyelinase knock out (ASMKO) mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs and Cynomolgus monkeys. The acid sphingomyelinase knock out (ASMKO) mouse model is a biochemical model of acid sphingomyelinase deficiency (ASMD) in humans that has an intermediate phenotype of neuropathic and non-neuropathic manifestation of disease, most similar to ASMD type A/B phenotype in human disease, and is used to study ASMD and evaluate potential therapies. Therefore, this non-clinical species is the most representative of the human patient population.

Analytical methods

An ELISA method was developed for the analysis of olipudase alfa in serum and tissue samples. The ELISA method appears sufficiently validated. Long-term stability data were provided for mouse (12 months), rabbit (292 days) and monkey (426 days). No long-term-stability data are available for rat and dog. The maximum sample storage was <9 months for rat and dog. The long-term stability should have also been investigated in serum from rat and dog, but will not be further pursued since the long-term storage was shown to be >9 months in mouse, rabbit, monkey and human serum. Incurred Sample Reanalysis was not required at the time the studies were conducted. However, ISR was performed in support of GLP study TER0698 (rabbit embryo-foetal toxicity) and met predefined acceptance criteria with an overall pass rate of 95.00%. As bioanalytical method used in GLP study TER0694 (CD-1 mouse embryo-foetal toxicity, for which ISR was not performed) was consisted in its design and used same reagents and concentration profiles were similar as in study TER0698 no impact to accuracy and precision of analysis in mouse samples is suggested.

Radioactivity in serum and tissue was analysed using the Cobra Gamma Counter.

Analytical methods were developed to measure anti-drug antibodies in serum from mouse, rabbit and monkey. No methods were developed for rat and dog. The provided analytical methods for the anti-drug antibodies in serum from mouse, rabbit and monkey appear sufficiently validated, but were not fully validated (no accuracy was determined). The precision and minimal dilution were sufficiently characterised. Only limited long-term stability data were provided for the analysis method used to determine the amount of anti-drug antibodies. However, based on literature it is known that anti-drug antibodies are stable for >3.5 years under frozen storage conditions (Michaut *et al.*, 2014; Hendriks *et al.*, 2014; Ferraz *et al.*, 2008; Rowe *et al.*, 1970). Therefore, studies investigating the long-term stability of anti-drug antibodies are not needed. No anti-drug antibodies were determined in dog, since dogs were only treated with a single dose. This is agreed. The Applicant provided information on the analytical method used to determine anti-drug antibodies in mouse and rabbit serum (studies DOS1706 and DOS1691, respectively), but did not provide the underlying report. Since the precision and minimal dilution are comparable to the precision and minimal dilution in mouse serum (study 08GST035) and monkey serum, this is agreed.

ADME

In CD-1 mice following once-daily dosing for 7 days, the AUC ranged from 83.1 $\mu\text{g} \times \text{h/mL}$ at a dose of 3 mg and 916 $\mu\text{g} \times \text{h/mL}$ at a dose of 30 mg/kg. In C57BL/6 mice following a single dose of 3 mg/kg, the AUC_{inf} ranged from 95.3 to 208 $\mu\text{g} \times \text{h/mL}$. In ASMKO mice following a single dose of 1 to 5 mg/kg, the AUC_{inf} ranged from 27.4 to 603 $\mu\text{g} \times \text{h/mL}$. In Sprague Dawley rats following a single or repeated once every two weeks dose of 3, 10 or 30 mg/kg, the AUC was $\sim 142 \mu\text{g} \times \text{h/mL}$, $\sim 500 \mu\text{g} \times \text{h/mL}$ and 1340 $\mu\text{g} \times \text{h/mL}$, respectively. The accumulation following repeated dosing ranged from 1.1-fold to 2.5-fold. In New Zealand White rabbits following once-daily dosing for 7 days, the AUC ranged from 598 $\mu\text{g} \times \text{h/mL}$ at a dose of 3 mg and 6350 $\mu\text{g} \times \text{h/mL}$ at a dose of 30 mg/kg. In Beagle dogs following a single dose of 3, 10 or 30 mg/kg, the AUC_{inf} ranged from 229 to 2496 $\mu\text{g} \times \text{h/mL}$. In Cynomolgus monkeys following a single or repeated once every two weeks dose of 3, 10 or 30 mg/kg, the AUC ranged from 202 $\mu\text{g} \times \text{h/mL}$ at a dose of 3 mg and 3500 $\mu\text{g} \times \text{h/mL}$ at a dose of 30 mg/kg. A decrease in exposure was observed following repeated dosing (0.48-fold to 0.82-fold), most likely due to the formation of anti-drug antibodies. In humans following repeated dosing once every 2 weeks, the AUC is $607 \pm 120 \mu\text{g} \times \text{h/mL}$ in adults, $529 \pm 35 \mu\text{g} \times \text{h/mL}$ in patients 12-17 years, $450 \pm 68 \mu\text{g} \times \text{h/mL}$, and $403 \pm 43 \mu\text{g} \times \text{h/mL}$ in patients <6 years. No accumulation was observed in humans. The exposure (AUC) in the non-clinical species at a dose of 3 mg/kg is lower than that in humans; doses of 30 mg/kg resulted in exposures higher than that observed in humans.

In vivo kinetic studies indicated a volume of distribution ~75 mL/kg in C57BL/6 mice, 160 mL/kg in ASMKO mice, 45 mL/kg in Sprague Dawley rats, ~110 mL/kg in Beagle dog and 230 mL/kg in Cynomolgus monkey. The volume of distribution increased with increasing dose and was highest in ASMKO mice (~150 mL/kg at a dose of 1 mg/kg and ~270 mL/kg at a dose of 5 mg/kg). Distribution studies conducted in C57BL/6 and ASMKO mice indicated that the majority of olipudase alfa was found in the liver (approximately 40% of the dose) with lower levels in the kidney, spleen, and lung (less than 1% of the dose for each tissue). There was no detectable olipudase alfa in brain tissue. No placental transfer studies or excretion studies into milk have been conducted.

The elimination half-life is ~2.3 h in C57BL/6 mice, ~4.2 h in ASMKO mice, ~1.5 h in Sprague Dawley rats, ~7 h in Beagle dogs and ~7.5 h in Cynomolgus monkey. The elimination half-life ranged from 32 to 38 hours in adult humans which is much longer than that observed in the non-clinical species. This is most likely because olipudase alfa is a human enzyme. Clearance was ~25 mL/h/kg in C57BL/6 mice, ~30 mL/h/kg in ASMKO mice, ~22 mL/h/kg in Sprague Dawley rats, ~13 mL/h/kg in Beagle dogs and ~29 mL/h/kg in Cynomolgus monkeys.

Anti-drug antibody formation

The anti-drug antibody formation was infrequent and sporadic in mice, rats and rabbits. Changes in exposure with repeated olipudase alfa infusions in non-human primates were observed (decrease of 30-50% from the first infusion to sixth and thirteenth infusion) with increased clearance and decreased half-life and correlated with increases in anti-olipudase alfa antibodies titres.

2.5.4. Toxicology

General

The pivotal studies in healthy animals were conducted according to GLP, as appropriate. With regard to the studies with the disease model ASMKO mice, the applicant claims that all pivotal studies except one were conducted at the own testing site and were GLP-compliant. However, as the testing site was never actually inspected by authorities, the statement of the GLP compliance cannot be confirmed. Nevertheless, considering the vulnerability of the test model, precluding its shipment and taking into account the overall quality of the reports, the studies can still be accepted as reliable and sufficient for evaluation.

2.5.4.1. Single dose toxicity

A total of 26 acute toxicity studies with olipudase alfa (rsASM) have been submitted by the applicant, which were performed in rats, mice, dogs and the disease model ASMKO mice. Of note is a much higher toxicity of olipudase alfa in the ASMKO mice compared to normal mice and other species. Dose levels of ≥ 10 mg/kg caused lethargy and mortality in ASMKO mice, while the dose levels of 30 mg/kg were well tolerated by normal animals. In the deceased animals, hepatic ballooning degeneration and inflammation, hepatocellular apoptosis, adrenal cortical degeneration/necrosis and adrenocortical cell apoptosis were evidenced together with increased levels of liver enzymes and cholesterol. The applicant has stipulated that this high toxicity was caused by the increased levels of ceramide, sphingosine and sphingosine-1-phosphate in the serum catabolites of accumulated sphingomyelin.

In order to further investigate the causes of the observed high toxicity in ASMKO mice, a number of additional non-GLP exploratory studies have been conducted. As sphingomyelin was shown to accumulate to a large extent in the spleen of ASMKO mice, the applicant has studied the toxicity of olipudase alfa in splenectomised animals. The toxicity of olipudase alfa appeared to be somewhat lower in splenectomised animals, as animals treated with 10 mg/kg survived until the scheduled termination,

whereas in previous studies, the dose of 10 mg/kg was lethal. However, all splenectomised ASMKO mice receiving 20 mg/kg olipudase alfa still succumbed to toxicity, indicating that splenectomy did not adequately protect against olipudase alfa toxicity. As sphingomyelin also progressively accumulates with age, the applicant has also performed studies with 22-28 weeks old ASMKO mice instead of standard 8-10 weeks old mice. No increased toxicity in older mice compared to younger mice was observed; however, the effects appeared to occur earlier in older mice compared to the younger animals. As TNF- α inhibitors previously have been shown to replenish glutathione stores and protect mice from ceramide and acetaminophen toxicity, additional studies were performed in the presence of N-acetyl-L-cysteine or S-adenosyl-L-methionine; however, none of the substances has affected the survival or prevented adverse clinical signs. The toxicity was not prevented when olipudase alfa was administered subcutaneously instead of intravenously. An additional study with heterozygous ASMKO mice demonstrated that in such mice, toxicity of olipudase alfa was comparable to normal animals.

No difference was seen between the toxicity of high and low molecular weight olipudase alfa.

2.5.4.2. Repeat dose toxicity

Pivotal studies with olipudase alfa were conducted in rats, monkeys and the disease model ASMKO mice. In rats, IV bolus injection every other week for 26 weeks (14 doses) followed by the 4 weeks recovery period resulted in the NOAEL at the highest tested dose level of 30 mg/kg. Hypersensitivity responses were noted in mid- and high-dose animals, which is common for the administration of a human protein to rodents. No or minimal amounts of anti-rhASM antibodies were detected in treated animals (titers < 1:1200-1:1600). Liver analysis indicated a dose-related increase of olipudase alfa in the liver 24 hr post-dose; however, after 28 days, the levels were comparable to controls at all dose levels, indicating the lack of accumulation of olipudase alfa in the liver. Other findings were uneventful.

Similarly, administration of rhASM to cynomolgus monkeys for 26 weeks every other week by 30 min IV injection resulted in the NOAEL of 30 mg/kg as the highest tested dose. Subcutaneous fluid accumulation at the catheter site was noted in a number of animals at all dose levels and was considered to be caused by catheter occlusion. However, this occurred with low incidence, no dose-response was seen and thus not considered to be an adverse local reaction due to the test substance administration. A dose-dependent increase in the anti-rhASM antibodies was observed at all dose levels after the 3rd administered dose, which was reflected in the decreased exposure to olipudase alfa after the repeated dosing compared to the first dose. Further findings were uneventful.

Two pivotal studies were performed with ASMKO mice, in which animals were dosed for either 12 or 13 weeks every other week with 0, 0.3, 1.0 and 3.0 mg/kg olipudase alfa. In both studies, a dose-dependent increase of anti-olipudase alfa antibodies was observed at the end of the treatment and post-recovery. In the 12-week study, a minimal degree of the adrenal cortical degeneration/apoptosis of zona fasciculata and a minor increase in the inflammatory foci within the hepatic parenchyma was seen in the treated animals, consistent with the adverse findings in liver and adrenals reported in the acute toxicity studies. The changes were reversible upon recovery and were not accompanied by changes in the serum liver enzyme levels, and therefore considered non-adverse. These findings were not noticed in the 13-week study. Instead, the decrease in the number and size of foamy macrophages and the decrease in the incidence and/or severity of cytoplasmic vacuolization was seen in multiple organs and tissues of the treated animals compared to the controls (liver, kidney, bone marrow, thymus, lymph nodes, adrenals, small intestine, spleen, stomach, trachea, pancreas, cervix, ovary, uterus, epididymis), which was consistent with the elimination of sphingomyelin in this disease model. Upon recovery, the resumption of the accumulation in select tissues was seen (liver, adrenals, spleen and bone marrow), while the other tissues from the recovery mice were comparable to the terminal sacrifice mice. Reduced relative liver weights were observed in both studies, which were likely related

to decreased sphingomyelin content due to the treatment. Olipudase alfa was detected in the liver of the treated mice in the 12-week study at the mid- and high-dose levels 24 hr post-dose; however, no detectable levels were noted post-recovery.

As severe toxicity was seen upon administration of high doses of olipudase alfa to ASMKO mice in the acute toxicity studies, which the applicant explained by the accumulation of the catabolites of sphingomyelin (ceramides, sphingosine and sphingosine-1 phosphate), the applicant has conducted a number of non-pivotal non-GLP studies in which low debulking doses of olipudase alfa were first administered, followed by the administration of high dose levels. In the non-GLP study 10-00262, considered pivotal by the applicant, a consecutive administration of four bulking doses of 3 mg/kg every other day, followed by subsequent administration of high (up to 30 mg/kg) doses of olipudase alfa for 13 weeks (7 doses every other week) resulted in the high dose levels being well tolerated. At all dose levels, a decrease in the number of foamy macrophages and a degree of cytoplasmic vacuolization in multiple organs and tissues was observed, suggesting sphingomyelin clearance (as the study did not include untreated controls, the histopathological findings were compared to the findings in the 13-week study 060301). The sphingomyelin loads were determined in the liver, spleen, kidney and lungs following the treatment. In the liver and spleen sphingomyelin levels after the treatment were almost negligible at all dose levels, whereas in kidneys, a dose-dependent decrease of sphingomyelin levels was seen. No significant reduction of sphingomyelin load in the lungs was seen, although a decreased lung weight following the treatment suggests that a clearance may still have occurred to some degree.

Consistent with the sphingomyelin degradation, increased serum ceramide levels were observed compared to the pre-dose and Day 9 of the study (after the administration of the 4th debulking dose). Mild to moderate leukocytosis and mild thrombocytosis were observed in several mice from all three treatment groups, which may indicate chronic inflammation. This correlated with statistically significant increases in the serum amyloid A (SAA) levels in all dose groups at the end of the study and in statistically significant increases in several cytokines, including IL-1 α , IL-6, KC/GRO and RANTES on Days 53 and 93 of the study compared to the predose levels. However, no adverse toxicological findings were noted, which could be attributed to these changes.

In summary, administration of olipudase alfa every other week for 26 weeks to healthy rats and monkeys did not result in adverse effects at the highest tested dose of 30 mg/kg. In the disease model ASMKO mice, no significant adverse effects were seen following administration of 3 mg/kg olipudase alfa every other week for 13 weeks. Administration of the low debulking doses of 3 mg/kg could prevent the toxicity of the high doses (up to 30 mg/kg) of olipudase alfa in this animal model. The olipudase alfa administration decreased the number of foamy macrophages and the degree of cytoplasmic vacuolization in multiple organs and tissues of the ASMKO mice, consistent with sphingomyelin elimination; the process of accumulation resumed following the recovery period.

2.5.4.3. Genotoxicity

The applicant has provided a justification for why the genotoxicity studies are not warranted for olipudase alfa. As the substance is a recombinant human enzyme for which no DNA reactivity is expected, it is agreed with the applicant that genotoxicity studies are not warranted in accordance with ICH S6 requirement.

2.5.4.4. Carcinogenicity

The applicant has provided a justification for non-performance of carcinogenicity studies with olipudase alfa, based on the following:

- There were no neoplastic or non-neoplastic proliferative findings in any nonclinical toxicity study conducted with olipudase alfa, including 6-month rat and monkey and a 3-month ASMKO mouse repeat-dose toxicity studies.
- Olipudase alfa is a recombinant human acid sphingomyelinase protein unlikely to be DNA-reactive. The structure of the final drug product does not suggest that the material has any mutagenic or carcinogenic potential.
- It is unlikely that rodents would be able to tolerate chronic administration of olipudase alfa due to hypersensitivity reactions, even with co-administration of diphenhydramine (DPH). Thus, long-term studies in rodents are not considered feasible.
- A review of the published literature on acid sphingomyelinase and its relationship to tumor development or cancer was conducted and no relevant citations were found. Furthermore, a review of the Pharmacovigilance Safety database for olipudase alfa found no association to neoplasm formation.

2.5.4.5. Reproductive and developmental toxicity

The reproductive toxicity package included a fertility and early embryo-foetal development study (FEED) in CD-1 mice, embryo-fetal development (EFD) studies in CD-1 mice and NZW rabbits, and a pre- and post-natal development (PPND) study in CD-1 mice. In the FEED study, administration of olipudase alfa at dose levels of 3.16, 10 and 30 mg/kg/dose every other day by IV bolus injection during pre-mating (M: 28 days, F: 15 days), mating and until sacrifice (M: D49-53, F: GD7) resulted in mortality at all dose levels which was attributed to hypersensitivity. It is noted that most deaths occurred at the lowest dose level of 3.16 mg/kg (7 M/6 F at 3.16 mg/kg, vs 4 M/4 F at 10 mg/kg and 0 M/0 F at 30 mg/kg). There were no effects on male and female fertility, including effects on the spermatogenesis, oestrous cycle, number of mated and pregnant females, number of implantations and corpora lutea, postimplantation loss and the number of viable embryos. The most notable finding was the lower number of pregnant females (18/23) and thus the reduced fertility index (78.3%) compared to controls in the highest dose group; however, it was still within the historical control range of the testing laboratory (76-100%). Based on the results of the study, the highest tested dose level of 30 mg/kg/dose is considered to be the NOAEL for fertility.

In the EFD study in mice, administration of 3, 10 and 30 mg/kg/day daily from GD6 to GD15 resulted in increased mortality (10/25) in the low dose group. Eight of the ten deceased females were pregnant and had litters which consisted of all non-viable conceptuses. Decreased activity was observed between GD14-16 and was considered to be caused by the hypersensitivity response. Anti-drug antibodies were detected in 47%, 20% and 15% mice from 3, 10 and 30 mg/kg/dose groups, respectively, with the highest titers (100-800) seen in the low-dose group. Serum concentration in the ADA-positive animals appeared to decrease by up to 73%; however, mean serum concentrations of olipudase alfa appeared to be unaffected, with C_{max} and AUC_{0-24} decreasing approximately dose-proportionately with the increasing dose levels.

There were no olipudase alfa-related effects on any ovarian or uterine parameters. Statistically significant increase in the number of early resorptions and post-implantation loss and a corresponding decrease in the number of live foetuses per litter was seen at 3 mg/kg; however, it was within the historical control data range (early resorptions: 1.4%; HCD: 0.6-2.%; post-implantation loss: 16.26%; HCD 3.9-23.2%; live foetuses per litter: 12.0; HCD: 11.2-14.0%). The incidence of foetuses and litters with open eyelids reached statistical significance in the 3 mg/kg/dose group; however, in the absence of the dose-response, the effect was not considered related to the treatment. Exencephaly was seen in 2 foetuses/1 litter in the 10 mg/kg/dose group (incidence 0.8% on the foetal basis and 4.8% on the

litter basis) and in 3 fetuses/1 litter in the 30 mg/kg/dose group (incidence 1.0% on the foetal basis and 4.3% on the litter basis). The incidence of exencephaly was slightly higher than historical control data. The relevance of this observation for humans is unknown.

There were 2 fetuses/2 litters and 5 fetuses/2 litters with skeletal malformations in the 10 and 30 mg/kg/dose groups. This included the malformations of ribs (absent, branched, and fused), skull bones (absent frontals and interparietals), and vertebrae (fused thoracic or lumbar arches, a thoracic or lumbar hemivertebra, absent thoracic arches, absent thoracic centra, fused thoracic centra, absent thoracic vertebrae). However, as the observed incidence was comparable to controls (2 fetuses/2 litters), the findings were considered to be incidental. No other notable developmental changes were observed. Based on the observation of exencephaly at ≥ 10 mg/kg/day, the low dose of 3 mg/kg/day was considered the NOAEL for developmental toxicity.

In rabbits, decreased body weights and weight gains were mostly observed in the low-dose group (mean body weights between GD6-29 74% of controls; maternal body weight gains between GD6-20 28% of controls). A reduced body weight gain during the dosing period was also seen in the high-dose group; however, to a much lesser extent (79% of controls between GD6-20), restored in the post-dosing period (104% of controls between GD6-29). Maternal food consumption was also reduced in the low-dose animals within the dosing period (78% of controls within GD6-20). Antidrug antibodies were detected at all dose levels, with the highest titers (400-3200) observed in the low-dose-group. There was no obvious correlation between ADA results and the exposure to the active substance on GD12. There was no treatment effect on uterine and ovarian examinations; numbers of early and late resorptions, corpora lutea and the number of live fetuses were not statistically different from controls. No foetal malformations were observed, which were considered to be related to treatment; all observed malformations were not dose-dependent, and their incidence was within the historical control data. The NOAEL for developmental toxicity was considered to be the highest tested dose of 30 mg/kg.

In the PPNP study with CD-1 mice, administration of olipudase alfa at the dose levels of 0 (two control groups), 3.16, 10 and 30 mg/kg every other day resulted in increased mortality of the dams in the low-dose group (5/25, one additional female euthanized due to the abortion of the litter). At the highest dose level of 30 mg/kg, there was an increased number of dams with stillborn pups (5 vs 0 and 1 in controls); however, there were no dams with no liveborn pups, and the overall percentage of stillborn pups was not statistically significantly increased. In addition, 2 dams of the high-dose group had a complete litter loss on PND 5-21, and 2 dams of the low-dose group had a complete litter loss on PND1-4 and PND5-21, respectively. This resulted in significantly reduced lactation indices of 87.9% and 87.7% at the low and high doses, respectively. The litter loss was attributed to reduced maternal care due to hypersensitivity response, as the deceased pups had no milk in their stomachs. In the F1 generation, two males of the low-dose group were euthanized in extremis on PND23. This was attributed to the failure to thrive post-weaning, as these mice had the lowest body weight and were from the same litter. There were no adverse effects on sexual development and fertility of the F1 animals and no effects on early embryo-foetal development of the F2 generation. No toxicokinetic measurements were conducted. There is also no information on the excretion of olipudase alfa in milk.

In summary, olipudase alfa does not appear to adversely affect the pre- and postnatal development in CD-1 mice when administered every other day during gestation and lactation up to the highest tested dose of 30 mg/kg. Decreased pup survival and reduced lactation index at the highest dose level were probably secondary to the reduced maternal care due to hypersensitivity reaction in the dams. Based on this the highest dose level of 30 mg/kg is considered the NOAEL for pre- and postnatal development.

2.5.4.6. Tolerance

The assessment of the infusion sites was incorporated in the repeated dose monkey study. Although liquid accumulation was seen in several animals, this was considered to be related to the catheter malfunctioning and not related to the test substance administration. No other test substance-related local effects were seen.

2.5.4.7. Other toxicity studies

A GLP-compliant hemocompatibility study in human whole blood was provided. The test was done in triplicate using 0.9% NaCl solution and 0.1% Na₂CO₃ solution as negative and positive controls, respectively. The percentage of haemolysis was measured as an optical density at 545 nm. Based on the results of the study, olipudase alfa at a concentration of 1.1 mg/mL has no haemolytic effect (- 0.5% haemolysis vs 100% in the positive and 0.0% in the negative control).

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has provided a justification that no environmental risk assessment is warranted for olipudase alfa, as it is a recombinant form of a natural human enzyme consisting of naturally occurring amino acids. Therefore olipudase alfa and its degradation products do not expect to present a concern for the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The applicant made use of a disease model for NPD, ASMKO mice. In this mice model, the ASM enzyme is removed. The absence of ASM activity was confirmed in brains, heart, liver, spleen, kidney and lung. The characteristic foam cells were mainly observed in bone marrow and spleen. In a moribund state, the animals had lower weight and the main organs were smaller. The hepatosplenomegaly, characteristic of the disease in humans, was thus not observed. In the brains, loss of Purkinje cells and atrophy of the cerebellum and midbrain were observed. In the animals, an increase in plasma cholesterol was also observed, but this was not used as a marker of disease in the studies presented in this dossier. The absence of ASM activity is also present in humans. However, the observation that organs get smaller due to the disease and the absence of hepatosplenomegaly is not common to human disease. Overall, it is regarded that this model is suitable to show proof of concept for the clinical use of olipudase alfa in NPD type B.

The applicant notes that *in vitro* preclinical studies were not performed as it was regarded not needed because of the animal study that allowed assessment of the activity *in vivo*. This reasoning can be followed, however information on the uptake and activity of the enzyme is considered relevant. The applicant refers to Section 3.2.S.3.1 - Elucidation of Structure, Structure Function Relationship for the *in vitro* characterization assay to measure cellular uptake of olipudase alfa. This document clarified that for olipudase alfa enzyme activity is shown in the lysate of cells that have taken up the enzyme. It is also shown that uptake occurs via the M6P route, but it is unclear in which cellular compartment the enzyme is taken up. In addition, the applicant presents data on the activity of the enzyme at different pH. While pH in early endosome is ~6.5, late endosome ~5.5 and lysosome ~4.5, it could be considered that this enzyme is most active in the late endosome. Bach et al., 1999[‡] seem to suggest

[‡] G Bach 1, C S Chen, R E Pagano, Elevated lysosomal pH in Mucopolipidosis type IV cells, Clin Chim Acta.1999 Feb;280(1-2):173-9. doi: 10.1016/s0009-8981(98)00183-1.

that the pH in lysosomes of cells from Nieman Pick Syndrome Type C or Type A is in the range of 4.3-4.5. As the *in vivo* data clearly show activity of the enzyme, olipudase alfa might rather become activated in the late endosome. Indeed, in their recently appeared review[§], Breiden and Sandhoff refer to ASM as an endo/lysosomal enzyme. This would explain the *in vivo* observed effects considering the *in vitro* data on activity.

In vivo, dose-dependent decreases of SPM were observed in ASMKO mice treated with 1, 3 or 5 mg/kg olipudase alfa. Whether these *in vivo* studies determine the final clinical dose regimen of 3 mg/kg QOW is not clear. In the preclinical PK section, it is noted that The C_{max} in humans cannot be compared to that in the non-clinical species since the infusion rate is much longer in humans (220 minutes) compared to the non-clinical species (<30 minutes). The exposure (AUC) in the non-clinical species at a dose of 3 mg/kg is lower than that in humans.

A single administration of olipudase alfa at 20 mg/kg results in a rapid increase in ceramide, sphingosine and sphingosine-1-phosphate in the serum of ASMKO mice. There appear to be two distinct phases to the generation of ceramide characterized by an early, rapid rise (2-45 min) followed by a second rise at 240 and 540 minutes postdose. SPH and S1P were significantly elevated at 240 minutes postdose and SPH remained elevated at 540 minutes postdose. Sphingosine-1-phosphate levels returned to baseline at 540 minutes postdose. The two phases of degradation products may indicate separate SPM breakdown events due to different sources of SPM. The applicant notes that the early phase likely represents an "easy to access" source that olipudase alfa can immediately target upon intravenous injection (e.g. the plasma membrane), while the latter phase, which takes several hours, may be due to tissue targeting. However, this explanation was not understood as it was anticipated that the enzyme is activated in the lysosome only. Upon request, the applicant provided a discussion on the activity of the enzyme at different pH and locations of SPM and of the enzyme. The initial production of ceramide in ASM KO mice (5-45 min. postdose) is likely the result of olipudase alfa mediated hydrolysis of sphingomyelin that is not present in lysosomes, but rather in an "easy to access" pool. It is unknown where this pool may reside but may include sphingomyelin found in the outer leaflet of the plasma membrane or in blood lipid particles. The early high peak of ceramide, following SPM degradation by olipudase alfa in ASM KO mice, was apparently not observed in ASM patients. This is reassuring for the safety. The second and later peak of ceramide likely reflects SPM degradation in the endolysosomal compartment.

After a debulking regimen with olipudase alfa (3 mg/kg QOD for four times), all ASMKO mice survived the final 20 mg/kg olipudase alfa dose. The debulking regimen eliminated the toxic response to olipudase alfa, and elevations of ceramide, SPH, and S1P seen with high doses of olipudase alfa. In addition, plasma ceramide, SPH, and S1P levels were significantly lower than those seen in historical controls up to 540 minutes. In summary, the increased levels of ceramide (C16) observed after a single dose of 20 mg/kg olipudase alfa to ASMKO mice that are correlated with increased lethality and poor clinical outcome are not observed in C57BL/6 mice and can be eliminated by applying a debulking regimen.

In ASMKO mice, high doses of olipudase alfa result in bradycardia accompanied by a statistically significant QT prolongation. This was composed of an initial increase in the QT interval 80 min post-dose, followed by a period where the QT appeared to decline to a normal interval, and then a steady increase beginning 4 hours post-dose. The applicant provided QTc data. Also, QTc was significantly increased 5,6,7, and 8 hours after administration of 20 mg/kg olipudase alfa. This is possibly linked to

[§] Bernadette Breiden¹ and Konrad Sandhoff Acid Sphingomyelinase, a Lysosomal and Secretory Phospholipase C, Is Key for Cellular Phospholipid Catabolism, *Int. J. Mol. Sci.* 2021, 22(16), 9001; <https://doi.org/10.3390/ijms22169001>

the toxic effects of a single high dose of olipudase alfa. Patients will not receive such a high dose. In addition, no QTc prolongation have been observed in the clinical study.

When olipudase alfa was administered to normal rats, mice, and dogs, no toxicity was observed up to a dose of 30 mg/kg. However, high doses of olipudase alfa ≥ 10 mg/kg administered to ASMKO mice resulted in unexpected toxicity characterized by cardiovascular shock, hepatic inflammation, adrenal haemorrhage, elevations in ceramide and cytokines (especially IL-6, G-CSF, and keratinocyte chemoattractant [KC]), and death. These toxicities are related to the sudden massive degradation of SPM in the disease model, which do not occur in the wildtype animals as there is no SPM accumulated.

Pharmacokinetics

Olipudase alfa is a recombinant form of the human enzyme acid sphingomyelinase and is administered to humans every 2 weeks as IV infusion over a dose range of 0.03 mg/kg to 3 mg/kg over a period of 18 minutes to 220 minutes, respectively. The non-clinical kinetics of olipudase alfa were investigated in the non-clinical species CD-1, C57BL/6, and acid sphingomyelinase knock out (ASMKO) mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs and Cynomolgus monkeys following single or repeated intravenous (IV) administration over a dose range of 0.3 mg/kg up to 30 mg/kg. In the non-clinical species, olipudase alfa is administered as a bolus dose or over an infusion period of <30 minutes. Therefore, the C_{max} in humans cannot be compared to that in the non-clinical species since the infusion rate is much longer in humans (220 minutes) compared to the non-clinical species (<30 minutes) at a dose of 3 mg/kg. The exposure (AUC) in the non-clinical species at a dose of 3 mg/kg is lower than that in humans.

Toxicology

The non-clinical toxicology package for olipudase alfa was conducted in accordance with ICH S6 guideline for biotechnology-derived pharmaceuticals and included acute toxicity studies in rats, mice, dogs and ASMKO mice, 26-week studies in rats and monkeys and 12 and 13-week studies in ASMKO mice; reproductive fertility study in mice; developmental toxicity studies in mice and rabbits and pre- and post-natal toxicity study in mice. The studies were conducted by IV bolus injection, with the highest administered dose of 30 mg/kg corresponding to the 10-fold MRHD.

In contrast to healthy animals, in which no clinical signs of toxicity were seen up to the highest tested dose, acute administration of olipudase alfa at dose levels of ≥ 10 mg/kg was lethal in ASMKO mice. The applicant suggested that this was due to the rapid formation of the sphingomyelin catabolites ceramides, sphingosine and sphingosine-1-phosphate. This is confirmed by the submitted pharmacodynamic studies, which indeed indicate that increased levels of ceramides, sphingosine and sphingosine phosphate were measured in ASMKO mice following olipudase alfa administration. The adverse histopathological findings in the deceased mice were observed primarily in the liver and adrenals and included hepatic ballooning degeneration and inflammation, hepatocellular apoptosis, adrenal cortical degeneration/necrosis and adrenocortical cell apoptosis. While the liver is one of the major sites of sphingomyelin accumulation along with kidney, spleen and lungs, and thus its high local exposure to the catabolite products could be expected, the mechanism of adrenal toxicity is less clear. The applicant states that the observed effects are likely to be secondary to the generalized inflammatory reaction and ensuing hypotensive shock observed in these animals and not a direct effect of olipudase alfa. It is noted that no additional information is provided to substantiate this claim. However, it can be agreed that, as adverse effects of olipudase alfa could be prevented by using the debulking regimen in the repeated dose toxicity studies, these effects are not likely to occur in patients for whom a debulking regimen of administration will also be applied.

Similarly to the acute toxicity studies, the repeated dose administration of up to 30 mg/kg olipudase alfa to healthy animals was well tolerated, without notable adverse effects. The anti-drug antibody

production was seen in both species, which in the case of monkeys was dose-dependent and resulted in the decreased exposure to olipudase alfa after the repeated dosing compared to the 1st dose. In ASMKO mice, the 12-week administration of olipudase alfa once every other week up to 3 mg/kg resulted in minimal/mild adrenal cortical degeneration and apoptosis in zona fasciculata and inflammatory foci in hepatic parenchyma, consistent with the observations in the acute toxicity studies. However, the findings were mild, and the dose of 3 mg/kg could be tolerated without overt toxicity. As high doses of olipudase alfa caused severe toxicity in ASMKO mice in the acute toxicity studies, the applicant has further conducted a number of non-pivotal non-GLP studies with low debulking doses of olipudase alfa were first administered, followed by the administration of high dose levels. It was observed that a consecutive administration of four bulking doses of 3 mg/kg every other day, followed by subsequent administration of high (up to 30 mg/kg) doses of olipudase alfa for 13 weeks, indeed resulted in the high dose levels being well tolerated. Of further note is the observed decrease in the number of foamy macrophages and in the incidence and/or severity of cytoplasmic vacuolization in the multiple organs and tissues following olipudase alfa treatment in ASMKO mice, which the applicant explained by the sphingomyelin clearance. The effect was reversible after the treatment was stopped. Consistent with this, increased serum ceramide levels were indeed measured in one of the studies using the debulking regimen. In addition, mild to moderate leucocytosis and mild thrombocytosis statistically significant increases in the levels of several inflammatory markers was also seen compared to the predose levels, suggesting that a chronic inflammatory process may accompany sphingomyelin clearance. However, in the submitted studies this was not associated with adverse toxicological findings.

The determination of sphingomyelin levels in the liver, spleen, lungs and kidney following the treatment showed that its load decreased to almost negligible in the liver and spleen, while in kidneys, a dose-dependent decrease was still seen, but the effect was less pronounced. However, there was no significant reduction of sphingomyelin load in the lungs in the submitted toxicological studies, although a decreased lung weight following the treatment suggests that a clearance may still have occurred to some degree. It is also noted that no difference in the number of foamy macrophages and the degree of epithelial vacuolisation was seen in the lungs in two pivotal studies, in contrast to other organs and tissues. Sphingomyelin clearance from lungs was reported in one study submitted as a part of the pharmacodynamics study package, in which sphingomyelin levels in the lung were reduced by 32%, 61% and 58% in ASMKO mice treated with 0.3, 1, and 3 mg/kg olipudase alfa every other week for 12 weeks compared to the vehicle group. In summary, animal studies do not offer conclusive evidence of sphingomyelin clearance from the lungs by olipudase alfa. However, considering that clinically relevant improvement was observed in the clinical studies, this issue will not be pursued further.

As the active substance is a recombinant human enzyme, the applicant did not submit any genotoxicity or carcinogenicity studies, which is in line with ICH S6 requirements. However, there is accumulating evidence that the bioactive sphingolipids, such as ceramides and sphingosine-1-phosphate, play a key role as effector molecules that regulate cell proliferation and differentiation and promote tumour growth and carcinogenesis. As these substances are formed upon degradation of the accumulated sphingomyelin, which may lead to high local concentrations in multiple organs and tissues, the applicant was asked to discuss the potential tumorigenic risk due to the formation of catabolites in patients following olipudase alfa treatment using public literature data. The Applicant stated that catabolite of sphingomyelin, sphingosine-1-phosphate (S1P) has been implicated in tumorigenesis, metastasis and angiogenesis; however, the production of this catabolite is expected to be mitigated by the dose escalation regimen and the action of endogenous S1P lyase, which converts S1P into hexadecenal and ethanolamine-phosphate. This is in agreement with the results of a study submitted as a part of the pharmacodynamics study package in which no increased levels of S1P were seen using the debulking regimen while significant increases of S1P (although still 100-fold lower than the circulating ceramide levels) were observed in mice administered a single high dose (20 mg/kg) of

olipudase alfa. Based on this it is concluded that tumorigenic risk from the presence of S1P appears to be controlled in patients due to the use of the debulking regimen, which is confirmed by the absence of sustained elevations of S1P in ASMD patients treated with olipudase alfa.

Olipudase alfa did not cause adverse effects on fertility, embryo-foetal and postnatal development in healthy animals when administered up to the highest dose of 30 mg/kg. It is however noted that clinical signs of toxicity (mortality in mice, reduced body weight and body weight gain in rabbits) were seen in both species at the low dose level of 3 mg/kg/dose, which appears to correlate with the highest incidence and/or titers of antidrug antibodies observed at this level. The Applicant stated that anti-drug antibody responses to human proteins administered to laboratory animals are not predictive of similar effects in humans, which is acknowledged.

The applicant has submitted a justification for a non-conductance of the juvenile toxicity study because the most sensitive species, the ASMKO mice, has reproductive and neurological deficiencies, making them unsuitable for the study. Furthermore, as olipudase alfa does not cross the blood-brain barrier, it would not affect neurological development in juvenile animals. The mode of action of olipudase alfa is established and is based on the degradation of the accumulated sphingomyelin; it is thus not expected that this would be different in juvenile animals. Therefore the justification of the applicant is considered acceptable.

As olipudase alfa does not cross the blood-brain barrier, the performance of dependence studies is not warranted. As the substance is a recombinant human enzyme, no additional studies with metabolites are necessary.

The substance is a recombinant form of a natural human enzyme consisting of naturally occurring amino acids, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore olipudase alfa and its degradation products are not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Pharmacodynamics of olipudase alfa was only studied in vivo in ASMKO mice at doses of 1, 3, 5, 10 and 20 mg/kg. Treatment with olipudase alfa resulted in the degradation of sphingomyelin from the liver, spleen, kidney and lung, which was most effective in the liver (possible due to high distribution of olipudase alfa to the liver) and less effective in the lung. Doses of 10 and 20 mg/kg were lethal to ASMKO mice but not to C57Bl/6 mice. A 5 mg/kg dose seems most effective, but exposure in mice is lower than in humans. Increased ceramide, one of the degradation products, was observed in 2-phases after treatment. The early, rapid rise was visible 2-45 min post-dose followed by a second rise at 240 and 540 minutes post-dose. Also, large dose-responsive increases in interleukin- (IL) 6 and G-CSF were observed at 3 and 4 hours postdose and continuing up to 9 hours postdose at doses of 3, 10, and 20 mg/kg. Smaller increases were seen in IL-1 α , IL-1 β , and MIP-1 α 3, 4, and 6 hours postdose at these doses. Also, a decrease in heart rate and activity was noted for 3, 10 and 20 mg/kg whereas a QT prolongation was noted for the lethally dosed animals (10 and 20 mg/kg).

The non-clinical kinetics were sufficiently investigated. At the clinically relevant dose of 3 mg/kg, the exposure (AUC) in the non-clinical species is lower than in humans. The C_{max} in the non-clinical species cannot be compared to that in humans since the infusion rate is much longer in humans (220 minutes) compared to the non-clinical species (<30 minutes).

Overall, the toxicology programme demonstrated that administration of olipudase alfa to the disease model ASMKO mice leads to the degradation of accumulated sphingomyelin, which causes severe toxicity when olipudase alfa is administered in high doses. The affected organs are primarily the liver

and adrenals. While the liver is one of the major sites of sphingomyelin accumulation along with the kidney, spleen and lungs, and thus its high local exposure to the catabolite products could be expected, the mechanism of adrenal toxicity is less clear, but could be secondary to the generalized inflammatory reaction and ensuing hypotensive shock observed in animals. The toxicity of olipudase alfa can be overcome by the use of a debulking scheme when the administration of high dose levels is preceded by the consecutive administration of several low doses. The degradation of sphingomyelin is accompanied by the raised levels of its catabolite products ceramides, sphingosine and sphingosine-1-phosphate in blood and an increase in the number of inflammatory markers. This did not lead to adverse toxicological changes following a 13-week administration with the debulking dosing regimen. The catabolite sphingosine-1-phosphate (S1P) has been implicated in tumorigenesis, metastasis and angiogenesis; however, the production of this catabolite is expected to be mitigated by the dose escalation regimen and the action of endogenous S1P lyase, which converts S1P into hexadecenal and ethanolamine-phosphate. The clearance of sphingomyelin was seen as a decrease in the number of foamy macrophages and the incidence and/or the degree of cytoplasmic vacuolisation in multiple organs and tissues; however, no consistent evidence of sphingomyelin clearance was observed from the lungs.

As a recombinant human enzyme olipudase alfa is not expected to be genotoxic. Studies in healthy animals did not reveal adverse effects on fertility and pre- and postnatal development. Antidrug antibodies were observed in all tested species.

Overall, the non-clinical aspects of Xenozyme have been adequately documented and meet the requirements to support this application.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The clinical development program for Xenozyme in ASMD includes 5 clinical trials with olipudase alfa treatment (Table 2), 5 reports were submitted with pharmacokinetic and pharmacokinetic/pharmacodynamic modelling data (Table 11), and 5 non-interventional natural history studies without olipudase alfa treatment (Table 4). The 5 clinical trials included a total of 67 patients with ASMD (47 adults, 20 paediatric patients). The studies DFI12712 ASCEND and LTS13632 are still ongoing.

Of the 5 non-interventional studies, 2 completed natural history studies MSC12840 (SPHINGO-001-00) and SPHINGO00302 are included in the dossier. The two non-interventional studies (MSC12840 [prospective]) and SPHINGO00302 [retrospective]) are used for comparison with the clinical data from the paediatric patients. The NHC studies will be helpful to inform on the disease course in paediatric ASMD patients.

The other 3 natural history studies are not included as they are ongoing or did not provide additional relevant information on the disease.

Table 2. Acid sphingomyelinase deficiency clinical trials of olipudase alfa treatment.

Protocol Number	Phase	Age Category	Protocol Title	Number of Patients	Treatment	Duration of Treatment	Study Status
SPHINGO00605	1a	Adult	A Phase 1, Single-center, Single-dose, Dose Escalation Study of Recombinant Human Acid Sphingomyelinase (rhASM) in Adults with Acid Sphingomyelinase Deficiency (ASMD)	11	Single arm, within patient dose escalation of 0.03 mg/kg (paediatric) or 0.1 mg/kg (adults) up to 3.0 mg/kg, intravenous infusion of rhASM every 2 weeks	Single dose	Complete
DFI13412 (SPHINGO00812)	1b		An Open-label, Multicenter, Ascending Dose Study of the Tolerability and Safety of Recombinant Human Acid Sphingomyelinase (rhASM) in Patients with Acid Sphingomyelinase Deficiency (ASMD)	5 (4 from SPHINGO00605)		26 weeks	Complete
DFI13803 (ASCEND-Peds)	1/2	Paediatric	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 Paediatric Patients Aged <18 Years with Acid Sphingomyelinase Deficiency	20		64 weeks	Complete
LTS13632	2	Paediatric / Adult	A Long-Term Study to Assess the Ongoing Safety and Efficacy of Olipudase alfa in Patients With Acid Sphingomyelinase Deficiency from studies DFI13803 and DFI13412).	25 (5 adult + 20 paediatric patients)		Up to 9 years or marketing approval	Ongoing
DFI12712 ASCEND	2/3	Adult	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	36 (1 from SPHINGO00605)	1:1 Randomization to placebo or olipudase alfa, blinded within patient dose escalation of 0.1 mg/kg up to 3.0 mg/kg, intravenous infusion of rhASM every 2 weeks	52 weeks PAP & up to 4 years and 3 months extension	PAP Complete ETP Ongoing

a LTS13632 includes 5 adult patients from DFI13412 (SPHINGO00812) and 20 paediatric patients from DFI13803 (ASCEND-Peds)

ASMD = Acid Sphingomyelinase Deficiency, ETP = extension treatment period, PAP = primary analysis period, rhASM = recombinant human acid sphingomyelinase

Table 3. Clinical studies with pharmacokinetic evaluation.

Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Modelling		
POH0494	Population pharmacokinetic analysis of olipudase alfa in adult and paediatric patients with ASMD	69
SIM0475	Population pharmacokinetic analysis of olipudase alfa in adult and paediatric patients with ASMD (updated POH0494 with ADA titer analysis)	69
POH0712	Population pharmacokinetic/pharmacodynamic analysis of olipudase alfa in adult and paediatric patients with ASMD	58 (lyso-SPM) 54 (spleen volume) 46 (DLco)
POH0610	Exposure-response analysis of olipudase alfa in adult and paediatric patients with ASMD	49 (spleen volume) 37 (DLco) 48 (platelet) 29 (hemoglobin)
QSP0068	Quantitative systems pharmacology analysis of olipudase alfa in adult and paediatric patients with acid sphingomyelinase deficiency	58 (lyso-SPM) 58 (ceramide) 54 (spleen volume) 46 (DLco)

Table 4. Acid sphingomyelinase deficiency natural history studies.

Protocol Number	Age Category	Study Design	Number of Patients	Study Status
MSC12840 (SPHINGO-001-00)	Paediatric / Adult	A Multi-center, multi-national, prospective, cross-sectional survey study of patients with NPD B	59 (30 Paediatric and 29 Adult)	Complete
SPHINGO00302	Adult	Multi-center, multi-national, Retrospective Natural History Study of Patients with ASM Deficiency	100	Complete
RHASHC09538	Paediatric	Natural History of Acid Sphingomyelinase Deficiency (ASMD) During Childhood and Adolescence: A Retrospective Observational Study (US)	1	Complete
RHASHC09539	Paediatric	Natural History of Acid Sphingomyelinase Deficiency (ASMD) Among European Patients During Childhood and Adolescence: A Retrospective Observational Study	~ 20	Ongoing
PIR16183	Paediatric / Adult	A prospective and retrospective cohort study to refine and expand the knowledge on patients with chronic forms of ASMD	~ 90	Ongoing

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Analytical methods:

For the analysis of olipudase alfa, 2 validated methods, both with sandwich immunoassay format, were developed to quantify olipudase alfa in plasma. In the first validated assay ITR-432-0409, a mouse monoclonal antibody against olipudase alfa was used as the detection reagent. Because the antibody used as the detection reagent could no longer be supplied, the method was then redeveloped to utilise a rabbit polyclonal anti--olipudase alfa antibody for the detection step (method ITR-653-0813]. This method was transferred to an external laboratory and revalidated (method PDV0079).

Validation proved that the methods were specific, precise and accurate. Stability was shown covering study sample handling and storage. Cross-validation between methods ITR-653-0813 and PDV0079 showed comparable results.

Based upon the analytical reports, run performance was within normal criteria. Furthermore, ISR data obtained by methods ITR-653-0813 and PDV0079 showed acceptable reproducibility.

For the analysis of ceramide, lyso-sphingomyelin (lyso-SPM), chitinase, chemokine (C-C motif) ligand 18 (CCL18), and angiotensin-converting enzyme (ACE), validated analytical methods or commercial assays were applied. Validation proved that the methods showed acceptable performance and stability of the analytes.

For the analysis of olipudase alfa IgG ADA in serum, immunogenicity was monitored using validated ADA assays and followed a tiered bioanalysis approach of screening, confirmation, and titration. Immunogenicity was assessed using a validated ELISA method to screen samples for ADAs, and a separate immunoprecipitation assay was used to confirm the specificity of the response. All assay acceptance criteria were met for the assay parameters tested.

Anti-drug antibody-positive samples identified with the ADA assay were further evaluated for the presence of NAb, both to inhibit enzymatic activity and to inhibit uptake into cells. The methods were validated and showed acceptable performance.

An assay capable of detecting NAb which inhibit the uptake of olipudase alfa into cells was developed and validated using human acid-sphingomyelinase deficiency (ASMD) primary fibroblast cells. Assay acceptance criteria were met for the assay parameters tested.

In the event that a patient experienced a moderate, severe, or recurrent infusion associated reaction suggestive of hypersensitivity, additional blood samples were collected for the evaluation of anti-olipudase alfa immunoglobulin E (IgE), serum tryptase, and complement activation. Samples were also analysed for circulating immune complex (CIC). IgE antibodies against olipudase alfa were quantified using an automated validated fluoroenzyme immunoassay using ImmunoCAP® specific IgE technology, showing acceptable selectivity, specificity and criteria for the assay parameters tested. For Serum tryptase, complement activation and CIC, commercially available standard CLIA methods were applied.

PopPK, PopPK/PD analysis:

A three-compartment PopPK model (report POH0494) was developed and validated for olipudase alfa with data from Phase I, Phase II, and Phase II/III studies conducted in paediatric (n=20) and adult (n=49) patients with a dosing regimen, after within-patient dose escalation, of 3.0 mg/kg every two

weeks administered through intravenous infusion. This model, parameterized with a first-order elimination process, showed good agreement between model-predicted and observed plasma concentrations.

Inter-patient variability in model parameters, when estimable (for CL, V1, V2, and V3) ranged between 14% (V3) and 24% (V1). The residual (intra-individual) variability, modelled through a proportional error model, was moderate with a ~23% CV.

Time-varying bodyweight dependent allometric scaling factors on CL, V1, V2, and V3 were included in the model. Bodyweight was identified as a significant covariate. Moreover, the olipudase alfa manufacturing process was also identified as a significant covariate affecting CL, V1, and V2.

The influence of anti-drug antibody factors (status and titers) on olipudase alfa PK in ASMD patients was evaluated using the previously developed PopPK model POH0494. The analysis (report SIM0475) was conducted using the same dataset (for patients of Phase I, II and III clinical studies) included in the popPK analysis POH0494. ADA status was not identified as a significant covariate.

Furthermore, the analysis did not indicate an effect of a different DLco, lyso-sphingomyelin, ceramide exposure and liver cirrhosis on olipudase alfa exposure.

Three PopPK/PD models were developed and validated (report POH0712). At the first step, a PopPK/PD model was developed to describe the relationship between olipudase alfa plasma concentrations and reduction of plasma concentrations of the Lyso-SPM biomarker. At the second step, the predicted plasma Lyso-SPM concentrations were used to link the olipudase alfa treatment effect with the time course of spleen volume reduction and recovery (increase) of DLco clinical endpoints.

The relationship between the plasma Lyso-SPM concentrations and the plasma olipudase alfa concentrations was best characterized by a turnover response model (type I – loss of induction) in which olipudase alfa plasma concentrations exerted an inhibitory effect on lyso-SPM production rate. The model was parametrized with Tturn, the turnover time of plasma Lyso-SPM (Tturn being the reciprocal of the first-order rate constant of lyso-SPM degradation Kout), Imax, the maximum drug-induced inhibitory effect and IC50, the olipudase alfa plasma concentration at 50% of maximum drug inhibitory effect. Visual predictive showed acceptable results. The covariate analysis indicated that body weight was a significant covariate for Imax, with lower values in patients with a higher body weight. Imax was estimated to be 0.953, 0.909, and 0.893, respectively (10th, 50th, and 90th percentiles of the baseline body weight). The Imax of 0.9 indicated that a near-maximal reduction in plasma Lyso-SPM was achieved.

Additionally, age was identified to significantly influence Tturn, with longer Tturn observed in younger patients. Of importance, IC50 was estimated to be 0.0003520, 0.00641 to 0.0154 µg/mL (10th, 50th, and 90th percentile of the baseline body weight, respectively), lower than the observed plasma concentrations over the 2-week dosing interval at the maintenance dose of 3.0 mg/kg in both adult and paediatric patients, suggesting that maximal reduction in plasma Lyso-SPM was maintained. None of the other tested covariates showed a significant effect on plasma lyso-SPM responses.

The relationship between the spleen volume data and the plasma Lyso-SPM concentrations was best described by a turnover response model (type III – stimulation of induction) with a stimulatory effect of plasma lyso-SPM on the expansion rate of spleen volume. The model was parametrized with the turnover time of spleen volume ([Tturn], the reciprocal of the first-order rate constant of spleen volume decrease [Kout], and alfa the coefficient of power function effect. Visual predictive showed acceptable results. None of the tested covariates showed a significant effect on spleen volume.

The relationship between the DLco data and the plasma Lyso-SPM concentrations was best described by a turnover response model (type IV – stimulation of loss) with a stimulatory effect of plasma lyso-

SPM on the reduction rate of DLco. In order to include patients with missing baseline DLco values, a Baseline parameter was a priori included and estimated in the model. The model was further parametrized with K_{in} , the zero-order rate constant of DLco recovery and α , the coefficient of the power effect function. Visual predictive showed acceptable results. None of the tested covariates showed a significant effect on DLco.

An exposure-response analysis (report POH0610) was conducted to evaluate the relationship between olipudase alfa exposure (i.e., cumulative AUC over the 52-week treatment) and the efficacy endpoints spleen volume (% change from baseline in spleen volume) and DLco, at Week 52 for studies DFI12712 ASCEND, DFI13803 Peds, and DFI13412/LTS13632. Additional markers including platelet, hemoglobin, and hematocrit. The cumulative AUC over the 52-week treatment period were computed using the POH0494 PopPK model for individual patients following their actual dosing regimen. Considering both adult and paediatric patients, none of the responses of spleen volume, DLco, platelet, and hemoglobin (adult patients only) had a clear relationship with olipudase alfa cumulative AUC over the 52-week treatment period.

In the modelling presented, the applicant justified that the analysis can be considered representative for commercial active manufacturing process.

Absorption:

The recommended starting dose of Xenpozyme is 0.1 mg/kg for adults and 0.03 mg/kg for paediatric patients, given every 2 weeks. The dose should be subsequently increased according to the SmPC recommended dose escalation regimen up to 3 mg/kg. Infusion rates and duration of infusion depend on the dose.

As olipudase alfa is administered intravenously, the absolute bioavailability is 100%.

After IV administration, olipudase alfa C_{max} values generally occurred at the end of infusion, and thereafter plasma concentrations declined in a multiphasic manner. Linear pharmacokinetics for AUC(0- τ) and C_{max} is observed over the range of 0.3 – 3.0 mg/kg. Olipudase alfa pharmacokinetics shows a low to moderate between-subject variability of about 20 – 40% for C_{max} and 15 – 25% for AUC.

No accumulation is observed after once every 2 weeks of dosing. After repeated doses at the 3.0 mg/kg dose, C_{max} and AUC(0- τ) were comparable across different PK visits, indicating no time dependency. However, in study LTS13632, individual AUC(0- τ) values following Q2W IV infusions of 3.0 mg/kg in adult patients showed increasing AUC(0- τ) values during the study period. A similar trend was observed in the paediatric population. The applicant sufficiently clarified that this was due to a change in formulation from olipudase alfa during the course of the study. After accounting for the differences in olipudase alfa exposure across different manufacturing processes, there were no apparent increases in olipudase alfa exposures when patients received the same process derived product during the course of the study.

The Q2W dosing was chosen based on non-clinical study results to maintain the reduction of sphingomyelin.

Comparison of AUC(0- τ) between ADA positive and negative patients showed similar AUC(0- τ) at the 3 mg/kg (IV Q2W) dose at each visit. There were no apparent effects of ADA on the exposure of olipudase alfa.

Bioequivalence:

During the clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process.

The applicant has provided a comparison of pharmacokinetic data across manufacturing processes. Clinical data did not indicate a different efficacy when patients switched to a different manufacturing process, and no difference in overall immunogenicity profile was observed.

Distribution:

Olipudase alfa, an enzyme, is not expected to bind to plasma proteins, and as such, drug-drug interactions due to protein displacement are not expected.

At the 3.0 mg/kg dose, the mean steady-state volume of distribution (V_{ss}) of olipudase alfa ranged from 0.148 to 0.181 l/kg (10.4-12.7 l in a 70 kg individual), which was confirmed by popPK analysis, i.e. 13.1 ± 2.3 l. These data indicate that olipudase alfa is primarily distributed in the vascular system with limited extravascular tissue distribution.

Olipudase alfa does not cross the blood-brain barrier.

Metabolism:

Olipudase alfa is a therapeutic protein, and its metabolism is expected to be limited to proteolytic catabolism to small peptides and individual amino acids.

Elimination:

Olipudase alfa is slowly eliminated from plasma. At the 0.3 to 3.0 mg/kg dose, mean clearance values of olipudase alfa ranged from 4.5 to 5.2 ml/h/kg, which was confirmed by popPK analysis, i.e. 4.7 ml/h/kg in a 70 kg individual. The terminal half-life values of olipudase alfa ranged from 32 to 38 hours at the 3.0 mg/kg dose in the adult patient population.

Special patient groups:

Following administration of 0.3, 1.0, and 3.0 mg/kg olipudase alfa to adolescents (aged 12 - <18 years), children (aged 6 to <12 years) and young children/infants (aged <6 years), maximale concentrations are observed at about the end of infusion. After the end of infusion, plasma concentrations declined in a multiphasic manner, with mean $t_{1/2}$ values ranging from 17.1 to 24.3 hours.

The popPK estimated plasma exposure indicated that olipudase alfa mean steady-state $AUC_{0-\tau}$ was about 13% lower in adolescent patients, about 26% lower in children and about 34% lower in young children/infants compared to adults.

The lower exposure in patients with lower body weight (i.e., paediatric patients) was not clinically relevant as generally consistent clinical responses of spleen volume reduction, and DLco increase were noted in these patients compared to the rest of the patients. These results support the current body weight-based dosing regimen for olipudase alfa (see clinical efficacy assessment).

In line with this, body weight appeared to be a covariate for olipudase alfa clearance. Increase of body weight increases the CL and consequently decrease exposure parameters like AUC. However, an increase in body weight due to the weight-based dose regimen increases the amount of injected enzyme and consequently an increase in AUC. As olipudase alfa is dosed based on the patient's body weight, as a result, following a 3.0 mg/kg dose regimen, the bodyweight effect translated into an increase in 8% of C_{max} and 16% of $AUC_{0-\tau}$ for virtual patients weighing 77.6 kg and a decrease in 30% of C_{max} and 40% of $AUC_{0-\tau}$ for virtual patients weighing 19.0 kg, when compared to virtual patients weighing 58.0 kg. The SmPC recommends a dose cut-off for patients with a BMI > 30 kg/m²; however, this dose recommendation was not further supported. In its response, the applicant clarified that as olipudase alfa is primarily distributed in the vascular system with limited extravascular tissue

distribution and the lower blood volume per kg in morbidly obese patients compared to normal weight patients, this would potentially result in higher than expected exposures in obese patients. In study SPHINGO00605, 1 obese subject showed an almost 2-fold increase in exposure, and therefore a dose cut-off at 30 mg/m² was applied in the subsequent clinical studies. Limited data in obese subjects showed no difference in clinical efficacy. On request, this dosing regimen was further substantiated by popPK analysis, showing that exposures in obese subjects with a BMI of 40 kg/m² would have resulted in an increased exposure by 35%, while applying the cut-off in dosing would result in a comparable exposure.

No studies have been carried out in subjects with renal or hepatic impaired function. The disposition of olipudase alfa is not expected to be impacted by renal or hepatic impairment. The population pharmacokinetic analysis did not show a difference in olipudase alfa exposure due to renal or hepatic impairment (liver cirrhosis). However, the covariate analysis of baseline albumin, baseline alanine aminotransferase, baseline aspartate aminotransferase, and baseline total bilirubin were not presented. Additional submitted data showed no impact of these covariates on olipudase alfa exposure.

The population pharmacokinetic analysis did not show a difference in olipudase alfa exposure between male and female subjects, race (Asian/other; n=4), and elderly (>65 years; n=2), although it should be noted that very limited data were included.

Interactions:

Drug-drug interactions (DDI) via cytochrome P450 enzymes or transporters is not expected, and therefore, no specific clinical DDI studies have been conducted with olipudase alfa. Literature data indicate that based upon *in vitro* data and *in silico* data, tricyclic antidepressants and some cationic amphiphilic drugs, including anti-histaminic drugs, may decrease olipudase alfa activity. The interactions are sufficiently described in section 4.5. of the SmPC.

2.6.2.2. Pharmacodynamics

Mechanism of action

Olipudase alfa, developed as an enzyme replacement therapy to supplement deficient ASM in ASMD patients, converts sphingomyelin into ceramide. PD assessments in the clinical program for olipudase alfa included the measurement of plasma ceramide and several biomarkers reflecting disease burden, namely plasma lyso-sphingomyelin (lyso-SPM), plasma chemokine [C-C motif] ligand 18 (CCL18), serum chitotriosidase (chitinase), and serum angiotensin converting enzyme (ACE).

Ceramide is a direct catabolite of olipudase alfa-mediated metabolism of sphingomyelin and serves as a PD marker of olipudase activity in ASMD patients.

Primary Pharmacology

In ASMD patients receiving an IV injection of olipudase alfa every other week, plasma ceramide levels showed transient post-infusion increases within 24 to 48 hours, with progressively lower pre-dose ceramide levels by the next infusion. Both pre- and post-infusion ceramide levels steadily decreased with continued olipudase alfa therapy. Lyso-SPM, a deacylated form of sphingomyelin was substantially elevated at baseline and above the upper limit of normal in plasma for both adult and paediatric patients. After receiving an IV injection of olipudase alfa every other week, plasma lyso-SPM levels declined significantly following treatment with olipudase alfa, reflecting debulking of sphingomyelin in tissue. This was confirmed by showing a reduction of liver sphingomyelin in liver biopsies. The change in mean pre-infusion plasma lyso-SPM from baseline to Week 52 was -78.0% in adult patients and -87.2% in paediatric patients, respectively. Serum chitotriosidase, plasma CCL18, and serum ACE,

the PD endpoints reflecting disease burden, were also reduced continuously over the entire treatment period of olipudase alfa in both adult and paediatric patients.

Table 5 shows the different key biomarkers/pharmacodynamic endpoints tested in adults (pivotal study DFI12712) and in the open label study in paediatrics (study DFI13803).

Table 5. Summary of the (percentage) change from baseline at Week 52 in selected key biomarker parameters - mITT population in DFI13803 and DFI12712.

Parameter	DFI12712				DFI13803 Olipudase alfa	
	Placebo (N=18) LS Mean (SE)	Olipudase (N=18) LS Mean (SE)	Difference LS Mean (SE)	P-value	(N=20) LS Mean (SE)	P-value
% change in Chitotriosidase (nmol/mL/h)	-12.3 (7.3)	-54.7 (6.9)	-42.4 (10.1)	0.0003	-58.0 (5.6)	<.0001
% change in CCL18 (ug/L)	9.3 (21.2)	-41.7 (20.5)	-51.0 (29.7)	0.0952	-64.7 (3.6)	<.0001
% change in ACE (ukat/L)	-20.1 (5.6)	-36.8 (5.2)	-16.6 (7.7)	0.0371	-27.4 (3.5)	<.0001
% change in plasma lysosphingomyelin (ug/L)	-5.0 (4.2)	-77.7 (3.9)	-72.7 (5.8)	<.0001	-87.2 (1.3)	<.0001
% change in plasma ceramide (mg/L)	-0.2 (5.6)	-36.4 (5.3)	-36.1 (7.8)	<.0001	-57.0 (5.0)	<.0001
% change in Liver Sphingomyelin (MS/MS) (mcg/mg)	7.4 (11.7)	-76.7 (12.1)	-84.0 (17.5)	<.0001	-	-
% change in average tissue area occupied by sphingomyelin (%) from liver biopsy	10.3 (7.8)	-92.0 (8.1)	-102.3 (11.3)	<.0001	-	-

*Abbreviations: ACE=angiotensin converting enzyme; CCL18=chemokine (CC motif) ligand 18; LS=least squares; MS/MS=liquid chromatography-tandem mass spectrometry; SE=standard error; % change=percentage change. *The LS mean (SE) were generated from MMRM model as specified in DFI12712 SAP, and the P values are nominal.*

The p-values and LS means (SE) from DFI12712 are based on a mixed model for repeated measures approach with baseline parameter value, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates per DFI12712 SAP.

The p-values and LS means (SE) from DFI13803 are based on regression of change from baseline with baseline value as the covariate.

The baseline is the last non-missing value prior to the first infusion of IMP (olipudase alfa or placebo).

Pharmacodynamic and pharmacokinetic/pharmacodynamic studies in healthy study participants

No PD and PK/PD studies were performed in healthy subjects.

Pharmacodynamic, pharmacokinetic/pharmacodynamic and quantitative systems pharmacology studies in patients

Exposure-response analysis (POH0610)

The data from adults and paediatric ASMD patients enrolled in DFI13412 (Phase 1b), DFI13803 (Phase 1/2), LTS13632 (Phase 2) and DFI12712 (Phase 2/3) clinical studies were considered to perform the POH0610 analysis (see section 2.1.2.3).

Responses to the clinical endpoints, spleen volume, DLco, platelet, and haemoglobin (adult patient only), with three categories of cumulative AUC values over 52 weeks of treatment (<25th, 25-75th, and >75th percentile) in each of the adult and paediatric patient populations are displayed in **Figure 2**.

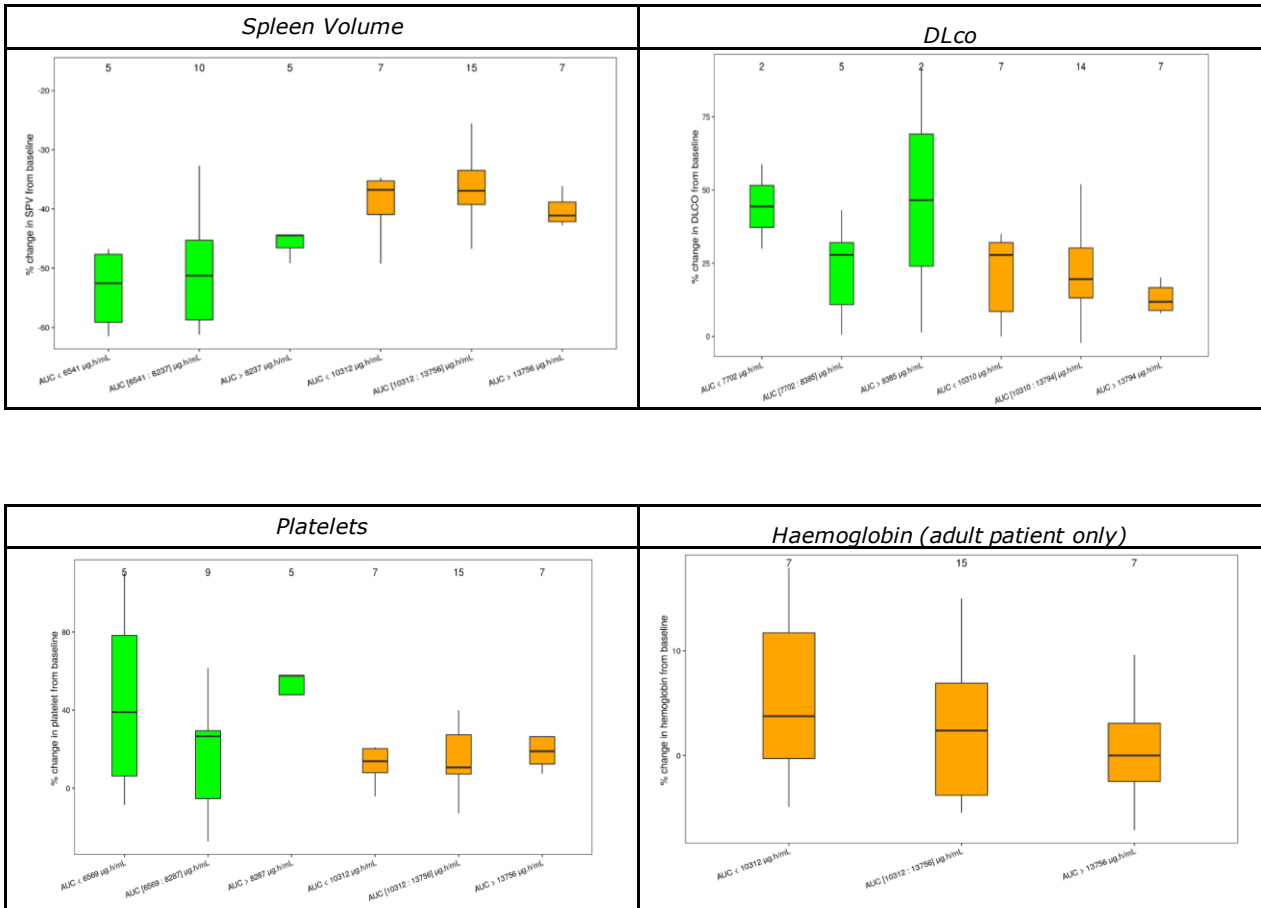


Figure 2. Relationship between percentage changes from baseline in Week 52 responses (spleen volume, DLco) and cumulative AUC values over 52 weeks of treatment with Q2W IV infusions in adult (orange) and paediatric (green) ASMD patients (POH0610).

Note: The box plot represents % change from baseline at Week 52 for the responses collected from three groups of patients with cumulative AUC (over 52 weeks of treatment) of <25th, 25-75th, >75th percentile in each adult and paediatric patient population. Adult and paediatric patients are displayed in orange and green respectively. The box represents the IQR of the response and the whiskers extend to the most extreme data point that is <1.5 times the IQR. Lower and upper boundary of the box represent the 25th and 75th percentiles, respectively and the line within the box marks the median. Numbers inside plot panel at the top of each group indicate the counts of patients in each category of covariate; AUC = cumulative AUC over the 52 weeks of treatment predicted by the PopPK model for individual patients following actual dosing regimen in the clinical trials; DLco = diffusing capacity of the lung for carbon monoxide (% predicted); SPV = spleen volume (multiple of normal).

Population pharmacokinetic/pharmacodynamic analysis (POH0712)

A Pop PK/PD analysis was performed to characterize the relationship between olipudase alfa plasma concentrations and reduction of plasma Lyso-SPM accumulation and subsequent reduction of spleen volume or elevation of DLco over the time course of treatment with olipudase alfa.

The covariate analysis indicated that near-maximal reduction in plasma Lyso-SPM was achieved in the overall population, with an I_{max} estimated to be about 0.89 – 0.95. IC_{50} ranged from 0.000352 to 0.0154 $\mu\text{g/mL}$, being lower than the observed plasma concentrations over the 2-week dosing interval at the maintenance dose of 3.0 mg/kg in both adult and paediatric patients, suggesting that maximal reduction in plasma Lyso-SPM was maintained.

Correlation between plasma Lyso-SPM decrease and spleen volume reduction or DLco improvement was demonstrated using indirect response models with a stimulatory effect of plasma Lyso-SPM on the expansion rate of spleen volume or reduced rate of DLco. No covariate was identified to impact either spleen volume or DLco responses driven by the plasma Lyso-SPM decline after the covariates had been integrated to account for variability in PK (body weight and manufacturing process) and plasma Lyso-SPM response (body weight and age).

Quantitative Systems Pharmacology Analysis of olipudase alfa in Adult and Paediatric Patients with ASMD

The QSP analysis aims to assess the degree of mechanistic similarity of disease and response to olipudase alfa in paediatric and adult ASMD patients applying a QSP model of ASMD that describes key pathophysiology and the mechanism of action of olipudase alfa. The QSP model was developed by integrating various data sources such as clinical data from paediatric and adult ASMD patients enrolled into Phase 1, Phase 2, and Phase 2/3 studies for olipudase alfa, along with natural history studies ASMD patients. These datasets were supplemented with preclinical data and published studies related to sphingomyelin biology and ASMD.

The QSP analysis supports mechanistic similarity of disease between paediatric and adult patients. The only clinically meaningful difference identified was ASM residual enzymatic activity, which indicates differences in severity of disease burden, not pathophysiology. Both modelling approaches demonstrated that the mode of action of olipudase alfa is similar between adult and paediatric patients. Based on these analyses, more severe patients (reflected by higher baseline values the different parameters for in the clinical data) observed in paediatric cohort tended to show greater response in PD markers of plasma lysosphingomyelin and ceramide, which is attributed to a higher reaction rate of conversion of sphingomyelin, and not actual differences in the pathophysiology of ASMD. Overall responses to the 2 key clinical endpoints following treatment with olipudase alfa are consistent between adult and paediatric patients. Furthermore, the QSP model predicts olipudase alfa to be efficacious in debulking tissue sphingomyelin in type A ASMD patients. Analyses using both modelling approaches support the similarity of disease and response to olipudase alfa between paediatric and adult ASMD patients.

The development of the QSP model is also published (Kaddi *et al.*, 2018).

Secondary Pharmacology

Immunogenicity

Immunogenicity was assessed in all clinical studies of olipudase alfa, which included active treatment of patients. For the adults, the integrated analysis set consisted of data pooled for adult patients enrolled in all repeat-dose studies (DFI13412, LTS13632, and DFI12712 ASCEND), while the paediatric analysis set consisted of data for paediatric patients enrolled in DFI13803 Peds and LTS13632.

Overall, 60 ASMD patients (40 adult and 20 paediatric) have received olipudase alfa for a median duration of 3.11 years (range 0.4 to 7.8). Overall, 48.3% (29 of 60 patients) of ASMD patients (40% [16 out of 40] of adults and 65% [13 out of 20] of paediatric patients) developed treatment-emergent ADA while receiving olipudase alfa. The majority had a low ADA response (≤ 400), with a median peak titer of 75 (range 50-3200) for adults and 200 (range 50-1600) for paediatric patients. Paediatric patients generally developed ADA in a shorter time period compared to adults (10 weeks in paediatric patients compared to 33.1 weeks in adults). Overall, 15% of the overall treated population (9 out of 60) developed NAb that inhibited catalytic activity (4 adults and 5 paediatric patients), with 6 patients NAb-positive at only 1 timepoint while 1 adult and 2 paediatric patients were persistent but intermittently NAb-positive. No patients showed NAb that interfered with cellular uptake.

Anti-drug antibody effect on PK of olipudase alfa

ADA status/titer or NAb positivity did not have a meaningful effect on olipudase alfa exposure in both adult and paediatric patients.

Anti-drug antibody effect on plasma lyso-sphingomyelin

Plasma Lyso-SPM was used as the clinically relevant PD marker to evaluate the impact of ADA. The mean baseline plasma Lyso-SPM was similar in adult and paediatric patients who were negative for treatment-emergent ADA compared to those patients who developed treatment-emergent ADA. Overall, with time, the decline in Lyso-SPM was similar between patients who developed ADA *versus* those who did not. At Week 52, there was a similar statistically significant decline in Lyso-SPM in adult and paediatric patients regardless of their ADA status. Patients' Lyso-SPM levels continued to decline or be stable beyond this time point, indicating no impact of ADA on this PD biomarker.

Pharmacodynamic interactions with other medicinal products or substances

No drug interaction studies have been performed. Because olipudase alfa is a recombinant human protein, no cytochrome P450 mediated drug-drug interactions are expected.

Based on available publications of *in vitro* data, ASM activity may be decreased in patients due to concomitant ingestion of several classes of medications (e.g., fluoxetine, chlorpromazine, tricyclic antidepressants [e.g., imipramine, or desipramine]) (Gulbins *et al.*, 2013). These classes of medications have been prohibited in olipudase alfa studies due to the potential drug-drug interactions. The lists of prohibited concomitant medications are provided in clinical study manuals.

Cationic amphiphilic antihistamines, such as loratadine, desloratadine, astemizole, ebastine, and clemastine, may decrease olipudase alfa activity (Kornhuber *et al.*, 2010). Therefore, the need for their use in oral or IV administration should be carefully considered. There is no restriction on topical antihistamines.

Genetic differences in PD response

The impact of SMPD1 genotype (e.g. homozygous for Arg610del, heterozygous for Arg610del, and other variants) was evaluated on efficacy (spleen volume and DLco) and PD parameters (plasma lyso-sphingomyelin and chitotriosidase). Overall, for both adult and paediatric patients, where $n > 5$, there was no major effect of SMPD1 genotype on efficacy or PD parameters in this subgroup analysis with limited sample sizes.

2.6.3. Discussion on clinical pharmacology

Plasma ceramide, a major product of olipudase alfa-mediated metabolism of sphingomyelin, increased transiently following each olipudase alfa infusion in both adult and paediatric patients, signifying

olipudase alfa bioactivity. A consistent decrease of mean plasma ceramide along with plasma lyso-SPM, and other PD markers (chitotriosidase, CCL18, and ACE) was observed with olipudase alfa treatment over time, consistent with the debulking of sphingomyelin and reflecting the olipudase alfa mechanism of action. Liver biopsies confirmed debulking.

The covariate analysis POF0712 indicated that near-maximal reduction in plasma Lyso-SPM was achieved in the overall population, with an I_{max} estimated to be about 0.89 – 0.95. IC_{50} ranged from 0.000352 to 0.0154 $\mu\text{g/mL}$, being lower than the observed plasma concentrations over the 2-week dosing interval at the maintenance dose of 3.0 mg/kg in both adult and paediatric patients, suggesting that maximal reduction in plasma Lyso-SPM was maintained. No covariate was identified to impact either spleen volume or DLco responses driven by the plasma Lyso-SPM decline after the covariates had been integrated to account for variability in PK.

The developed QSP model is predictive of the pharmacodynamic effect of olipudase alfa in ASMD patients. The model showed that similar efficacy results in type A and/or type A/B patients can be expected. Therefore, the QSP model can be considered robust and well capable of predicting the treatment effect of olipudase alfa on the visceral organs in all types of ASDM patients. From a clinical point of view, it can be expected that based on the MoA of olipudase alfa and the ASMD disease pathophysiology, no large differences in the clinical efficacy outcome are expected. Albeit, no effect is expected on the neurological symptoms, as olipudase alfa cannot cross the BBB. Although the QSP model is predictive for a similar PD effect in type A patients, it is to be noted that there were no ASMD type A patients included in the clinical studies. Only a few patients with type A/B were included (patients had some neurological symptoms), and most patients had type B ASMD. Type A patients (infantile-onset) have a rapid disease progression, with death around the age of 3 years.

Given that, to date, no treatment exists to successfully treat the CNS manifestations in ASMD type A patients, olipudase alfa as a treatment modality in this severely affected subpopulation is undesirable from a clinical perspective and probably from a patients/caregiver perspective. The visceral manifestations may be alleviated and thus may result in some extended life expectancy, on the other hand the CNS manifestations which are not treated (as olipudase alfa does not cross the BBB) will result in a severely handicapped child. By leaving the CNS related issues untreated, the child eventually will succumb. Therefore, the indication excludes the treatment of ASMD type A patients, which is agreed.

In the studies conducted, olipudase alfa produced by the target process was not used in the ascending dose phase. The drug made by different methods shows some slight differences in AUC and C_{max} . After accounting for the differences in olipudase alfa exposure across different manufacturing processes, there were no apparent increases in olipudase alfa exposures when patients received the same process derived product during the course of the study. Further, the comparison of treatment-emergent adverse events (TEAEs), infusion-associated reactions (IARs), and hypersensitivity-related IARs across the manufacturing processes showed that the overall tolerability was not meaningfully different and was comparable in adult and paediatric patients. There appears to be no difference in the safety profile from the safety data across the manufacturing processes.

The absence of DDI studies can be agreed with, as olipudase alfa is a recombinant enzyme, such interactions are not expected.

No dedicated QTc studies were performed. Olipudase alfa as an ERT is not likely to cause QTc interval prolongation. In the clinical study, none of the adult patients had an increase ≥ 500 ms in QTc (updated ICH E14 guideline), and none had a clinical event indicative of QT prolongation (see safety assessment).

The applicant proposed to include in the SmPC that careful consideration of the use of tricyclic antidepressants and some cationic amphiphilic drugs, including anti-histaminic drugs, is warranted as

they may decrease olipudase alfa activity. This statement is based on literature and on *in silico* data. In the clinical program, some of these drugs were prohibited. As these are theoretical drug interactions, it is agreed not to include them in the SmPC. The potential pharmacodynamic drug interactions of olipudase alfa with two potential functional inhibitors of acid sphingomyelinase, citalopram and fluoxetine, were evaluated in ASMKO mice. Both drugs did not seem to have an effect on the efficacy of olipudase alfa in the mouse model when co-administrated, however, some influence on the effect on the spleen could not be ruled out.

Immunogenicity was assessed in all clinical studies of olipudase alfa, which included active treatment of patients. Overall, 15% of the overall treated population (9 out of 60) developed NAb that inhibited catalytic activity (4 adults and 5 paediatric patients), with 6 patients NAb-positive at only 1 timepoint while 1 adult and 2 paediatric patients were persistent, but intermittently NAb-positive. None of the patients showed NAb that interfered with cellular uptake. Subgroup analyses between ADA-positive and ADA-negative patients on the efficacy parameters (reduction on sphingomyelin, spleen volume and DLco) showed no indication that the ADA-status had a relevant impact on treatment outcome (see clinical efficacy). Longitudinal measures of plasma lyso-sphingomyelin for the 3 patients with repeated NAb-positive results showed no marked effect of antibody-positive on the results; even after the development of NAb that inhibited catalytic activity in these 3 patients, the spleen volume and liver volume reduced, indicative of treatment response. For % predicted DLco, there was variability observed even during the visits with negative NAb, and thus there were no clear trends. Overall, the decline in pre-infusion plasma lyso-sphingomyelin and mean spleen volume was similar between patients regardless of ADA status. In particular, the 3 patients with intermittent positive NAb against catalytic activity had achieved treatment responses similar to the overall population.

From the preclinical data and the QSP model, a biphasic production of ceramide was observed. In ASMKO mice this was observed at non-clinically relevant doses in WT or ASMKO heterozygous mice or in patients following administration of olipudase alfa. The data suggest that the initial production of ceramide in ASMKO mice is the result of olipudase alfa mediated hydrolysis of sphingomyelin that is not present in lysosomes, but rather in an "easy to access" pool. It is unknown where this pool may reside but may include sphingomyelin found in the outer leaflet of the plasma membrane or in blood lipid particles. Studies to investigate whether olipudase alfa can degrade sphingomyelin in circulating LDL particles or at the plasma membrane have not been conducted. It is agreed with the applicant that the lack of both early ceramide production in ASMD patients and increased early IARs during infusion or shortly after the infusion, suggests that if such degradation occurs, it does not adversely impact the safety profile of olipudase alfa.

2.6.4. Conclusions on clinical pharmacology

The key biomarkers (chitotriosidase, CCL18, plasma lyso-sphingomyelin, plasma ceramide, ACE, and liver sphingomyelin) showed reductions for BL to week 52 in both adult and paediatric patients. In general, it is observed that under olipudase alfa treatment up to week 26 marked reductions for these parameters are observed, thereafter reductions seem to plateau and remain at these low levels up to week 52 and beyond (data available up to week 232 for some adults). As expected from the MoA all PD parameters point in the same direction, suggestive for improvement. In addition, liver histopathology samples confirm that under olipudase alfa treatment, debulking of sphingomyelin occurs, confirming the MoA. Notably, consistent with the observations on these biomarkers, reductions in spleen volume (which is one of the two primary endpoints) and liver volume were observed in both the adults (pivotal study DFI12712) and paediatrics (Study DFI13803).

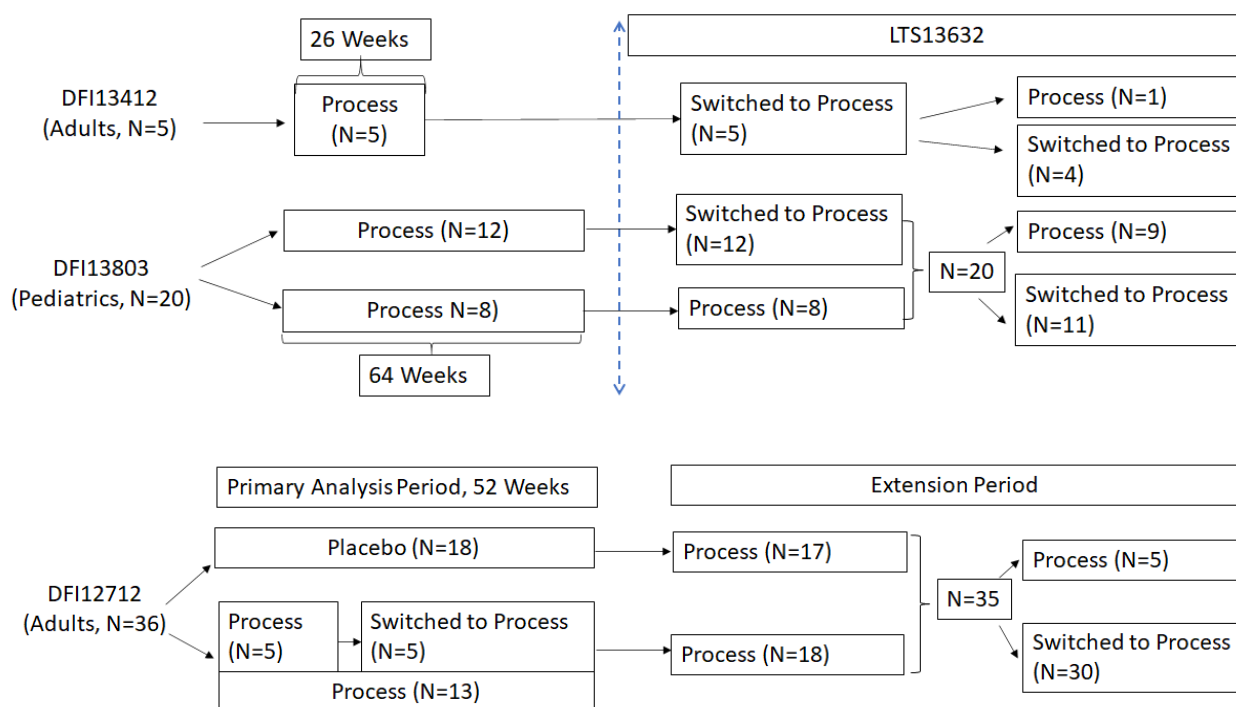
Although the QSP model suggests that olipudase alfa can be used for treatment of the visceral symptoms in ASMD type A patients, like in type A/B and B patients, the indication is restricted to ASMD type A/B and type B patients only. This is agreed, as despite potential beneficial treatment effect on the visceral symptoms, the neurological symptoms are not treated – as olipudase alfa does not cross the BBB – and treatment for these patients seems not desirable given the rapid fatal outcome.

Overall conclusion regarding pharmacokinetics: The proposed posology in patients with a BMI >30 kg/m² is sufficiently substantiated. Further, no studies have been carried out in patients with renal or hepatic impaired function, but the disposition of olipudase alfa is not expected to be impacted by renal or hepatic impairment. In addition, population pharmacokinetic analysis did not show a difference in olipudase alfa exposure due to renal or hepatic impairment (liver cirrhosis). Drug-drug interactions are sufficiently described in the SmPC.

2.6.5. Clinical efficacy

- **Use of different manufacturing batches of olipudase alfa**

During the clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process and the different manufacturing process batches have been used in the clinical studies.



As there were no important issues with respect to the different manufacturing batches, this will not be further discussed in the overview. Full details can be found in the Clinical Day 60 Assessment Report.

2.6.5.1. Dose response studies

Study SPHING0605 was a phase 1, single-centre, single-dose, dose-escalation study of olipudase alfa in adults with ASMD. The tolerability and safety of olipudase alfa were evaluated after single,

ascending doses of olipudase alfa were administered to 11 adult patients with ASMD. Doses administered were 0.03 mg/kg (3 patients), 0.1 mg/kg (3 patients), 0.3 mg/kg (2 patients), 0.6 mg/kg (2 patients), and 1.0 mg/kg (1 patient).

Eleven adults with confirmed ASMD were treated in this study, 6 males and 5 females, all white. Age ranged from 18 to 54 years (mean 31 years) at the time of infusion. Nine patients were diagnosed in childhood, the other 2 in adulthood. Baseline ASM activity ranged from 6% to 29% of normal in peripheral leukocytes (mean: 16% of normal).

Per the inclusion criteria, all patients had a spleen volume at least twice that of normal. One patient had had a partial splenectomy; the other 10 patients had fully intact spleens. Liver volumes were also increased (mean 1.6 multiples of normal (MN) \pm 0.4 MN). None of the patients had cirrhosis or had liver function test values (ALT, AST, total bilirubin) outside the range permitted at entry. Mean liver function test values for the 11 patients were within the normal range at baseline: AST, 45.5 U/L (\pm 28.6 U/L; normal range, 1 to 50 U/L); ALT, 50.6 U/L (\pm 36.4 U/L; normal range, 1 to 53 U/L); total bilirubin, 0.82 mg/dL (\pm 0.37 mg/dL; normal range, 0.1 to 1.2 mg/dL).

All but 1 patient had a body mass index (BMI) that was within the normal range (BMI < 30 kg/m²). All 11 patients had 2 identified mutations in the SMPD1 gene.

Results

Plasma ceramide levels showed a temporal relationship to treatment that also appeared to be dose-dependent (see **Figure 3** for by-cohort mean plasma ceramide levels over time).

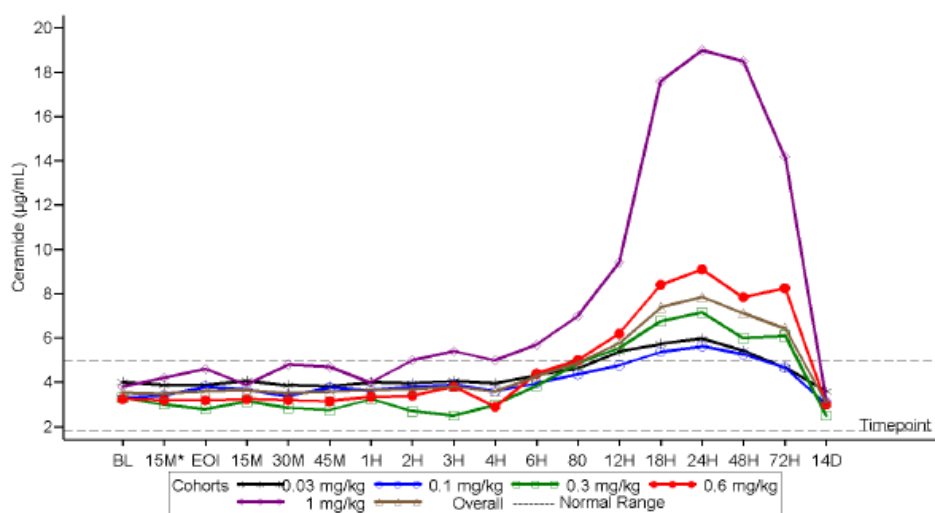


Figure 3. Ceramide Levels by study cohort.

Plasma and dried blood spots (DBS) were collected to measure sphingomyelin levels to evaluate the mean changes in sphingomyelin in plasma and DBS by dose cohort throughout the study. The single patient in the 1.0 mg/kg cohort showed a noticeable peak in sphingomyelin levels in both plasma and DBS at 72 hours post-infusion.

The relationships between the baseline plasma sphingomyelin levels and the safety response biomarkers (e.g., peak plasma ceramide, total bilirubin, and hsCRP) were difficult to assess. Overall, there were no apparent correlations between baseline plasma sphingomyelin levels and safety response biomarkers when all patient data were considered.

Study DFI13412 was an open-label, multicenter, ascending dose study of the tolerability and safety of olipudase alfa in ASMD patients. This ascending dose study was to evaluate the safety, tolerability,

pharmacokinetic, and pharmacodynamic profile of olipudase alfa in adult patients with ASMD. Repeated IV infusions of olipudase alfa were administered every 2 weeks for 26 weeks. Six patients aged 18 to 65 years, inclusive, were studied. The study was designed to evaluate a gradual dose escalation strategy as a means of providing safe and tolerable repeat doses of olipudase alfa to patients with ASMD by slowly reducing accumulated substrate. Results of this study were used to refine the design of the planned Phase 2 study.

Adults aged between 18 and 65 years inclusive, with non-neuronopathic ASMD characterised by spleen volume ≥ 6 multiples of normal (MN); diffusing capacity of carbon monoxide (DLco) measured at $>20\%$ and $\leq 80\%$ of the normal, predicted value; and retained liver function, characterised by alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 250 IU/L, total bilirubin ≤ 1.5 mg/L, and INR ≤ 1.5 .

Results

Pulmonary function tests (FVC, FEV1, TLC and DLco)

At baseline, all patients were within the normal range ($\geq 90\%$ of normal) of FVC, FEV1, and TLC and remained in this range throughout the study. Under treatment (baseline to week 26) the lung function parameters improved FVC % predicted, +1.5 (6.5); TLC % predicted, +3.9 (7.7); FEV1 % predicted, +0.6 (4.9). DLco % predicted improved by +13.4 (16.0)%.

The applicant also investigated this at the patient level (Table 6). The data indicates improvement based on the DLco predicted; however, none of these 5 patients switched their initial severity category.

Table 6. By-patient listing of DLCO % predicted.

Patient ID	Baseline		Week 26	
	%predicted	severity ^a	%predicted	severity ^a
826001002	43.7	moderate	50.8	moderate
840001001	48	moderate	65	mild
840001002	77	mild	83	mild
840001003	43	moderate	50	moderate
840001004	80	mild	73	mild

^a Severity of reduced DLCO: mild = $>60\%$ to $<LLN$, moderate = 40-60%; severe = $<40\%$ (Pellegrino et al., 2005).

Spleen and liver

Table 7 shows the overall and by-patient spleen and liver volumes at baseline and week 26.

Table 7. Overall and by-patient spleen and liver volumes at baseline and week 26 - Exploratory efficacy population (N = 5).

Patient ID	Spleen volume (multiples of normal)			Liver volume (multiples of normal)		
	baseline	Week 26	change (%)	baseline	Week 26	change (%)
826001002	14.5	11.1	-23.2	2.2	1.4	-37.8
840001001	17.9	12.7	-29.0	2.2	1.5	-33.5

840001002	7.4	4.9	-33.4	1.2	1.1	-8.0
840001003	16.1	10.9	-32.1	1.8	1.3	-27.7
840001004	8.0	5.6	-29.1	1.3	1.3	-2.6
Mean (SD)	12.8 (4.8)	9.1 (3.5)	-29.4 (3.9)	1.7 (0.5)	1.3 (0.1)	-21.9

Normal spleen volume in MN is 2 cm³/kg x body weight (kg). Normal liver volume in MN is 25 cm³/kg x body weight (kg).

Ceramide

Mean values for plasma ceramide increased following all olipudase alfa infusions and generally peaked at 48 hours post-infusion (Figure 4), signifying olipudase alfa bioactivity. During the dose-escalation period and the repeated 3.0 mg/kg olipudase alfa infusions, ceramide concentrations measured pre-infusion were attenuated as compared with values observed during previous study weeks. Similarly, ceramide concentrations measured post-infusion decreased throughout the treatment period.

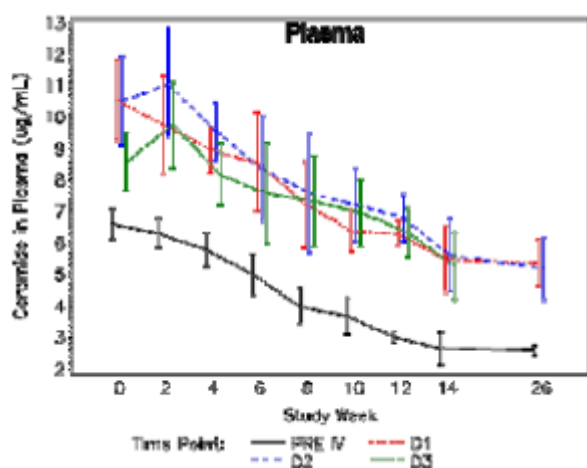


Figure 4. Mean ceramide in plasma before and after olipudase alfa infusions.

Abbreviations: Pre IV = preinfusion; D1 = 24 hours postinfusion; D2 = 48 hours postinfusion; D3 = 72 hours postinfusion. Normal range of ceramide in plasma = 1.8 to 6.5 µg/mL

2.6.5.2. Main study(ies)

DFI12712

Title: 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 adult patients.

Methods

Design

The study was divided into 2 consecutive periods: 1) a randomized placebo-controlled, double-blind primary analysis period (PAP) from Day -60 to Week 52 followed by 2) an extension treatment period (ETP) where patients from the placebo group crossed over to olipudase alfa treatment from week 52 to week 104. After week 104, patients could remain in the trial in a long term follow-up part.

Study Participants

Inclusion criteria

1. The patient is male or female, aged 18 years or older.
2. The patient has documented deficiency of ASM as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes; and a clinical diagnosis consistent with NPD B.
3. The patient has DLCO $\leq 70\%$ of the predicted normal value.
4. The patient has spleen volume ≥ 6 multiples of normal (MN) measured by MRI; patients who have had partial splenectomy will be allowed if the procedure was performed ≥ 1 year before screening/baseline and the residual spleen volume is ≥ 6 MN.
5. The patient has an splenomegaly-related score (SRS) ≥ 5 .

Exclusion criteria

1. The patient has received an investigational drug within 30 days before study enrolment.
2. The patient has a medical condition, including significant intercurrent illness; significant cardiac disease; active hepatitis B or hepatitis C, or infection with human immunodeficiency virus (HIV); malignancy diagnosed within the past 5 years (other than non-melanoma skin cancer), or any other serious medical condition that may preclude participation in the study.
3. The patient has a platelet count $< 60 \times 10^3/\mu\text{L}$ based on the average of 2 samples.
4. The patient has an international normalized ratio (INR) > 1.5 .
5. The patient has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 250 IU/L or total bilirubin > 1.5 mg/dL (except for patients with Gilbert's syndrome).

Treatments

Patients were randomly assigned in a 1:1 ratio into placebo (saline 0.9% sodium chloride solution) or 3.0 mg/kg olipudase alfa target dose. During the extension treatment period, only olipudase alfa was received.

Dosing with study drug was by intravenous infusion every 2 weeks (± 3 days) from the date of the first infusion (Day 1). The 52-week treatment period of the PAP began on Day 1 with the first infusion of study drug.

To maintain the double-blind, all patients underwent escalation under the same conditions, regardless of treatment assignment and according to the schedule provided in Table 8.

All infusions were to take place in a monitored setting with ready access to emergency resuscitation equipment and medications. One rechallenge each was allowed for doses administered at Week 0 (0.1 mg/kg olipudase alfa or placebo) and at Week 4 (0.3 mg/kg olipudase alfa or placebo). Patients who were unable to tolerate the re-challenge at those doses were discontinued from the study; however this appeared not necessary in this study. During the PAP and ETP, in-patient hospitalization was required pre-infusion and for at least 24 hours after the infusion during dose escalation (i.e., through Week 16 and Week 70, respectively) and may be required at the quarterly and yearly visits up through the end of Year 2; in-patient hospitalisation might be necessary during quarterly and yearly study visits in Years 3 through 5.

Home infusion during the extension treatment period (ETP)

Home infusion was not used during the primary analysis period but could be initiated in the ETP during the COVID-19 pandemic by trained home nurses every 2 weeks (± 3 days).

Rescue treatment

For treatment periods during both the PAP and ETP, dose-limiting toxicity (DLT) criteria were applied. A rescue strategy was provided during the blinded period for patients who may experience significant clinical decline.

Dose escalation

A dose-escalation scheme was followed for dose selection (Table 8). Patients were admitted to the hospital during dose escalation (PAP and ETP) as described in the visit schedule. Dose escalation followed the criteria described in Section 8.4.5. Patients unable to tolerate the target dose received the highest tolerated dose once every 2 weeks for the remainder of the study. The minimum active dose planned to be administered was 0.3 mg/kg.

The same dose-escalation schedule and conditions were applied for patients who crossed over from the placebo group to the active treatment group in the ETP.

The following criteria determined the next dose of study drug to be administered, provided the patient did not meet the DLT criteria. These criteria applied to AEs considered related to study treatment:

1. If the patient experiences no AE or a mild AE, escalate to the next dose
2. If the patient experiences a moderate AE, repeat the same dose
3. If the patient experiences a severe AE, decrease to the prior dose

If a patient presented on the day of infusion either with an unresolved AE or an acute illness, neither of which met the patient DLT criteria, then study drug infusion may have been withheld or administered at the discretion of the Investigator.

Table 8. Olipudase alfa administration schedule.

Adult patients (≥ 18 years old)	
First dose (Day 1/Week 0)	0.1 mg/kg
Second dose (Week 2)	0.3 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth dose (Week 14)	3 mg/kg (recommended maintenance dose)

Dosing will be based on weight. For patients with a body mass index (BMI) >30 kg/m², the dose will be based on the mass in kilograms corresponding to a BMI of 30 given the patient's height.

Objectives

Primary Objective

To evaluate the efficacy of olipudase alfa administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD by assessing changes in:

- 1) spleen volume as measured by abdominal magnetic resonance imaging (MRI)
- 2) infiltrative lung disease as measured by the pulmonary function test diffusing capacity of the lung for carbon monoxide (DLco).

Secondary objectives

- To confirm the safety of olipudase alfa administered IV once every 2 weeks for 52 weeks

- To characterize the effect of olipudase alfa on the patient perception related to spleen volume as measured by SRS after 52 weeks of study drug administration (For the United States, the effect of olipudase alfa on SRS was part of the primary objective)
- To characterize the effect of olipudase alfa on the following endpoints assessed sequentially:
 1. The effect of olipudase alfa on liver volume after 52 weeks of study drug administration
 2. The effect of olipudase alfa on platelet count after 52 weeks of study drug Administration
 3. The effect of olipudase alfa after 52 weeks of study drug administration on fatigue
 4. The effect of olipudase alfa after 52 weeks of study drug administration on pain
 5. The effect of olipudase alfa after 52 weeks of study drug administration on dyspnoea

Additional objectives: To characterize the effect of olipudase alfa on liver function tests (LFTs), infiltrative lung disease, pulmonary functioning, fasting lipid profile, bone disease, cardiopulmonary functioning, biomarkers, inflammatory and vascular biomarkers, the nuclear magnetic resonance (NMR) profile of high-density lipoprotein, liver function, haematology parameters, health-related quality of life, Physician's global assessment of change, clearing sphingomyelin accumulation in liver and/or blood, characterize the multiple-dose plasma pharmacokinetic profile of olipudase alfa.

Outcomes/endpoints

Two primary endpoints:

- Percentage change in % predicted DLco from baseline to Week 52
- Percentage change in spleen volume (in multiples from normal (MN) from baseline to Week 52

Secondary endpoints included:

- Fatigue severity as measured by Item 3 of the Brief Fatigue Inventory (BFI) scale
- Pain severity as measured by Item 3 of the Brief Pain Inventory-Short Form (BPI SF) scale
- Dyspnoea severity as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-dyspnoea tool
- SRS patient perception related to spleen volume and was part of the combination spleen primary endpoint for the US. The SRS rates 5 items: abdominal pain, abdominal discomfort, early satiety, abdominal body image, and ability to bend down.

Tertiary endpoints:

- PFTs
 - forced vital capacity (FVC) (L)
 - forced expiratory volume in the first 1 second (FEV₁)
 - total lung capacity (TLC) (L)
- Pulmonary imaging
 - both lungs ground glass (GG) appearance by high-resolution computed tomography (HRCT)
 - both lungs interstitial lung disease (ILD) by HRCT and chest X-ray
 - both lungs reticulonodular density (RND) by HRCT
 - both lungs pleural thickening by HRCT
- Cardiopulmonary performance by treadmill ergometry (CPET)

Randomisation, blinding (masking) and Matching

Eligible patients were randomized 1:1 to study treatment or placebo. The design of the study requires patients to be hospitalized for infusion, and the randomization happens when the patient is hospitalized.

The randomisation was performed centrally by Interactive Response Technology when the patient is hospitalized, using blocks of 4, without any stratification factors.

Note: The first patient was enrolled 18 December 2015; the last patient completed the primary analysis period in March 2021. In amendment 7, 1 Feb 2016: The 1 mg arm had been removed, changing the randomization ratio from 2:1:2 to 1:1 during the primary analysis period.

During the PAP, patients, Investigators, and the Sponsor study team were blinded to the identity of study treatment; an unblinded team at the Sponsor was in place to manage certain activities. Also, patients and Investigators did not have access to the randomization (treatment codes) until after the database lock for PAP, and all patients had undergone dose-escalation portion of ETP, except under specific circumstances as described below. The Sponsor was blinded until the database lock for PAP.

At the facilities where the PK measurements, ADA, and selected biomarkers were assessed, the samples were analysed prior to the database lock for PAP that resulted in unblinding of responsible bioanalysts.

A detailed operational plan was implemented to maintain the blinding and access to restricted data in the study until the patients, investigators, partners, and Sponsor were unblinded.

Statistical methods

Analysis populations

Efficacy populations

Efficacy analyses will use mITT population unless specified otherwise.

The modified intent-to-treat (mITT) population: randomized patients who received at least 1 infusion, partial or total.

The per-protocol population is a subset of the mITT population that has no critical or major protocol deviations that are expected to interfere with assessments of the primary efficacy endpoints (the list to be finalized before the database lock and unblinding in PAP).

The mITT-C population is the subset of mITT population which excludes patients who had exposure to non-commercial scale material of olipudase alfa in the active treatment group.

Rescue therapy population: patients who had rescue therapy initiated in the PAP. Since in the ETP all subjects get olipudase alfa, the rescue therapy was relevant only for the PAP.

Safety population

The safety population included randomized patients who received at least 1 infusion (partial or total). In this population, patients were analysed according to the actual treatment received during the PAP, irrespective of the treatment patients who received at least 1 infusion (partial or total). In this population patients were analysed in the treatment group to which they were randomized. This was the primary population for the efficacy analysis.

For the efficacy populations (mITT / PP) patients were analysed in the treatment group to which they are randomized, for the safety population, patients were analysed according to the actual treatment received.

Primary outcomes and hypothesis tested

Two primary outcomes have been defined, the percentage change in predicted DLco and the percentage change in spleen volume. The overall 5% significance level for the two hypothesis tests will be maintained using the Hochberg method; if the highest $p < 0.05$, both DLco and spleen volume are significant. If a higher p -value ≥ 0.05 , and a lower p -value < 0.025 , then the endpoint associated with a lower p -value is significant, but one associated with a higher p -value is not significant. For Europe and ROW: from the sponsor perspective, the study will be declared positive if at least one of the primary endpoints is statistically significant by the above method.

Efficacy analyses used the mITT population unless specified otherwise. This included patients who used rescue therapy, but their data after rescue was NOT included in the analysis. Sensitivity analyses, including data beyond rescue therapy, was undertaken if appropriate.

DLco

The percentage change in DLco (% predicted) from baseline to 52 weeks was analysed in the mITT population using a mixed model for repeated measures (MMRM), including baseline DLco, 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. If this model fails to converge, the following variance-covariance structures were tested in this order: Toeplitz (equal variances and a separate correlation for each level of separation between the time points), AR(1) (first-order autoregressive, equal variances, and exponentially decreasing correlations), CS (compound symmetry, equal variances and equal pairwise correlations across fixed time points). 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.

The MMRM assumes data missing-at-random (MAR) and included all DLco observations except for measurements made after the initiation of rescue therapy. In addition, for patients who do not have Week 52 value available but have a PFT value measured after Week 38 infusion (e.g, patients discontinuing the study or initiating rescue therapy after Week 38 but before Week 52 may have the PFT measurements available from early discontinuation visit or right before rescue therapy starts), these values were used as Week 52 value for analysis purposes; Week 52 DLco will not be considered missing in such situations. This idea is based on the clinical concept that PFT measurements are similar within a 12-week period.

In addition to evaluating the percent change from baseline, a *responder analysis* was performed to assist in the interpretation of a clinically meaningful result. International guidelines for clinically meaningful changes in DLco have been published for idiopathic pulmonary fibrosis (IPF), including 2017 Spanish IPF guidelines and the 2017 French IPF guidelines indicate a decrease of $>15\%$ DLco in absolute values is associated with an increased risk of mortality (Xaubet *et al.*, 2017; Cottin *et al.*, 2017). At the same time, the Connective Tissue Disease- associated interstitial lung disease (CTD-ILD) -OMERACT CTD-ILD working group has a consensus guideline indicating that a relative 15% change constitutes a clinically meaningful change (Khanna *et al.*, 2015). In addition, Pellegrino *et al.* (2005), set a clinically meaningful threshold at 10%, and similar values in the range of approximately 10-14% have been reported reviewing datasets from larger studies Horita *et al.*, 2015; Punjabi *et al.*, 2003). Therefore, a responder analysis was performed using a threshold of 15% improvement in DLco from baseline. This means if a patient has a change from baseline on DLco (% predicted) $\geq 15\%$ at Week

52, then this patient was a responder.

A binary measure of responder (yes vs no) at Week 52 was analysed with logistic regression, including treatment and baseline as covariates. Patients who had missing data at Week 52 were counted as non-responder. The number and % of responders, as well as odds ratio, 95% CI and p-value from the logistic regression model, were provided.

Spleen volume

The *percentage change* in spleen volume (MN) and the change in the splenomegaly-related score were analysed using an analogous MMRM model. Baseline values are generally the latest value before the first infusion of the study drug, except for platelets and haemoglobin, which are part of haematology parameters; for haematology parameter baseline definition, please refer to Section 2.6.1.

In addition to evaluating the percent change from baseline, a *responder analysis* was performed to assist in the interpretation of a clinically meaningful result. In Gaucher disease, therapeutic goals for splenomegaly include a reduction in spleen volume of 30-50% within year 1 of enzyme replacement therapy (Pastores *et al.*, 2004). Therefore a responder analysis was performed, setting the threshold for response at $\leq -30\%$ change from baseline in spleen volume at 52 weeks.

A binary measure of responder (yes vs no) at Week 52 was analysed with logistic regression, including treatment and baseline as covariates. Patients who had missing data at Week 52 were counted as non-responder. Number and % of responder, as well as odds ratio, 95% CI and p-value from the logistic regression model, were provided.

Sensitivity analyses for the primary efficacy endpoints included the following:

1. The MMRM described above was run using the per-protocol population. This analysis will demonstrate whether the results vary depending on the population analysed.
2. The MMRM described above will exclude observations made after the initiation of rescue therapy. As a sensitivity analysis, the observations collected after the initiation of rescue therapy was included in the MMRM; the treatment arm for rescued patients remained as randomized treatment. The MMRM planned for the primary efficacy analysis assumes MAR. To assess the robustness of the primary results to that assumption a pattern mixture model was used (see Section 2.6.6 for details).
3. The MMRM planned for the primary efficacy analysis assumes multivariate normality. To assess the robustness of conclusions under this assumption, nonparametric testing method was used: A Wilcoxon-Mann-Whitney (WMW) was used to compare the primary efficacy endpoints; missing Week 52 data will be imputed using LOCF, excluding patients who initiate rescue therapy.

Analysis of secondary outcomes

The MMRM model as used in the primary analysis of spleen volume under primary efficacy endpoints was used to compare treatment groups for the following secondary outcomes from baseline to Week 52, using mITT population: liver volume, platelet counts, BFI-scale item 3, BPI-scale item 3, FACIT-dyspnoea symptom score, splenomegaly related score. For all secondary outcomes listed supportive summary in mITT-C population were provided. Sensitivity analyses are not planned, but may be undertaken if necessary.

If statistical significance was reached on both the DLco and spleen volume using the Hochberg method, then hypothesis testing of the secondary efficacy endpoints proceeded using sequential testing at 5% level with the order as specified below. At any step when the endpoint is not significant at 5% level,

the formal testing in subsequent steps would stop; the p-values for the subsequent endpoints in the sequence were considered exploratory, and hence interpreted at the nominal level. This controls the overall type I error level at 5%, using the closed testing principle. If either of the primary endpoints is not significant, then hypothesis testing for the secondary endpoints was considered to be exploratory, and p-values were interpreted at the nominal level.

For Europe and ROW, the order of testing for secondary endpoints is as follows:

1. Percentage change in liver volume from baseline to Week 52
2. Percentage change in platelet count from baseline to Week 52
3. Change in BFI scale, Item 3 - from baseline to Week 52
4. Change in BPI scale, Item 3 - from baseline to Week 52
5. Change in FACIT-Dyspnea symptom score from baseline to Week 52
6. Change in SRS from baseline to Week 52

Interim analysis

No formal interim analysis has been planned.

Subgroup analysis

The consistency of the treatment effect in PAP was evaluated for percentage change from baseline to Week 52 of spleen volume (MN) by baseline spleen volume severity (severe, defined as >15 multiple of normal, vs not severe). For % predicted DLco by baseline % predicted DLco severity (severe vs not severe, with severe defined as baseline % predicted DLco <40%).

In addition, for the endpoints of percentage change from baseline to Week 52 of spleen volume (MN), SRS, and % predicted DLco, the consistency of treatment effect in PAP was assessed by the following subgroups: Baseline ALT or AST abnormality (ALT or AST \geq 1 ULN vs ALT and AST <1 ULN); Baseline total bilirubin abnormality (total bilirubin \geq 1.5 ULN vs total bilirubin <1.5 ULN); Presence vs absence of portal hypertension at baseline.

Due to the small sample size in these subpopulations, treatment differences within the subgroup was difficult to interpret. Therefore, the focus of these analyses was on the assessment of interaction between subgroups and the treatment.

For each subgroup, same MMRM models for the primary efficacy endpoints using data from the specific subgroup only were conducted to provide estimate of treatment effect within each subgroup. To assess the interactions between subgroup and treatment, the same MMRM models for the primary efficacy endpoints were applied with the addition of subgroup, subgroup-by-visit interaction, subgroup-by-treatment interaction, subgroup-by-treatment-by-visit interaction. The p-value for overall subgroup-by-treatment interaction, subgroup-by-treatment-by-visit interaction, subgroup-by-visit interaction as well as the p-value for subgroup-by-treatment interaction at week 52 will be provided.

Results

Participant flow

Table 9 summarizes the patient disposition.

Table 9. Summary of patient disposition study DFI12712- All patients.

	Placebo	Olipudase alfa	Overall
Screened patients, n			62
Eligible patients, n			38
Nonrandomized but treated patients, n			0
Randomized patient, n	18	18	
Randomized but not treated patients, n (%)	0	0	
Randomized and treated patients, n (%)	18 (100%)	18 (100%)	
Patients who had been rescued during PAP, n (%)	0	0	
Patients who did not complete the study treatment period as per protocol, n (%)	2 (11.1%)	2 (11.1%)	
Primary reason for permanent treatment/study discontinuation, n (%)			
Adverse event	0	0	
Related to COVID-19	0	0	
Not related to COVID-19	0	0	
Withdrawal of consent	0	1 (5.6%)	
Progressive disease	0	0	
Lack of efficacy	0	0	
Poor compliance to protocol	1 (5.6%)	0	

Baseline data

Demographic characteristics of patients in the mITT population are summarized in Table 10. For full details refer to the CSR.

Table 10. Summary of demographic and baseline characteristics - mITT population.

	Placebo (N = 18)	Olipudase alfa (N = 18)	Overall (N = 36)
Age at Week 0/Day 1 (years)			
Number of patients with value	18	18	36
Mean (SD)	33.5 (17.1)	36.2 (12.7)	34.8 (14.9)
Median	24.1	34.9	29.9
Min : Max	18.6:65.9	18.8:59.9	18.6:65.9
Gender, n (%)			
Number of patients with value	18	18	36
Male	5 (28%)	9 (50%)	14 (39%)
Female	13 (72%)	9 (50%)	22 (61%)
Race, n (%)			
Number of patients with value	18	18	36
Asian	1 (6%)	1 (6%)	2 (6%)
White	16 (89%)	16 (89%)	32 (89%)
Other	1 (6%)	1 (6%)	2 (6%)
Ethnicity, n (%)			
Number of patients with value	18	18	36
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%)

Note: Percentages are calculated using the number of patients who have available data in each treatment group as the denominator. Current data cutoff: 15MAR2021

Baseline disease characteristics

Baseline disease characteristics were comparable between treatment groups and are summarized in

Table 11.

Table 11. Summary of baseline disease characteristics - mITT population.

	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			
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)	0.268 (0.234)	0.284 (0.188)	0.276 (0.210)
Spleen status, n (%)			
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 Dlco adjusted for haemoglobin and ambient barometric pressure, n (%)

Mean (SD)	48.5 (10.8)	49.4 (11.0)	-
Severely reduced (<40%)	4 (22.2%)	3 (16.7%)	7 (19.4%)

CHIT1 genotype classification, n (%) Number of patients with value

Normal / 2 functional alleles	9 (50.0%)	14 (77.8%)	23 (63.9%)
Heterozygous mutation / 1 functional allele	6 (33.3%)	2 (11.1%)	8 (22.2%)
Homozygous mutation / 2 non-functional alleles	3 (16.7%)	2 (11.1%)	5 (13.9%)

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%)

Note: Percentages are calculated using the number of patients who have available data in each treatment group as the denominator.

Medical/surgical history

Medical/surgical history findings in the MITT population were consistent with those expected in this patient population, and none of the findings were thought to affect the validity or interpretation of study data. The most commonly reported medical history findings by body system were gastrointestinal disorders, hepatobiliary disorders, musculoskeletal and connective tissue disorders, metabolism and nutrition disorders, blood and lymphatic system disorders, and respiratory, thoracic, and mediastinal disorders.

Medical history by SMPD1 variant

Ongoing nervous system disorders were observed in 13.3% of patients with the pArg610del. No ongoing nervous system disorders were detected in patients with any other SMPD1 variant.

SMPD1 genotype

The variant pArg610del was the most frequent variant observed in 15 (41.67%) patients. Sphingomyelin Phosphodiesterase 1 (SMPD1) genotype testing showed 13.9% of patients were homozygous and 27.8% of patients were heterozygous for Arg610del, which is the most common mutation in patients with the chronic visceral form of disease. There was no specific trend noticed in the distribution of severe cases among different variants.

Renal function

At baseline in study DFI12712, most patients had normal renal function (CRCL (≥ 90 mL/min/1.73m²) (n=31; 86.1%). There were 2 patients each in the olipudase alfa and placebo groups that had mild renal impairment (60 to <90 mL/min/1.73m²). There were no patients with moderate or severe impairment and none with renal failure.

Concomitant medication

All patients in the olipudase alfa and the placebo group were taking at least one concomitant medication. Cardiovascular concomitant medications were used by 72% of patients in the placebo group (33% patients had lipid lowering agents), and 50% of patients in the olipudase alfa group (28% patients had lipid lowering agents).

One patient reported taking citalopram and another reported taking sertraline. Both antidepressants did not belong to the group of prohibited drugs (tricyclic antidepressants) as defined in the protocol. There are no data to indicate that antidepressants other than the group indicated by the protocol may affect olipudase alfa efficacy.

Numbers analysed

A total of 36 adult patients were included in this study; in placebo and olipudase alfa 18 subjects were analysed in each group. In the olipudase alfa group 17/18 patients randomised to olipudase alfa were treated according to the protocol versus 16/18 in the placebo group. The applicant provided the number of patients treated with olipudase alfa who received the different manufacturing processes.

Outcomes and estimation

Percent predicted DLco

The percentage change in % predicted DLco from baseline to Week 52 (PAP) is summarised in Table 12.

Table 12. Analysis of the percentage change in DLco (% predicted) from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population.

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
BASELINE	Number of patients with value	18	18	
	Mean (SD)	48.5 (10.8)	49.4 (11.0)	
	Min : Max	30.9 : 69.1	25.4 : 67.3	
WEEK 26	Number of patients with value	17	17	
	LS Mean	1.4	15.5	14.1
	95% CI [1]	(-4.5,7.26)	(9.7,21.3)	(5.8,22.4)
	P-value for the difference between groups [1]			0.0015
	Mean (SD)	1.5 (9.4)	15.9 (14.4)	
WEEK 52	Number of patients with value	17	17	
	LS Mean	3.0	22.0	19.0
	95% CI [1]	(-3.9,9.9)	(15.2,28.8)	(9.4,28.7)
	P-value for the difference between groups [1]			0.0004
	Mean (SD)	3.1 (11.2)	22.1 (17.0)	

SD=standard deviation; SE=standard error; C=confidence interval; LS=least squares.

[1] The 95% CI and p-values are based on a mixed model for repeated measures approach with baseline Derived % Predicted DLco 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.

Note: Mean (SD) reported at each visit are based on the available data in each treatment group.

Percentage change in % predicted DLco in the PAP + ETP

At Week 52 (start of the ETP), patients initially randomized to placebo had crossed over to olipudase alfa and, by Week 104, had also received olipudase alfa for 52 weeks. After 52 weeks of treatment with olipudase alfa, the mean percentage change from baseline in % predicted DLco improved by 25% and 22% in the placebo/olipudase alfa group (n=10) and the olipudase alfa/olipudase alfa group (n=17), respectively. This group of patients showed improvement in DLco at Week 104, similar to the patients initially randomized to olipudase alfa at Week 52.

Figure 5 shows the mean DLco (% predicted) over time.

The decline observed at Week 184 in the olipudase alfa/olipudase alfa group is explained by the availability of data for only 1 patient who missed 6 consecutive missed infusions from Week 174 to Week 184.

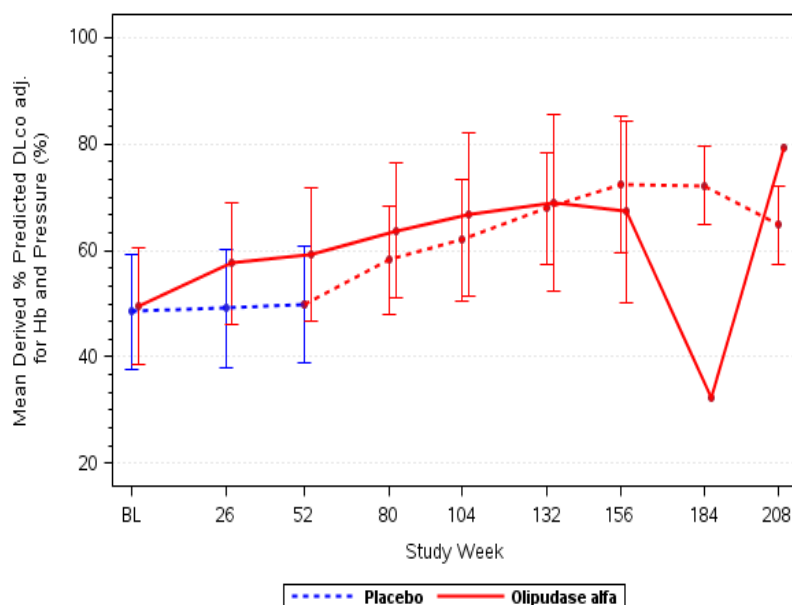


Figure 5. Summary plot of mean DLco (% predicted) over time (same baseline for both treatment groups) in PAP + ETP - mITT population.

Note: After Week 52 all patients received olipudase alfa.

Note: The vertical bars represent standard deviations.

Note: The baseline is the last non-missing value prior to the first infusion of study treatment.

Prespecified responder analyses in PAP

The prespecified responder analysis was performed, in order to assist with the interpretation of a clinically meaningful result, using a threshold of a 15% absolute improvement in DLco from baseline. A total of 5/18 patients (27.8%) patients in the olipudase alfa group were responders versus none in the placebo group (0/18), OR 14.4 with 95% CI 0.8-271.1. Patients with missing data at Week 52, were considered non-responders. Within the group of responders heterogeneity was seen for other endpoints, pointing in similar directions for improvements. At Week 104, a post hoc analysis showed that 8/10 patients (80%) in the placebo/olipudase alfa group and 7/10 patients (70%) in the olipudase alfa/olipudase alfa group were responders.

Percentage change in spleen volume

Percentage change in spleen volume from baseline to Week 52 in PAP

The mean spleen volume (calculated in MN) at baseline was similar between the olipudase alfa (mean=11.7 MN) and placebo (mean=11.2 MN) groups, indicating moderate splenomegaly. Using MMRM, during PAP in mITT population, the LS mean percentage change in spleen volume MN from baseline to Week 52 demonstrated a reduction in the olipudase alfa group (39.5%) compared to an increase in the placebo group (0.5%); resulting in a difference of -39.9% (p <0.0001). The results remain statistically significant after multiplicity adjustment. Some improvement was seen already at Week 26, suggesting an early response.

Table 13. Analysis of the percentage change in spleen volume (MN) from baseline to 52 weeks using a mixed model for repeated measures in PAP - mITT population.

Visit	Statistic	Placebo (N=18)	Olipudase alfa (N=18)	Difference
BASELINE	Number of patients with value	18	18	
	Mean (SD)	11.2 (3.8)	11.7 (4.9)	
	Min : Max	6.05 : 18.1	6.24 : 20.9	
WEEK 26	Number of patients with value	17	18	
	LS Mean	-2.4	-30.	-28.5
	95% CI [1]	(-7.0,2.2)	(-35.2,-26.4)	(-34.9,-22.1)
	P-value for the difference between groups [1]			<.0001
	Mean (SD)	-2.4 (9.8)	-30.786 (8.40)	
WEEK 52	Number of patients with value	17	18	
	LS Mean	0.48	-39.5	-39.9
	95% CI [1]	(-4.6,5.6)	(-44.4,-34.5)	(-47.1,-32.8)
	P-value for the difference between groups [1]			<.0001
	Mean (SD)	0.4 (12.0)	-39.4 (8.1)	

SD=standard deviation; CI=confidence interval; LS=least squares.

[1] 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.

Percentage change in spleen volume in PAP + ETP

Patients initially randomized to placebo who crossed over to olipudase alfa showed improvement in spleen volume after 52 weeks (thus Week 104) of treatment. This was similar to the patients initially randomized to olipudase alfa in the PAP. At Week 104, the LS mean percentage change in spleen volume from baseline in the placebo/olipudase alfa group patients (n=11) was reduced by 35.9% and by 47.0% in the olipudase alfa/olipudase alfa group (n=14). A further reduction was seen at Week 132 with 43.0% in the placebo/olipudase alfa group (n=11) and 52.18% in the olipudase alfa/olipudase alfa group (n=13), and at Week 156, the LS mean percentage change in spleen volume from baseline in the placebo/olipudase alfa group patients (n=8) was reduced by 48.6% and by 49.9% in the olipudase alfa/olipudase alfa group (n=6).

Prespecified responder analyses in PAP

In order to assist with the interpretation of a clinically meaningful result, a patient was considered a responder if the patient had a reduction of $\geq 30\%$ in the spleen volume (MN) at Week 52. A total of 17/18 patients (94.4%) in the olipudase alfa group and none in the placebo group were responders.

Secondary endpoints

The order of testing for secondary endpoints is as follows:

1. Percentage change in liver volume from baseline to Week 52
2. Percentage change in platelet count from baseline to Week 52
3. Change in BFI scale, Item 3 - from baseline to Week 52
4. Change in BPI scale, Item 3 - from baseline to Week 52
5. Change in FACIT-Dyspnoea symptom score from baseline to Week 52
6. Change in SRS from baseline to Week 52

Percentage change in liver volume

In the PAP, the mean liver volume (calculated in MN) at baseline was similar between the olipudase alfa (mean=1.44 MN) and placebo (mean=1.6 MN) groups, indicating moderate hepatomegaly. The LS mean percentage change in liver volume from baseline to Week 52 demonstrated greater reduction in the olipudase alfa group (28.0%) compared to the placebo group (1.5%, $p < 0.0001$). The results remain statistically significant after multiplicity adjustment.

The improvement from baseline was observed for the percentage change in liver volume at Week 26 with greater improvement in olipudase alfa compared with placebo (nominal p -value < 0.0001), suggesting an early response.

At Week 52 (start of the ETP), patients initially randomized to placebo had crossed over to olipudase alfa and by Week 104, had also received olipudase alfa for 52 weeks. This group of patients showed improvement in liver volume at Week 104, similar to the patients initially randomized to olipudase alfa at Week 52.

At Week 104, the LS mean percentage reduction in spleen volume from baseline was 30.66% in the placebo/olipudase alfa group patients ($n=11$), and by 33.42% in the olipudase alfa/olipudase alfa group ($n=14$), a further reduction from 26.52% at Week 52. A further reduction of 30.94% was seen at Week 132 in the placebo/olipudase alfa group ($n=11$), and a reduction of 35.22% was observed in the olipudase alfa/olipudase alfa group ($n=13$).

At Week 156, a further reduction of 34.39% was seen in the placebo/olipudase alfa group ($n=8$), and a reduction of 33.91% was observed in the olipudase alfa/olipudase alfa group ($n=6$).

Percentage change in platelet counts

In the PAP, the mean platelet count at baseline was similar between olipudase alfa (mean = $107.18 \times 10^9/L$) and placebo (mean = $115.6 \times 10^9/L$) groups reflecting mild thrombocytopenia. The LS mean percentage change in platelet counts from baseline to Week 52 was greater in the olipudase alfa group (+16.8%) compared to the placebo group (+2.5%), $p = 0.0185$ (**Figure 6**) These results reflected a modest improvement in thrombocytopenia and remained statistically significant after multiplicity adjustment

The improvement from baseline for the percentage change in platelet count was apparent at Weeks 26 and 38 with greater improvement in the olipudase alfa group compared with the placebo group (nominal p -values = 0.0013 and 0.0076, respectively), indicating an early response.

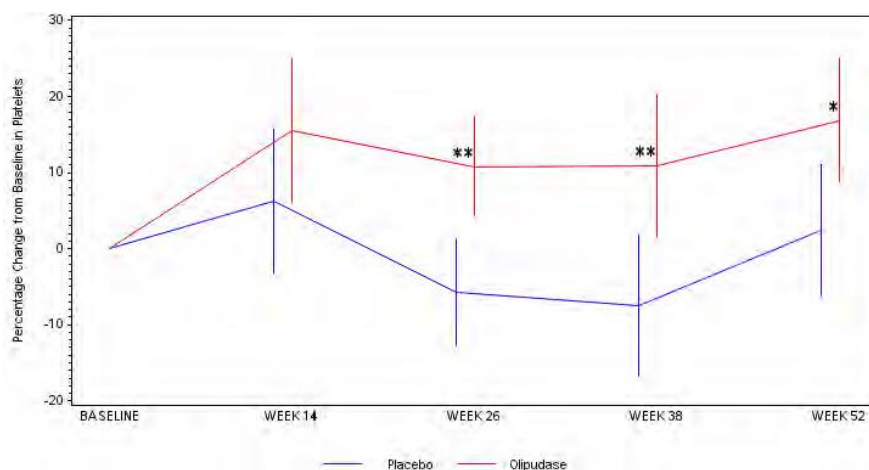


Figure 6. Summary plot of the LS means from the MMRM of the percentage change in preinfusion platelet counts from baseline to 52 weeks in PAP - mITT population.

Note: The vertical bars represent the 95% CIs for the LS means.

Note: The LS means and 95% CIs 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. Note: * indicates nominal p-value <0.05, ** indicates nominal p-value <0.01, *** indicates nominal p-value <0.001.

At Week 104, the LS mean percentage change in pre-infusion platelet counts from baseline was 21.73% in the placebo/olipudase alfa group (n = 15) and 24.94% in the olipudase alfa/olipudase alfa group (n = 13), showing an improvement of the thrombocytopenia in both groups. **Figure 7** shows the mean pre-infusion platelet counts over time.

At Week 156, the sustained positive trend supports this improvement despite the known interindividual variations of the platelets count, 13.59% in the placebo/olipudase alfa (n = 9) and 27.36% in the olipudase alfa/olipudase alfa group (n = 6).

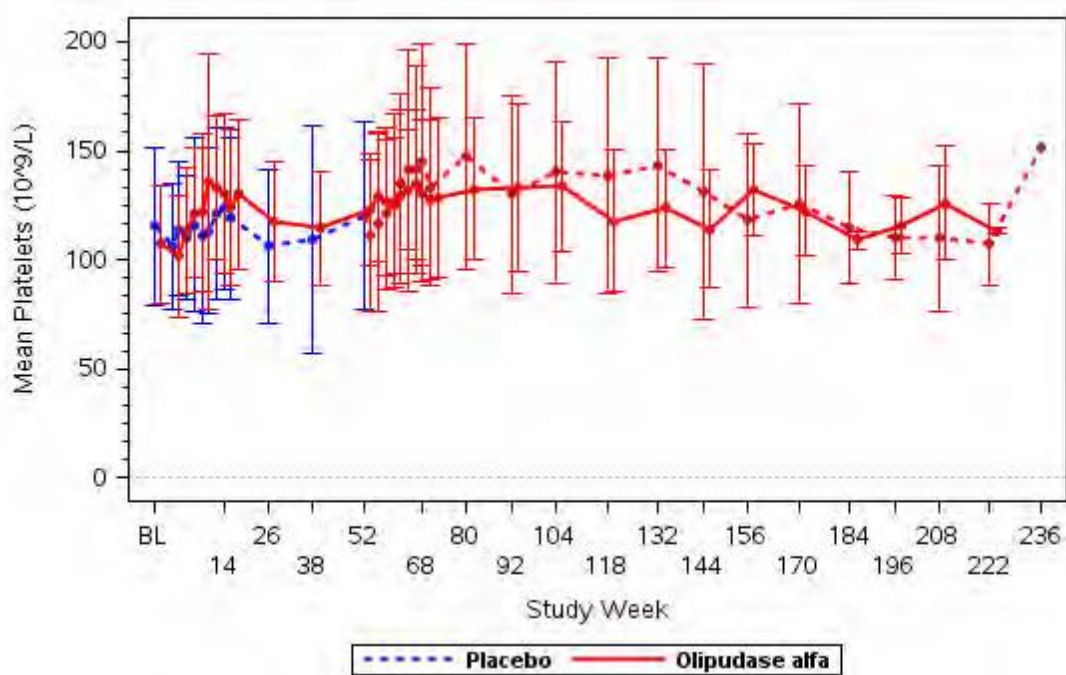


Figure 7. Summary plot of the mean pre-infusion platelet counts (10⁹/L) over time (same baseline for both treatment groups) in PAP+ETP - mITT population.

Note: After Week 52 all patients received olipudase alfa.

Note: The vertical bars represent standard deviations.

Note: Baseline is the average of all available values before the first infusion of study treatment.

Note: For yearly visits, the average value of the earliest data from haematology & differential panel and the latest data from the hemogram panel at pre-infusion was used.

Change from baseline in fatigue and dyspnoea severity

The mean fatigue severity at baseline was similar between olipudase alfa and placebo. Although there was a reduction in fatigue in both groups, the LS mean change in BFI scale -Item 3 from baseline to Week 52 was not statistically significantly different in the olipudase alfa group compared to the placebo group. Thus, hierarchical testing of the secondary endpoints stopped.

Responses to the FACIT-Dyspnoea at baseline indicated the presence of floor effects as many patients reported no shortness of breath while dressing (45.2%), walking 50 steps (29%), preparing meals

(73.3%), washing dishes (73.1%), sweeping or mopping (25%), making a bed (31%), and carrying 10-20lbs (27.6%) (data presented in the separate Psychometric Analysis Technical Report; module 5.3.5.1).

The FACIT-Dyspnoea symptom scale score at baseline were similar between the olipudase alfa and placebo groups. The LS mean change BPI scale –Item 3 and FACIT Dyspnoea symptom score from baseline to Week 52 (**Figure 8**) were not different between the olipudase alfa and placebo groups.

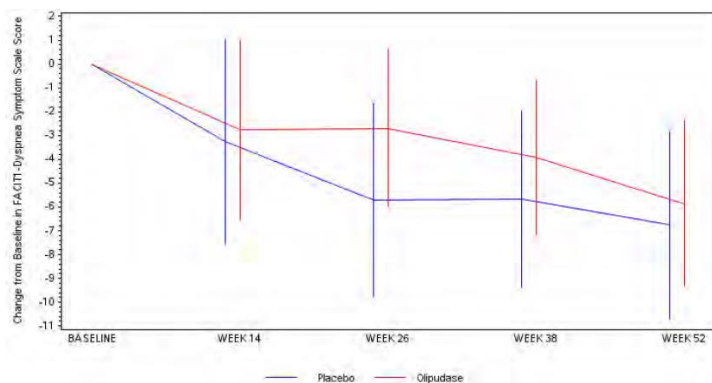


Figure 8: Summary plot of the LS means from the MMRM of the change in FACIT-Dyspnoea symptom scale score from baseline to 52 weeks in PAP – mITT.

Note: The vertical bars represent the 95% CIs for the LS means.

Note: The LS means and 95% CIs are based on a mixed model for repeated measures approach with baseline FACIT1-Dyspnea Symptom Scale Score, baseline age, treatment group, study visit, and study visit by treatment group interaction as covariates.

Tertiary endpoints

Several tertiary endpoints were evaluated. Only the most important are presented here.

Other pulmonary endpoints

Pulmonary function tests

The means of pulmonary function tests were comparable at baseline and reflected mild to moderate disease. The mean % predicted FVC was 81.6% and 83.1% in the olipudase alfa and placebo groups, respectively. The LS mean percentage change in % predicted FVC from baseline to Week 52 showed greater improvement in the olipudase alfa group (6.8%) compared to the placebo group (1.5%), with a difference of 5.28% (nominal p-value = 0.0258).

The mean % predicted FEV₁ and TLC at baselines was 75.3% and 79.9% in the olipudase alfa group and 78.6% and 77.9% in the placebo group. Similar trends were observed for percentage change in % predicted FEV₁ and percentage change in % predicted TLC from baseline to Week 52 (nominal p values >0.05).

The LS mean percentage change in observed values from baseline to Week 52 followed a similar trend in FVC, FEV₁, and TLC.

PAP+ETP: At Week 156, the LS mean percentage change in % predicted FVC from baseline was 7.2% in the placebo/olipudase alfa group (n = 5) and 12.4% in the olipudase alfa/olipudase alfa group (n = 5). The LS mean percentage change in % predicted FEV₁ and TLC followed a similar trend.

Patient global impression of change scale (PGIC)

Change from baseline to Week 52 on the PGIC shortness of breath item was different between the treatment groups: Patients in the olipudase alfa group (n = 17) reported greater improvement (LS

mean = 1.11) than the placebo group (n = 16, LS mean = 0.30) (0 = no change, 1 = a little better). There were no other substantial differences in the PGIC items at Week 52.

In addition, patients were categorised as a responder at Week 52 if they reported an improvement on the PGIC (numeric value of 3, 2, or 1). Otherwise, patients were categorised as a non-responder if the numeric value was 0, -1, -2, -3 or missing. For the shortness of breath item, the responder rate in the olipudase alfa group was significantly higher than in the placebo group (61.1% versus 27.8%). The treatment groups were not different based on the nominal p-values in other PGIC items at Week 52.

Similar trends were observed on the PGIC items during the ETP.

Treadmill test

To be noted: the treadmill test was hampered by physiologically implausible data (~3%) and missing data. The physiologically implausible data were excluded and the majority of the missing data was re-captured by direct computation based on first physiologic principles using primary data outputs from the CPET evaluation. Lastly, all predicted normative values were recomputed by a uniform set of equations.

At baseline, the mean values for exercise capacity determined from the O₂ uptake at peak exercise were at the lower limits of normal in both groups and were similar in the placebo group as compared to the olipudase alfa group when data were expressed either as a % predicted normal or are normalised to patient body weight (kg) or body surface area (METS):

- Mean calculated percent predicted O₂ uptake (SD): 79.5 (30.8)% predicted in the placebo group (n=17) and 78.2 (28.6)% predicted in the olipudase alfa group (n=17)
- Mean calculated maximum oxygen uptake (SD): 28.4 (12.9) mL/min/kg in the placebo group (n=17) and 27.6 (10.3) mL/min/kg in the olipudase alfa group (n=17)
- Mean calculated maximum workload (SD): 7.8 (3.6) METS in the placebo group (n=17) and 7.8 (2.7) METS in the olipudase alfa group (n=17)

At baseline, subject effort was optimal in both treatment arms.

At Week 52, the results in the placebo group from MMRM demonstrated a reduction in exercise capacity that was evident in every metric of maximal workload and achieved nominal statistical significance for most parameters (O₂ Uptake, calculated percent predicted O₂ uptake, calculated maximal oxygen uptake expressed as mL/min/kg, and calculated maximal workload expressed in METS). Based on the mean change in the O₂ uptake at maximal exercise, there was an approximate 26.5% decline in exercise capacity at Week 52 as compared to baseline in the placebo group (mean change of -456.0 ml/min relative to the baseline value of 1723.5 mL/min). The results in the olipudase alfa group from the MMRM demonstrated an increase in exercise capacity that was evident in every metric of maximal workload and achieved nominal statistical significance for CO₂ Output. Based on the mean change in the O₂ uptake at maximal exercise, there was an approximate 8.0% increase in exercise capacity at Week 52 as compared to baseline in the olipudase alfa group (mean change of 147.3 ml/min relative to the baseline value of 1852.9 mL/min).

Comparison between the placebo and olipudase alfa groups at Week 52 demonstrated nominally statistically significant improvements from baseline in exercise capacity in the olipudase alfa group as compared with placebo that was evident in calculated CPET parameters including O₂ Uptake at peak exercise, calculated percent predicted O₂ uptake, calculated maximal oxygen uptake expressed as mL/min/kg, calculated maximum workload expressed in METS, and CO₂ Output.

PAP + ETP

During PAP+ETP, after crossover to olipudase alfa, all parameters improved in the placebo/olipudase alfa group. Specifically, at Week 104 an improvement in exercise capacity to values similar to, or slightly higher than baseline was observed for all metrics (n = 9). Thus, the decline in exercise capacity observed during the PAP was reversed after crossover to active treatment in the placebo/olipudase alfa group. At Week 104, the olipudase alfa/olipudase alfa group demonstrated a progressive improvement in exercise capacity and it was observed in all metrics (n = 7). Based on the mean change in the O2 uptake at maximal exercise there was an approximate 25.9% increase in exercise capacity at week 104 as compared from baseline in the olipudase alfa/olipudase alfa group (mean change 480.0 ml/min relative to baseline value 1852.9 ml/min). Several tertiary endpoints were evaluated amongst others liver function tests (e.g. ALT, AST, bilirubin). The liver function tests showed consistent improvements in line with the improvements of the liver (reduction of liver volume). A similar trend was observed for the lipid profile, which improved in the treated group.

Ancillary analyses

Ancillary analyses included investigation the impact of olipudase alfa produced by different processes, and impact of the COVID-19 pandemic on the PD and efficacy parameters investigated in the clinical program. No impact was observed.

Sensitivity Analyses

Sensitivity analyses supported the primary analyses.

Summary of main efficacy results

Table 14 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy and the benefit-risk assessment (see later sections).

Table 14. Summary of efficacy for trial DFI12712.

Title: 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.		
Study identifier	DFI12712 (EudraCT: 2015-000371-26)	
Design	Phase 2/3, multicenter, repeat-dose, divided into 2 consecutive major periods: 1) a randomized placebo-controlled, double-blind primary analysis period (PAP) from Day -60 to Week 52, followed by 2) an extension treatment period (ETP). Initially, the ETP will be double-blind as patients in the placebo arm cross over to active treatment	
	Duration of Run-in phase:	Screening period 60 days
	Duration of main phase:	52 weeks
	Duration of Extension phase:	up to 4 years dependent upon continued regulatory approval of this protocol.
Hypothesis	Superiority of olipudase alfa compared with placebo on DLco and spleen volume.	
Treatments groups 36 patients randomized	Olipudase alfa	Dose escalation to 3.0 mg/kg administered intravenously once every 2 weeks. Double-blind Primary Analysis period (PAP): 52 weeks Followed by an open-label Extension-Treatment Period (ETP): up to 4 years.

	Placebo	Placebo administered intravenously once every 2 weeks. Double-blind Primary Analysis period (PAP): 52 weeks Followed by an open-label Extension-Treatment Period (ETP) with olipudase alfa: up to 4 years		
Endpoints and definition	Primary efficacy endpoints (dual)	Percentage change in DLCO (in % predicted of normal) from baseline to Week 52		
		Percentage change in spleen volume (in MN) from baseline to Week 52		
	Secondary efficacy endpoints (hierarchically tested)	Percentage change in liver volume (in MN) from baseline to Week 52		
		Percentage change in platelet counts from baseline to Week 52		
		Change in fatigue severity as measured by item 3 of the BFI (Brief Fatigue Inventory) scale from baseline to Week 52		
		Change in pain severity as measured by item 3 of the BPI-SF (Brief Pain Inventory - Short Form) scale from baseline to Week 52		
		Change in dyspnea severity as measured by the FACIT (Functional Assessment of Chronic Illness Therapy) dyspnea tool from baseline to Week 52		
Change in SRS from baseline to Week 52				
Interim Cut-off date	15 March 2021			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Modified intent-to-treat (mITT) population at week 52			
Effect estimate per comparison	Treatment group	Placebo	olipudase alfa	Comparison between olipudase alfa vs. Placebo Difference with 95% CI
	Number of subjects	18	18	
Primary	LS mean % change in % predicted DLCO (SE)	2.96 (3.38)	21.97 (3.34)	19.0 (9.3 - 28.7) n=0.0004*
	LS mean % change in spleen volume (SE)	0.48 (2.50)	-39.45 (2.43)	-39.9 (-47.0 - -32.8)
Secondary (tested hierarchically)	LS mean % change in liver volume (SE)	-1.47 (2.54)	-28.06 (2.49)	p<0.0001*
	LS mean % change in platelet counts (SE)	2.49 (4.19)	16.82 (3.96)	p=0.0185*
	LS mean change in BFI scale (SE)	-1.81 (0.53)	-1.86 (0.51)	-0.06 (-1.6 - 1.5) p = 0.94**
	LS mean change in BPI scale (SE)	-2.29 (0.59)	-1.40 (0.57)	0.89 (-0.80 - 2.58)

	LS mean change in FACIT-Dyspnoea symptom scale score (SE)	-6.77 (1.91)	-5.86 (1.69)	0.91 (-4.35 – 6.16)
	LS mean change in SRS (SE)	-9.28 (2.42)	-7.66 (2.35)	1.62 (-5.30 – 8.54)
Notes	<p>*only p-values are reported for variables that were tested taking into account multiplicity adjustment.</p> <p>**hierarchical testing of the secondary endpoints stopped after this endpoint.</p> <p>Change in the quality of life questionnaires was not different between the treatment groups.</p>			

2.6.5.3. Clinical studies in special populations

No specific studies in elderly were conducted. In the studies with olipudase alfa two (2) patients between 65 and 75 years of age were included. A separate clinical study in paediatric patients was conducted.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

- **Analysis of key pulmonary imaging data**

Table 15 shows key pulmonary imaging data from DFI12712 ASCEND and DFI13803 Peds. Chest X-ray interstitial and the HRCT parameters of ground glass and ILD showed similar results, reflecting structural change.

Table 15. Summary of the change from baseline at Week 52 in key pulmonary imaging parameters - mITT population in DFI12712 and DFI13803.

Parameter	DFI12712						DFI13803			
	Placebo		Olipudase alfa				P-value*	Baseline (N=20) Mean (SD)	Week 52 (N=20) Mean (SD)	Change from baseline
	Baseline (N=18) Mean (SD)	Week 52* (N=18) LS Mean (SE)	Baseline (N=18) Mean (SD)	Week 52* (N=18) LS Mean (SE)	Difference* LS Mean (SE)					
CXR interstitial improvement both lungs										
Number	16	16	17	17			14	14	14	
Mean (SD or SE)	1.78 (1.08)	0.28 (0.125)	1.82 (0.88)	-0.91 (0.121)	-1.19 (0.175)	<.0001	2.79 (0.43)	2.14 (0.79)	-0.64 (0.66)	
HRCT ground glass appearance both lungs										
Number	18	17	18	18			20	19	19	
Mean (SD or SE)	0.53 (0.64)	0.18 (0.161)	0.65 (0.72)	-0.49 (0.156)	-0.67 (0.224)	0.0056	0.79 (0.75)	0.36 (0.72)	-0.40 (0.86)	
HRCT Interstitial Lung Disease both lungs										
Number	18	17	18	18			20	19	19	
Mean (SD or SE)	2.13 (0.79)	0.09 (0.155)	2.02 (0.77)	-0.36 (0.151)	-0.45 (0.217)	0.0474	2.49 (0.74)	1.96 (1.01)	-0.61 (0.89)	
HRCT Pleural Thickening both lungs										
Number	18	17	18	18			20	19	19	
Mean (SD or SE)	0.00 (0.00)	0.00 (0.005)	0.00 (0.00)	0.01 (0.005)	0.01 (0.007)	0.3191	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	
HRCT Reticulo-nodular Density both lungs										
Number	18	17	18	18			20	19	19	

Parameter	DFI12712						DFI13803			
	Placebo		Olipudase alfa				P-value*	Baseline (N=20) Mean (SD)	Week 52 (N=20) Mean (SD)	Change from baseline
	Baseline (N=18) Mean (SD)	Week 52* (N=18) LS Mean (SE)	Baseline (N=18) Mean (SD)	Week 52* (N=18) LS Mean (SE)	Difference* LS Mean (SE)					
Mean (SD or SE)	0.34 (0.84)	-0.06 (0.146)	0.31 (0.85)	0.01 (0.142)	0.07 (0.204)	0.7256	0.62 (1.10)	0.24 (0.61)	-0.41 (1.13)	

**For DFI12712 ASCEND, the LS mean (SE) were generated from MMRM model as specified in DFI12712 SAP, and the P values are nominal.*

For DFI12712 ASCEND, the baseline is the last non-missing value prior to the first infusion of IMP (olipudase alfa or placebo).

For DFI13803 Peds: CXR, exam performed at selected sites due to local regulations.

- **Comparative Paediatric Analysis of DFI3803 Peds Versus Natural History Study (MSC12840)**

For the comparison of paediatric patients on olipudase alfa from trial DFI13803 Peds with historical data from a prospective natural history study (MSC12840), the following efficacy measures were compared: spleen volume, liver volume, platelet count, % predicted DLco, ILD assessed via chest X-ray, ILD via HRCT, and height Z-score.

The data from 4 child patients and 10 adolescent patients in the MSC12840 study were compared with data from 11 child patients and 4 adolescent patients in DFI13803 Peds. No statistically significant differences were observed in most of the demographic baseline characteristics with the exception of age and sphingomyelin in plasma (551.3 mg/L overall in the MSC12840 group versus 394.6 mg/L overall in the DFI13803 Peds group).

Efficacy outcome data over time

Table 16 provides an overall summary of the comparative analysis of DFI13803 Peds versus the prospective natural history study MSC12840 for the parameters measured in both over the course of 1 year.

Table 16. Summary of efficacy parameters for comparative paediatric analysis of DFI13803 Peds versus natural history study (MSC12840) change over 1 year.

Parameters 1-year change or % change from baseline (LS Mean) (95% CI)^a	MSC12840 (N=14)	DFI13803 Peds (N=15)	Difference (95% CI)	p-value
% predicted DLco (% change) ^b	27.9 (-8.8,64.5)	27.8 (7.8,47.8)	-0.06 (-42.4,42.3)	0.9977
% predicted DLco (excluding patient 303) (% change) ^c	17.7 (-18.3,53.7)	26.7 (7.3,46.1)	9.0 (-31.8,49.8)	0.6286
% predicted FVC (% change)	3.5 (-6.4,13.4)	14.9 (3.1,26.6)	11.31 (-4.3,26.9)	0.1462
Spleen volume (% change)	-1.5 (-6.6,3.7)	-47.71 (-53.3,-42.1)	-46.3 (-54.1,-38.5)	<.0001
Liver volume (% change)	8.7 (-6.94,24.3)	-39.52 (-44.3,-34.8)	-48.2 (-64.2,-32.2)	<.0001
Platelet count (% change)	-11.0 (-29.8,7.9)	34.82 (18.4,51.2)	45.8 (19.4,72.1)	0.0015
Height Z-score (change)	-0.03 (-0.2,0.2)	0.61 (0.2,1.0)	0.64 (0.23,1.1)	0.0044
Chest X-ray ILD (change)	-0.3 (-0.8,0.2)	-0.87 (-1.5,-0.3)	-0.60 (-1.3,0.1)	0.1063
HRCT ILD (change)	0.3 (0.2,0.4)	-0.49 (-1.0,-0.01)	-0.79 (-1.3,-0.3)	0.0037
HRCT GG (change)	0.2 (-0.3,0.6)	-0.60 (-0.9,-0.3)	-0.78 (-1.3,-0.3)	0.0051
HRCT RND (change)	0.6 (-0.02,1.2)	-1.06 (-1.3,-0.9)	-1.63 (-2.3,-1.0)	<.0001

Abbreviations: CI = confidence interval; DLco = diffusing capacity of carbon monoxide; GG = ground glass; HRCT = high resolution computed tomography; ILD = interstitial lung disease; LS = least squares; RND = reticulonodular density; % change = percentage change.

Only patients who have non-missing value at both baseline visit and Year 1 visit are included in the analysis.

a These values are from a mixed model testing for a difference between the 2 groups adjusting for baseline value, baseline age and baseline neurological manifestation.

b Including 1 DFI13803 patient whose DLco was performed at the Week 64 visit but within the Week 52 analysis window as described in the DFI13803 SAP.

c Patient 303 from MSC12840 was identified as an outlier patient due to the greatest improvement in % predicted DLco among selected MSC12840 patients (percent change of 109%). After removing this patient, the difference between MSC12840 compared with DFI13803 Peds is numerically greater although the nominal p-value is still greater than 0.05.

- **Efficacy-related COVID-19 impact subgroup analysis**

The COVID pandemic did not impact the efficacy results.

- **Treatment effect based on baseline dyspnoea status.**

The presence or absence of dyspnoea at baseline did not make a difference in DFI12712 ASCEND on % predicted DLco over time up to 104 weeks. As similar trend in improvement was observed in both groups.

- **Change over time for DLco % predicted by ILD severity**

There is no difference in % predicted DLco increase based on ILD severity at baseline in the adult population up to Week 104. As similar trend in improvement was observed in both groups.

2.6.5.6. Supportive study(ies)

Study DFI13803

DFI13803 is a Phase 1/2, multi-center, open-label, repeated-dose study to evaluate the safety, tolerability, PK, PD, and exploratory efficacy of olipudase alfa administered Q2W for 64 weeks in paediatric patients <18 years of age with non-central nervous system manifestations of ASMD. At least 20 patients were planned to be enrolled into 3 age cohorts and to receive 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 at least a 16-week duration. Patients unable to tolerate 2 consecutive doses of 0.3 mg/kg olipudase alfa were to be replaced.

The 64-week treatment period allowed for a broader understanding of olipudase alfa safety and tolerability in a patient population that is undergoing rapid physiological change, relative to shorter studies. Depending on the efficacy assessments, changes from baseline in exploratory efficacy parameters were evaluated through 52 weeks or 64 weeks of olipudase alfa administration.

Over the conduct of the clinical program, incremental changes to the manufacturing process were implemented.

After the 64-week treatment phase, patients were eligible to enrol in the long-term study LTS13632 to continue receiving olipudase alfa. The end of the DFI13803 study was defined as the day that the last patient entered in the LTS13632.

Objectives

The primary objective was to evaluate the safety and tolerability of olipudase alfa administered IV in paediatric patients Q2W for 64 weeks. The secondary objective was to characterize the PK profile and evaluate the PD and exploratory efficacy of olipudase alfa administered IV in paediatric patients Q2W for up to 64 weeks.

In- and exclusion criteria

Only the most important in-and exclusion criteria are mentioned (see CSR for full details).

Inclusion criteria

1. Male or female <18 years of age on the date of signed informed assent/consent.
- 2.. Documented deficiency of ASM consistent with NPD, as measured in peripheral leukocytes, cultured fibroblasts, and/or lymphocytes.

3. Spleen volume ≥ 5 multiples of normal (MN) measured by magnetic resonance imaging (MRI); patients who have had partial splenectomies were allowed if the procedure was performed ≥ 1 year before screening and the residual spleen volume was ≥ 5 MN.

4. Patient's height was -1 Z-score or lower.

Exclusion criteria

1. The patient had received an investigational drug within the 30 days before study enrolment.

2. The patient had any of the following medical conditions:

- a) An active, serious, intercurrent illness;
- b) Active hepatitis B or hepatitis C infection;
- c) Infection with human immunodeficiency virus (HIV);
- d) Cirrhosis (determined by clinical evaluation);
- e) Significant cardiac disease (e.g., clinically significant arrhythmia, moderate or severe pulmonary hypertension or valvular dysfunction, or $<40\%$ left ventricular ejection fraction by echocardiogram);
- f) Malignancy diagnosed within the previous 5 years (except basal cell carcinoma);
- g) Any other extenuating circumstance that could have significantly interfered with study compliance, including all prescribed evaluations and follow-up activities.

3. The patient had acute or rapidly progressive neurological abnormalities.

4. The patient was homozygous for SMPD1 gene mutations R496L, L302P, and fs330 or any combination of these 3 mutations.

Treatment

For all dose levels, dosing with olipudase alfa was by IV infusion Q2W (± 3 days). The dose escalation phase and the 64-week treatment period began with the first IV infusion of 0.03 mg/kg olipudase alfa on Day 1/Week 0, and all subsequent olipudase alfa administrations were scheduled relative to that day. The dose escalation phase was to end with the first infusion at 3.0 mg/kg or with the identification of a patient-specific highest tolerated dose.

Patients who tolerated the 0.03 mg/kg dose at Day 1/Week 0 (one re-challenge of the 0.03 mg/kg dose was allowed) received a dose of 0.1 mg/kg 2 weeks later. Patients who tolerated the 0.1 mg/kg dose (one re-challenge of the first 0.1 mg/kg dose was allowed) received a dose of 0.3 mg/kg 2 weeks later. Patients tolerating 2 consecutive doses of 0.3 mg/kg were dose escalated step-wise to receive 2 consecutive doses at 0.6 mg/kg, followed by infusions of 1.0 mg/kg and 2.0 mg/kg, and to the final target dose of 3.0 mg/kg, which was maintained for the remaining duration of the treatment period. Patients unable to tolerate 3.0 mg/kg olipudase alfa received the highest tolerable dose Q2W until the end of the treatment period. Decisions regarding dose escalations were discussed between the Investigator and the Sponsor upon review on an individual patient basis.

Patients were expected to receive IV olipudase alfa over a period of approximately 20 minutes to 3.7 hours, depending on the dose. The length of the infusion time was adjusted based on the patient's tolerance of the infusion. In addition, the mode of infusion included multiple steps starting with a slow rate of infusion that was progressively increased, if there was no sign of poor tolerance.

If more than 1 infusion was missed during dose escalation, the next dose was decreased by 1 level. If more than 1 infusion was missed after the patient has completed dose escalation, the last previously

tolerated dose level of olipudase alfa was administered or the dose could be decreased by 1 level at the Investigator's discretion.

All infusions took place at study sites in a monitored setting with ready access to emergency resuscitation equipment and medications.

Outcomes

Baseline characteristics

Demographic characteristics and disease characteristics at baseline are presented in Table 17 and Table 18. Full details are available in the CSR.

Table 17. Summary of demographic and baseline characteristics - Safety Population.

	Age cohort			
	Adolescent	Child	Infant/early child	Overall
Age at Day 1/Week 0 (years)				
Number of patients with value	4	9	7	20
Mean (SD)	14.8 (2.2)	8.7 (1.7)	3.8 (1.4)	8.2 (4.4)
Gender, n (%)				
Male	3 (75%)	4 (44%)	3 (43%)	10 (50%)
Female	1 (25%)	5 (56%)	4 (57%)	10 (50%)

Note: Percentages are calculated using the number of patients who have available data at each age cohort as the denominator.

A summary of baseline disease characteristics is presented in Table 18.

Table 18. Summary of baseline disease characteristics - Safety Population.

	Age cohort			Overall (N = 20)
	Adolescent (N = 4)	Child (N = 9)	Infant/Early Child (N = 7)	
Age at symptom onset (years)				
Number of patients with value	4	8	6	18
Mean (SD)	1.4 (0.6)	1.6 (1.3)	1.2 (0.9)	1.4 (1.0)
Min : Max	0.8 : 2.1	0.4 : 3.9	0.2 : 2.5	0.2 : 3.9
Age at diagnosis (years)				
Number of patients with value	4	9	7	20
Mean (SD)	2.1 (0.7)	3.3 (3.4)	1.551 (1.2)	2.5 (2.5)
Min : Max	1.42 : 3.09	0.02 : 11.09	0.21 : 3.10	0.02 : 11.09
ASM activity (peripheral leukocytes), nmol/h/mg				
Number of patients with value	4	9	6	19
Mean (SD)	0.21 (0.09)	0.13 (0.06)	0.10 (0.07)	0.14 (0.08)

Spleen volume, n (%)				
Number of patients with value	4	9	7	20
Severe splenomegaly (>15 MN)	1 (25.0%)	5 (55.6%)	6 (85.7%)	12 (60.0%)
Symptoms present at disease onset, n (%)				
Number of patients with value	4	9	7	20
None	0	1 (11.1%)	0	1 (5.0%)
Splenomegaly	3 (75.0%)	8 (88.9%)	7 (100%)	18 (90.0%)
Hepatomegaly	4 (100%)	7 (77.8%)	7 (100%)	18 (90.0%)
Respiratory disease	1 (25.0%)	4 (44.4%)	2 (28.6%)	7 (35.0%)
Thrombocytopenia	0	4 (44.4%)	1 (14.3%)	5 (25.0%)
Failure to thrive	1 (25.0%)	4 (44.4%)	3 (42.9%)	8 (40.0%)
Short stature	0	4 (44.4%)	4 (57.1%)	8 (40.0%)

Note: Percentages are calculated using the number of patients who have available data at each age cohort as the denominator.

All patients had their spleen intact at baseline. For only 9/20 (3 adolescents, 6 children) patients the predicted DLco adjusted for haemoglobin was available at BL. 1 out of 3 adolescents had a DLco <40% (severe category).

Despite the small sample size of the study population, the exploratory analysis of distribution of selected baseline characteristics by SMPD1 pathogenic variants showed graphically that patients carrying the c.1829_1831delGCC (p.Arg610del) pathogenic variant trended to have a less severe disease than the other patients in the population investigated (e.g., later mean age of symptom onset, lower incidence of severe splenomegaly, higher incidence of higher height Z-score).

Medical history

The medical/surgical history findings in the safety population were consistent with those expected in this patient population, and none of the findings were considered to affect the validity or interpretation of study data. Overall, the most commonly reported medical history findings by body system were Blood and lymphatic system disorders and Hepatobiliary disorders, which were reported in all patients.

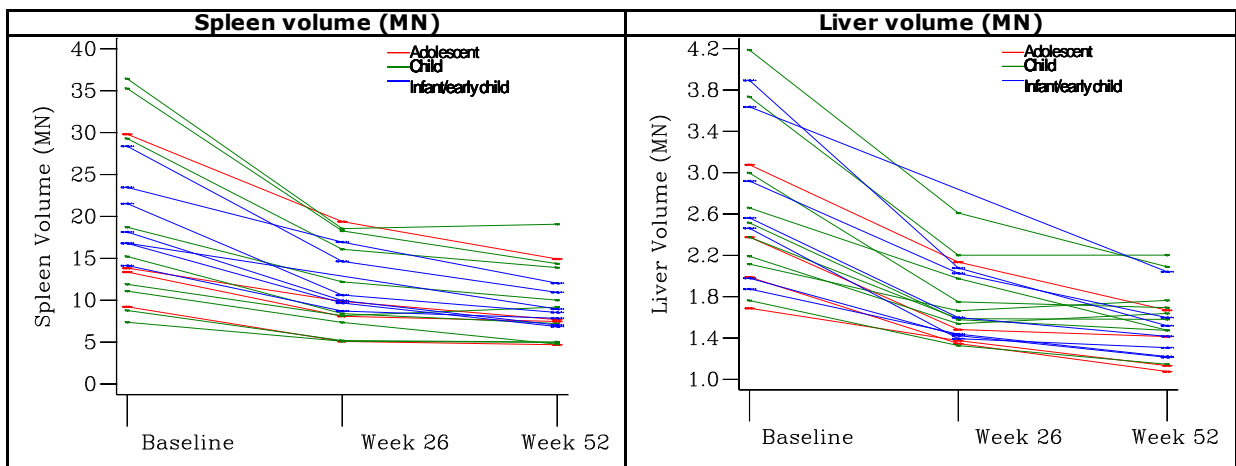
Prior and/or concomitant medication

No prohibited medications were taken during the study.

Efficacy /PD results

Spleen and liver volumes, and liver function tests

Figure 9 displays the effect of olipudase alfa on individual spleen and liver volumes, respectively, expressed in MN after 26 and 52 weeks of treatment. An effect of olipudase alfa could be observed in all patients from the first post-dose assessment at Week 26 on both spleen and liver volumes. After 1 year of treatment (52 weeks), in the overall group (ie, all age cohorts combined), spleen volumes decreased by 49.2% in mean MN (individual patient decreases ranged from 22.9% to 61.5%).



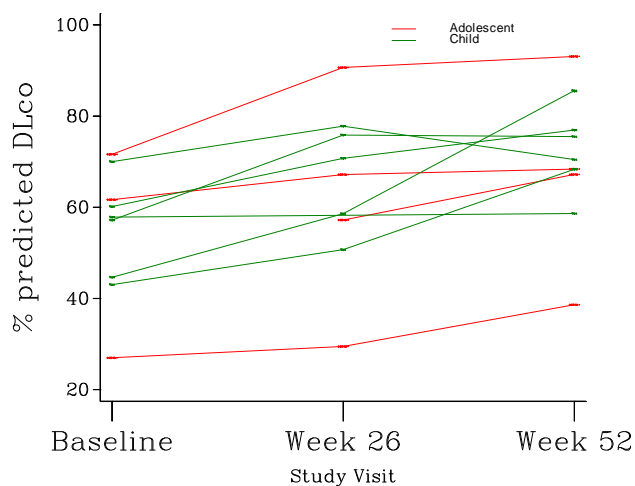
Current data cutoff: 01Mar2021.

Figure 9. By-patient plot of Spleen and liver volume (MN) over time - mITT Population.

Pulmonary Function Testing

The effect of olipudase alfa on % predicted DLco adjusted for haemoglobin is displayed by patient in . After 1 year of treatment (52 weeks), % predicted DLco adjusted for haemoglobin increased by a mean of 32.9% (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 significantly different from baseline. Of the 9 patients who performed the test at baseline, 5 patients (55.6%) had a change from baseline value on % predicted DLco (absolute change) $\geq 15\%$ at Week 52.

Improvements were also observed on % predicted FVC, % predicted FEV₁, and % predicted TLC with mean percent change from baseline in the overall group of 15.2% (n=13), 9.1% (n=13), and 19.9% (n=8) at Week 52, respectively.



Including 1 patient whose DLco was performed at the Week 64 visit but within the Week 52 analysis window as described in the SAP. Current data cutoff: 01Mar2021.

Figure 10. By-patient plot of percent predicted DLco adjusted for haemoglobin over time, age cohort=overall - mITT Population.

Cycle ergometry

As in the pivotal study, ergometry (cycle) was also performed in some of the patients (3 adolescents; 2 children). In the 5 patients who performed the test, a trend toward improvement on cycle ergometry was observed in the following parameters: mean Maximum Workload (+31.2 Watts overall at Week 52), mean percent predicted Maximum Workload (+3.4% absolute change overall at Week 52), mean

Working Time (+2.8 min overall at Week 52), mean maximum O₂ Uptake (+691.8 mL/min overall at Week 52), and mean Maximum CO₂ Output (+561.2 mL/min overall at Week 52).

Height Z score

After 52 weeks of treatment, 15 patients (78.9%) improved their height Z score category and 4 patients (21.1%) remained in the same category. Improvements in height Z scores were generally similar across all age groups. The mean overall increase was 0.56 at Week 52, and 0.78 at end of study at Week 64.

Health outcome questionnaires

PedsQL Generic Core Scale and Multidimensional Fatigue Scale showed significant improvement on the majority of subtests at Week 52 compared to baseline.

For the Generic Core Scale, out of the 6 subtests, 4 subtests (Total Score, Physical Functioning, Psychosocial Health, Emotional Functioning) had statistically significant mean positive changes at Week 52 in the overall group on both child and parent report measures. In addition, the Week 52 mean positive change from baseline on Social Functioning was also statistically significant on the parent reports. The School Functioning subset was the only one with no statistically significant changes overall, neither in child nor parent reports.

Regarding the PedsQL Multidimensional Fatigue Scale, statistically significant positive changes were observed at Week 52, in the overall group compared to baseline, in 3 of 4 subtests in both child and parent reports. In addition, the Week 52 mean positive change from baseline on the Cognitive subscale was statistically significant on the child reports but not on the parent reports (highest baseline mean).

Bone biomarkers

Mean bone-specific AP increased from baseline to Week 52 in all age groups except for the adolescent cohort. Mean (SD) percent change from baseline to Week 52 was +32.4 (54.3)% in the overall group, -9.2 (50.6)% in the adolescent cohort, +44.8 (50.1)% in the child cohort, and +35.0 (62.0)% in the infant/early child cohort.

Mean C-telopeptide increased from baseline to Week 52 in all age groups, with a mean (SD) percent increase from baseline to Week 52 of 74.7 (70.9)% in the overall group. The mean (SD) percent increase from baseline to Week 52 was 69.0 (93.7)% in the adolescent cohort, 92.5 (78.4)% in the child cohort, and 50.6 (37.0)% in the infant/early child cohort.

Study LTS13632

Study LTS13632 is an ongoing long-Term Study to Assess the Ongoing Safety and Efficacy of olipudase alfa in Patients With Acid Sphingomyelinase Deficiency.

Study design

This study had a first interim database lock for with a data cut-off of 10 Dec 2019, for Regulatory purposes. The data presented in this second CSR encompasses all the data up to the second interim cut-off date of 01 March 2021.

All five patients from the study DFI13412 and all 20 patients from the DFI13803 study were enrolled in this long-term follow-up study. Patients were enrolled directly into this study from their previous study. Enrolled patients will receive olipudase alfa every 2 weeks for up to 9 years, or until marketing approval, whichever comes first.

Study objectives

The primary objective of this study is to obtain data regarding the safety of olipudase alfa in patients with ASMD who were exposed to long term treatment with olipudase alfa. The secondary objectives of this study are to obtain data regarding the efficacy of olipudase alfa and to characterise olipudase alfa pharmacodynamics (PD) and pharmacokinetics (PK) following long term administration.

In and exclusion criteria

Patients were included in the study according to the following criteria.

I 01. The patient completed the treatment period of a previous study of olipudase alfa with an acceptable safety profile in the opinion of the Investigator and Sponsor.

Any patient who met the following exclusion criteria was not to be enrolled in the study:

E 01. The patient has any new condition or worsening of an existing condition which in the opinion of the Investigator would make the patient unsuitable for enrolment or could interfere with the patient participating in or completing the study.

E 02. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

Treatment

Patients started this study at the same dose they were receiving at the end of their original study provided that they had not missed more than 1 biweekly dose before the entry into this study.

Home Infusion

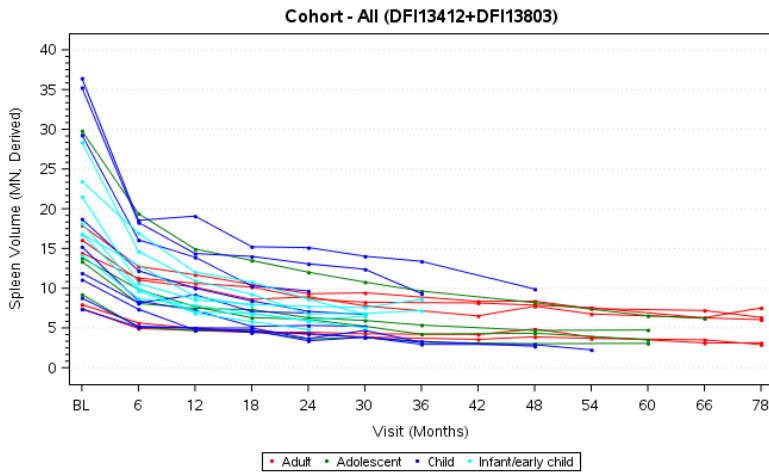
Home infusion was possible. Patients must have met the eligibility requirements outlined below. In addition, the Investigator and the Sponsor must have agreed that home infusion was appropriate. Quarterly visits occurred at the site. If the site visit was not possible due to site closure or extenuating circumstances that prevented an in-person site visit (e.g., during the COVID-19 pandemic) and home infusion was already approved for the eligible patient, quarterly visits were done at home.

Outcomes

Spleen volume and liver volume assessed by MRI

Spleen Volume

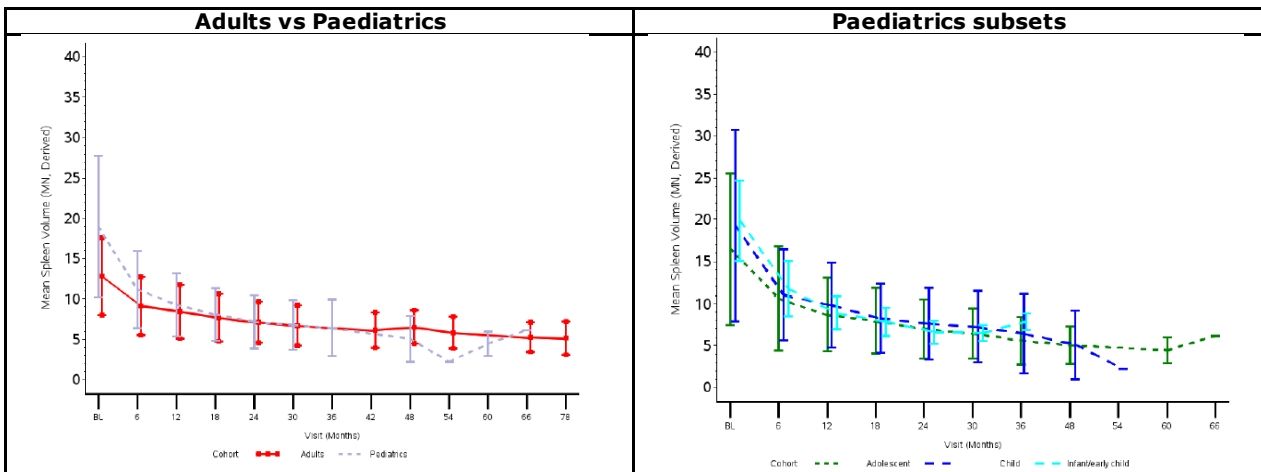
A reduction of spleen volume (MN) was observed at all timepoints starting as early as Month 6 and continued up to Month 78 in the overall population. This reduction was observed in all patients as demonstrated in the by patient plot in Figure 11. This reduction was sustained up to the latest time points for both adults and paediatric patients.



Note: Study Month is considered on the basis of cumulative exposure of the study drug from the first infusion in the original study. Current data cutoff: 01Mar2021.

Figure 11. By patient plot of spleen volume (MN) over time - Safety Population.

Additional analysis show that the observed effect on reduction of spleen volume is similar in adults and patients and between the difference paediatric age groups (**Figure 12**). This will also add to the extrapolation of the data from adults to the paediatric population.

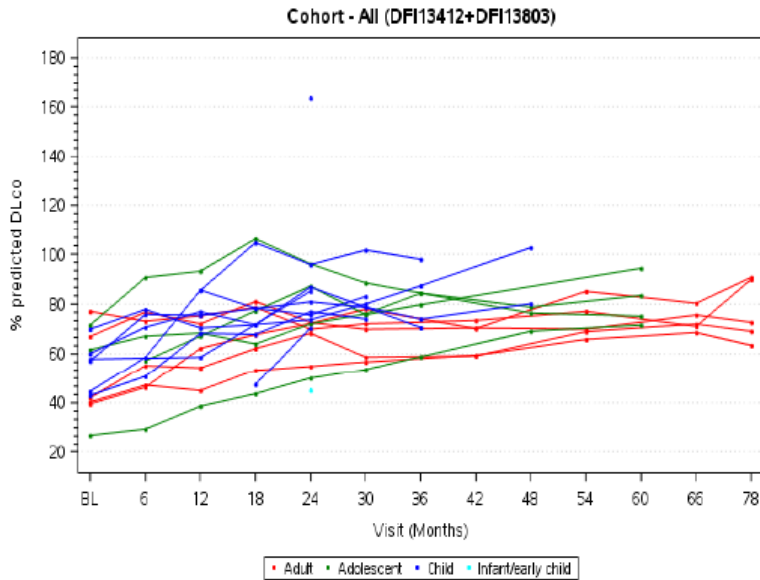


Note: The vertical bars represent standard deviation. Current data cutoff: 01Mar2021

Figure 12. Summary plot of mean spleen volume (MN) over time (Adults and Paediatrics, paediatric subsets) – Safety Population.

Pulmonary function tests

A summary plot of mean derived percent predicted DLco (adjusted for haemoglobin) (adults and paediatrics) that demonstrates increase over time in the mean of derived percent predicted DLco is demonstrated in **Figure 13**.



Note: Study Month is considered on the basis of cumulative exposure of the study drug from the first infusion in the original study. Current data cutoff: 01Mar2021

Figure 13. By-patient plot of Derived % predicted DLco (adjusted for Haemoglobin) over time – Safety Population.

Paediatric Subgroup analysis

Analyses by disease severity

In paediatric patients, the effect of olipudase alfa on spleen volume (MN) was also analysed according to the severity of the patient’s baseline splenomegaly. At baseline, 12 patients were categorized in the severe splenomegaly category (spleen volume >15 MN) and 8 patients in the not-severe category.

By Month 24, the mean percent reduction from baseline in spleen volume (MN) was 65.2% (SD= 5.1, range, -76% to -59%) in the severe category (11 patients) ($p < 0.0001$), and 55.0% (SD= 9.3, range, -69% to -42%) in the not severe category (8 patients) ($p < 0.0001$).

The results were maintained up to month 48, though patients numbers were limited.

Analyses by response to ADA

The effect of olipudase alfa on spleen volume (MN) was analysed according to response to ADA (positive and negative). A positive response includes 13 patients, and a negative response includes 7 patients.

By Month 24 for 12 patients in the positive group and 7 patients in the negative group, the mean percent change (reflecting improvement) in spleen volume (MN) was similar (-61.8% [SD= 7.4, range, -71% to -42%] and -59.4% [SD= 11.0, range, -76% to -42%] in the positive and negative response groups respectively) ($p < 0.0001$).

The results were maintained up to month 48, though patients numbers were limited.

Cycle Ergometry

Cycle ergometry was performed every 6 months (starting at Month 3 in this study for paediatric patients) for the first 2 years in this study, and yearly thereafter. For patients transitioning from DFI13803 Peds, this assessment was not required during the extension study in patients that were ≤ 6

years of age or <120 cm in height on Day 1/Week 0 in the original paediatric study and was performed only in patients who have completed these assessments in DFI13803 Peds.

Adult patients

By Month 54, mean (SD) workload increased by 12.4 (31.9) Watts (range, -22 to 61) for the 5 adult patients. Mean O₂ uptake in adult patients improved in most of the visits with some fluctuations. By Month 54 mean (SD) O₂ uptake increased by 169 (478) mL/min (range, -507 to 678) in the 5 adult patients. By Month 54, mean (SD) CO₂ Output increased by 279 (569.4) mL/min (range, -347 to 908) in the 5 adult patients.

Paediatric patients

By Month 30, mean (SD) workload increased by 87 (34) for 3 paediatric patients (range, 61 to 125), while percent predicted workload improved by 10.7%, (SD= 21.8, range, -7% to 35%).

In paediatric patients, mean O₂ uptake increased from baseline in all visits. By Month 30, O₂ uptake increased from baseline by 1442 mL/min (range, 948 to 1948) for 3 patients.

Mean (SD) CO₂ output increased in most visits. By Month 30, mean CO₂ output increased by 1557 mL/min (430) in 3 paediatric patients (range, 1268 to 2052).

Retrospective NHC study SPHINGO00302

Title: A Retrospective Natural History Study of ASM Deficiency (Niemann-Pick Disease Types A & B).

This study is published as McGovern *et al.* Morbidity and mortality in type B Niemann-Pick disease. Genetics in medicine | Vol. 15, Number 8, August 2013.

Only the high-level data is described, as for the benefit-risk assessment some of the results were considered relevant.

Study objectives

The overall objective of the study was to define the natural history of ASMD (NP Disease Types A and B). The specific aims of the study were to:

- Assess morbidity related to ASMD (NP Types A & B)
- Estimate the mortality rate of patients with ASMD
- Determine the causes of death for patients with ASMD
- Determine predictors of major morbidity and mortality among patients with ASMD
- Define, where possible, the incidence and prevalence of ASMD in the studied regions

Each of the above objectives aims was examined both for the overall population of ASM deficient patients and separately for patients with NP Disease Types A and B.

In this retrospective study 81 ASMD type B patients were retrieved. The mean (SD) age at diagnosis was 9.3 (9.4) years. 29/81 patients are males (35.8%), and 52/81 (64.2%) are females.

ASMD type B patients have several morbidities, of which Hepatobiliary Disorders, Respiratory/Thoracic/Mediastinal Disorders, Infections and Infestations and Gastrointestinal Disorders are amongst the most reported. These may be considered when reviewing the safety data of the patients in the clinical studies.

The primary causes of death for the 2 Disease Type B patients were the 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).

Prospective NHC MSC12840

Title: A prospective, cross-sectional survey study to collect natural history data in patients with Niemann-Pick B disease.

This study is published as McGovern *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) 16:212.

Only the high level data is described, as for the benefit risk assessment some of the results were considered of relevance, notably this study collected 11 years of clinical data in 59 ASMD type B patients. More detail are available in the clinical assessment report.

Study objectives

The objective of this survey study was to prospectively collect natural history data on patients with Niemann-Pick B disease of varying severity. The intent was to use the data to improve the design of future clinical trials that will evaluate the safety and efficacy of olipudase alfa in patients with Niemann-Pick B disease.

This information is intended to:

1. Determine the range of values/performances of the planned tests in this patient population
2. Help to define the most appropriate inclusion/exclusion criteria for future clinical trials
3. Assist in choosing the best clinical endpoints for determining efficacy in future clinical trials
4. Help to characterize and understand the natural history of Niemann-Pick B disease

Study design

This was a prospective, multicenter, multinational, cross-sectional survey study to collect natural history data in patients with NPD B. Because little is known about the natural history of the disease, a prospective study design was chosen to ensure uniform collection of data in a well-controlled clinical setting. This information was to be used to choose clinical endpoints and surrogate markers to support the clinical development plan of olipudase alfa. Thus the clinical endpoints described in this prospective NHC study are in line with the clinical endpoint used in the clinical program.

Baseline data

At the baseline visit, patients were predominantly Caucasian (91.5%). Approximately equal numbers of men and women enrolled. Mean age (SD) was 22.2 ± 13.84 years; median age was 17.0 years (range, 7 to 64 years). Approximately equal numbers of patients were younger and older than 17 years. Of the 30 paediatric patients (≤17 years old), 20 were male and 10 were female. Of adults, 11 were male and 18 were female.

Diagnosis

The first symptoms and age of diagnosis for Niemann-Pick B disease occurred before 18 years of age in most patients. The mean age at symptom onset and diagnosis was 5.23 years and 10.08 years, respectively. The median age at symptom onset and diagnosis was 2.50 years and 5.50 years,

respectively. At disease onset, the most commonly reported symptoms were hepatosplenomegaly (39%), splenomegaly alone (6.8%), and hepatomegaly alone (3.4%).

Height z-scores

For the 6 to 11 year old group, mean height-for-age Z-scores were -0.9 and -1.1 at baseline and year 1, respectively. For the 12 to 17 year old group at the same time points, mean Z-scores were -2.7 and -2.6. The mean Z-scores at the final visit are not meaningful because data are available for only 3 or fewer patients.

Lung function

Most patients had ILD and reticulonodular density (66%, 62%, and 78% at baseline, year 1, and the final visit, respectively). At every visit, a higher percentage of patients had severe ILD and reticulonodular density as opposed to mild or moderate. The percentage of patients with ILD increased from 66% to 78% over the study and the percent of patients with severe ILD increased from 42% to 50% of patients. So this is indicative for disease progression.

Ergometry

Based on the prospective data on the ergometry, it is observed that the % Predicted Hb-adjusted DLco in patients who had shortness of breath at baseline (n=25) over the course of 1-year the DLCO remained similar, after 1 year 1 in the final study visits a decline in DLco is observed, though the number of patients are limited. For those patients who had no shortness of breath at BL (n=34) the % Predicted Hb-adjusted DLco also remained more or less constant up to the final visit (Table 19).

Table 19. Age, percent haemoglobin-adjusted diffusing capacity of lung for carbon monoxide, percent predicted forced vital capacity, and 6-minute walk test by worst interstitial lung disease severity (amended by Assessor).

parameter	timepoint	statistic	Absent	Mild	Moderate	Severe
Age (y)	Baseline	N	1	7	3	43
		Mean	48.0	29.6	18.7	21.3
		(SD)	(...)	(17.7)	(2.1)	(13.5)
	Year 1	N	0	0	6	39
		Mean	26.3	21.3
		(SD)			(11.9)	(12.5)
	Final visit	N	0	2	4	41
		Mean	...	49.0	28.3	26.1
		(SD)		(12.7)	(10.8)	(13.1)
% Hb-adjusted DLCO (mL/min)	Baseline	N	1	6	3	36
		Mean	142.7	67.1	56.5	65.8
		(SD)	(...)	(24.6)	(17.4)	(25.7)
	Year 1	N	0	0	6	36
		Mean	73.3	69.2
		(SD)			(16.1)	(20.2)
	Final visit	N	0	2	4	40
		Mean	...	111.2	81.5	64.0
		(SD)		(10.6)	(10.8)	(19.9)

% predicted FVC	Baseline	N	1	7	3	40
			Mean	110.1	92.0	71.2
		(SD)	(..)	(16.0)	(11.2)	(16.6)
	Year 1	N	0	0	6	38
			Mean	82.8 (10.3)
		(SD)				(16.5)
	Final visit	N	0	2	4	40
			Mean	...	114.3	91.7
		(SD)		(0.1)	(11.3)	(15.3)

Visits with fewer than 5 patients were not presented in a table and were only presented in listings.

DLCO=diffusing capacity for carbon monoxide; FVC=force vital capacity; Hb=haemoglobin

Results for patient who had shortness of breath at baseline (N=25/59) and those who had not (n=34/59) are presented in Table 20 and

Table 21.

Table 20. Summary of Pulmonary Function on Subset with No Shortness of Breath at Baseline -Full Analysis Set.

Parameter	Summary Statistic	Baseline (N= 34)	Year 1 (N= 28)	Final visit			Total (N= 18)
				Years 5-7 (N= 4)	Year 10 (N= 11)	Year 11 (N= 3)	
FVC (L)	N	32	28	4	11	3	18
	Mean	2.9	2.7	4.5	3.6	4.3	3.9
	Std. Dev.	1.43	1.23	0.77	1.34	1.75	1.30
% Predicted Hb-adjusted Dlco	N	27	25	4	9	3	16
	Mean	73.4	81.0	66.0	63.8	86.7	68.7
	Std. Dev.	27.76	32.05	13.19	31.00	21.06	26.22
Predicted FVC (L)	N	32	28	4	11	3	18
	Mean	3.3	3.3	5.1	4.5	4.4	4.6
	Std. Dev.	1.33	1.10	0.20	1.06	0.92	0.91
% Predicted FVC (mL)	N	32	28	4	11	3	18
	Mean	86.3	81.3	87.0	79.9	93.4	83.7
	Std. Dev.	16.64	17.29	14.54	27.23	22.79	23.73

FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume in 1 second, TLC = Total Lung Capacity, Dlco = Diffusing Capacity.

Shortness of Breath defined from Medical History. Source listing for this table is Listing 16.2.6.3.9

Visits with less than 5 patients are not presented in a table and are only presented in listings.

Table 21. Summary of Pulmonary Function on Subset with Shortness of Breath at Baseline - Full Analysis Set.

Parameter	Summary Statistic	Baseline (N= 25)	Year 1 (N= 22)	Final visit			Total (N= 14)
				Years 5-7 (N= 7)	Year 10 (N= 4)	Year 11 (N= 3)	
FVC (L)	N	23	21	7	4	3	14
	Mean	2.6	2.7	3.5	2.6	3.3	3.2
	Std. Dev.	1.10	1.02	1.09	0.49	0.63	0.90
%Predicted Hb-adjusted Dlco	N	21	19	7	4	3	14
	Mean	61.8	65.3	61.3	50.6	44.2	54.6
	Std. Dev.	26.63	22.37	24.94	9.00	4.66	19.06
Predicted FVC (L)	N	23	21	7	4	3	14
	Mean	3.3	3.4	4.0	3.9	4.6	4.1
	Std. Dev.	1.02	0.89	0.58	0.30	1.13	0.68
% Predicted FVC (mL)	N	23	21	7	4	3	14
	Mean	76.4	78.7	86.6	68.1	73.0	78.4
	Std. Dev.	14.79	16.33	19.05	7.47	13.93	16.89

FVC = Forced Vital Capacity, FEV1 = Forced Expiratory Volume in 1 second, TLC = Total Lung Capacity, Dlco = Diffusing Capacity.

2.6.6. Discussion on clinical efficacy

Dose finding

Study DFI13412

This was an open-label, multicenter, ascending dose study of the tolerability and safety of olipudase alfa in nonneuropathic adult patients with ASMD (aged between 18 and 65 years inclusive). The in- and exclusion criteria are selected the patient population intended to be treated. Patients with a BMI >30 kg/m² were excluded; however, patients with a BMI >30 kg/m² could be included in the rest of the clinical program. For patients with a BMI >30 kg/m², the dosing is based on body weight (e.g. *Body weight (kg) to be used for dose calculation = 30 × (actual height in m)²*). Although there was very limited information to assess the effect of body weight on olipudase alfa PK prior to the initiation of pivotal studies, olipudase alfa exposures were ~2-fold higher in one obese patient (BMI 40.2 kg/m²) with 0.3 mg/kg dose in the first-in-human study (SPHINGO00605). Therefore, olipudase alfa dosing for patients with BMI >30 kg/m² was limited to a dose corresponding to a BMI of 30 kg/m² out of caution in the subsequent clinical studies DFI12712 ASCEND and LTS13632. The provided clinical data support the dose recommendation in obese patients.

Study SPHINGO605

This was a phase 1, single-centre, single-dose, dose-escalation study of olipudase alfa in adults. The in- and exclusion criteria selected the patient population intended to be treated.

The tolerability and safety of olipudase alfa was evaluated after single, ascending doses of olipudase alfa were administered to 11 adult patients with ASMD. Doses administered were 0.03 mg/kg (3 patients), 0.1 mg/kg (3 patients), 0.3 mg/kg (2 patients), 0.6 mg/kg (2 patients), and 1.0 mg/kg (1 patient).

Efficacy studies

General

Overall inclusion and exclusion criteria are considered acceptable. The indication is "*Xenpozyme is indicated 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*". This is acceptable. Although type A patients may also have some benefit from treatment in reducing organomegaly, olipudase alfa does not cross the BBB and thus the severe neurological symptoms are not treated, adding only limited contribution to life expectancy. The applicant, therefore, restricted the indication to type A/B and B ASMD.

Pivotal study DFI12712

Study DF12712 (ASCEND) is a double-blinded placebo-controlled study in adult ASMD type B patients. The eligibility criteria select the nonneuropathic visceral ASMD patient intended for treatment. No exclusion criterion for the absence of neurological symptoms is included. The study consists of a 52-week blinded primary analysis period (PAP) in which patients were randomised 1:1 to placebo or olipudase alfa. The PAP was followed by extended 52 weeks (ETP) of treatment in which placebo patients crossed over to olipudase alfa treatment. Patients were able to remain on the study after week 104 in a long-term follow-up part, which is ongoing. The final study results are awaited in due time; a commitment is provided. The PAP part of the pivotal study was finalised prior to the COVID-19 pandemic. The applicant conducted post-hoc subgroup analyses based on the results from impacted patients with unimpacted patients; no relevant differences in efficacy between the two groups were observed.

Treatment

The dose-escalation scheme – which was based on the experience in animal studies - as applied in the clinical studies is in line with the proposed SmPC and is considered adequate.

Preclinical data suggests that a dose of 5 mg/kg body weight could even be more efficacious; however, this dose has not been evaluated clinically. This is based on the preclinical data for which it was concluded by applicant that a single dose of olipudase alfa as low as 1 mg/kg was highly efficient at reducing sphingomyelin levels in the liver (76% reduction) and the spleen (67% reduction). Single doses of 3 mg/kg of olipudase alfa also significantly reduced kidney sphingomyelin levels (66% reduction, study 05-0129Pnp) and a single dose of 5 mg/kg showed a significant reduction of sphingomyelin in the lung (43% reduction, study 01-0220PnP). However, results with the 5 mg/kg dose in the lung were variable and did not show a consistent trend over time.

In studies testing every other week dosing for 12 weeks, sphingomyelin levels were reduced to the background in the liver and spleen, and substantial reduction was observed in the lung at 3 mg/kg olipudase alfa (Studies 02-1084Pnp and 04-0813Pnp). These data demonstrate that the chosen dosing regimen of 3 mg/kg olipudase alfa every other week was highly effective at reducing and maintaining low tissue sphingomyelin levels in ASMKO mice. Extending the dosing regimen beyond every other week, to every 21 days for instance, was not investigated as more substantial sphingomyelin re-accumulation was observed at later timepoints (>14 days) which may lead to tissue damage. Therefore, the maximum dose was set to 3 mg/kg body weight and the dosing interval Q2W.

In SmPC section 4.2, an infusion rate/infusion time is recommended for each specific dose. Patients are expected to receive IV olipudase alfa over a period of approximately 20 minutes to 3.7 hours, depending on the dose to be administered. The length of the infusion time was adjusted based on the patient's tolerance of the infusion. Given that the rapid metabolism of accumulated sphingomyelin by olipudase alfa generates pro-inflammatory breakdown products, the stepwise manner of the infusion aims to minimize the risk of infusion associated adverse events. In the clinical program, accelerated infusion time was not tested (it was possible to slow, pause or discontinue). Based on the compliance measurements, it can be concluded that compliance in both adults and paediatric patients was high.

Endpoints

The primary endpoints were 1) the percentage change in % predicted DLCO from baseline to Week 52 and 2) the percentage change in spleen volume (in MN) from baseline to Week 52. The use of these endpoints is in line with the SA received and agreed upon.

DLco was chosen as a primary endpoint because this pulmonary function test (PFT) reflects the underlying pathophysiological infiltration manifested by disease foam cells and changes in DLco can objectively show the effect of olipudase alfa treatment on lung function and reducing local inflammation. For the prespecified responder analysis, an improvement of $\geq 15\%$ in DLco was set based on international guidelines on the management of lung fibrosis. In ASMD there are no data available that directly support that a 15% increase in DLco% is clinically relevant, therefore this cut-off value was borrowed from other lung diseases, e.g. IPF and autoimmune pulmonary alveolar proteinosis (PAP-1). For instance, this $\geq 15\%$ improvement in DLco in IPF is linked to a reduced mortality in IPF patients. The applicant further substantiated with literature data that this 15% indeed is considered clinically relevant. This approach and substantiation are agreed; it is in line with what was requested during SA and the presubmission meeting. In addition to the above, there are few data on the change in DLco over time in ASMD in the literature. However, a spontaneous improvement of DLco (or other pulmonary parameters) in ASMD patients has not been reported in the literature, nor has it been observed in the prospective natural history study (MSC12840), therefore improvement in DLco is considered clinically relevant.

For the reduction of spleen volume – the second primary endpoint- the cut off value of a 30% reduction from BL to week 52 was set for the responder analysis. In Gaucher disease, therapeutic goals for splenomegaly included a reduction in spleen volume of 30-50% within year 1 of enzyme replacement therapy (Pastores *et al.*, 2004). The 30% reduction of spleen volume in ASMD can be considered clinically meaningful. Notably, spleen reduction can also be considered as a pharmacodynamic endpoint.

In addition to the two primary endpoints, secondary endpoints include, amongst others, reduction of liver volume, platelet counts, Week 52 change from baseline in fatigue severity as measured by item 3 of the BFI scale, week 52 change from baseline in dyspnoea severity as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnoea tool. Additional lung function tests were added as tertiary endpoints. The quality of life (QoL) measurements are of interest as they may help understand whether the treatment provides a relevant effect for the patient regarding day-to-day functioning.

Study DFI13802

Study DFI13802 is a Phase 1/2, multi-centre, open-label, repeated-dose study to evaluate the safety, tolerability, PK, PD, and exploratory efficacy of olipudase alfa administered Q2W for 64 weeks in paediatric patients <18 years of age with non-central nervous system manifestations of ASMD. Enrolled patients were divided into 3 age cohorts (adolescents, child and infants/early child) and received olipudase alfa per 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 at least a 16-week duration (in line with the proposed SmPC).

In line with the adult study, the paediatric patients also received IV olipudase alfa over a period of approximately 20 minutes to up to 3.7 hours, depending on the dose.

Study LTS13632

This ongoing phase 2, a multinational, multicenter, nonrandomized, open-label, long-term study, was designed to assess the ongoing safety and efficacy of olipudase alfa in patients with acid sphingomyelinase deficiency who already participated in studies with olipudase alfa. Patients previously treated in studies DFI13412 and DFI13803 were to enrol. Patients started this study at the same dose they were receiving at the end of their original study, provided that they had not missed more than 1 biweekly dose before the entry into this study. It was confirmed that all patients from the previous studies, except one, rolled over without treatment interruption.

Comparative study for paediatric data

The efficacy data from BL to week 52 was compared to the data collected in the prospective NHC study MSC12840, which included 30 paediatric patients. The comparison analysis selected paediatric patients in DFI13803 Peds with age at screening ≥ 5 . In comparing efficacy parameters at Week 52/Year 1 between DFI13803 Peds and MSC12840, the imbalance in age at baseline between the two studies was considered so that the age at baseline was one of the covariates in the analyses of covariance model (ANCOVA). Further, the applicant showed that the imbalance in age at baseline on the observed efficacy parameters did not affect the overall interpretation of the results; for 3 out of 4 measures, age had no effect.

Efficacy data and additional analyses

Dose finding studies

Both dose-finding studies (DFI13412 and SPHING0605) showed that under olipudase alfa treatment for the PD parameters ceramide, an increase in plasma levels was observed indicative for the MoA of olipudase alfa in ASMD patients. In the multiple dose study (under continued treatment) the ceramide post-infusion levels decreased over time which is considered indicative for the removal of accumulated sphingomyelin from the tissues; this was confirmed by liver biopsies.

Data on spleen and liver volume in study DFI13412 showed a decrease from baseline to week 26; In study DFI13412, spleen volume reduced by 29%, which is considered clinically meaningful, liver volume reduced 22% from baseline. Given the limited number of patients (n=5), no firm conclusions can be drawn. For 2/5 patients, the reductions from baseline in liver volume were low, likely because they had near-normal liver volumes at baseline (MN=1). These two patients may have a less severe disease burden.

It is observed that after 26 weeks of olipudase alfa treatment, the results for the lung function parameters were stable or improved very slightly. Given the limited number of patients, no firm conclusions can be drawn, and the study duration of 26 weeks could be too short to improve DLco. One out of 5 patients showed an improvement $>15\%$ from baseline in DLco, the generally accepted minimum for a conclusion of a treatment effect in the most common restrictive pulmonary disease IPF (see above). The small improvements of FVC % predicted (1.5% (6.5)), TLC % predicted (3.9% (7.7)), FEV₁ % predicted (0.6% (4.9)) could be within the range of variation of the test at least for FEV₁. Only one patient switched from the category moderate to mild.

DFI12712

A total of 36 adult patients were randomised in this placebo-controlled study; given the rarity of the disease, this number is considered acceptable. Seventeen out of 18 patients randomised to olipudase alfa were treated according to the protocol. Generally, both groups were well balanced with respect to the baseline characteristics. The 18 patients in the treatment group had a mean age (SD) of 21.4 (20.3) years, and 18 patients in the placebo groups had a mean age (SD) of 14.6 (16.1) years when first diagnosed. A detailed analysis was submitted showing no statistically significant effect for age at ASMD for % change in % predicted DLco (p-value=0.81). A borderline statistically significant for age at ASMD diagnosis was shown for % change in spleen volume (p-value=0.052). However, there was no statistically significant age at ASMD diagnosis-by-treatment interaction (p-value=0.52). This indicates that a difference in age at ASMD diagnosis unlikely had major impact on olipudase alfa treatment effect.

Further, there is a slight disbalance for gender; in the placebo group, more females than males were included. This is not a problem as the population pharmacokinetic analysis did not show a difference in olipudase alfa exposure between male and female patients.

The mean % predicted DLco at baseline was similar in both groups (48.5% in the placebo group and 49.4% in the olipudase alfa group) and reflected an overall moderate impairment of diffusion capacity. At baseline 7 patients (4 placebo; 3 treatment) had a DLco <40% of predicted. This is considered having severe lung disease. There were no patients with oxygen therapy at baseline in the olipudase alfa clinical development program. A total of ten patients had history of oxygen use (7 patients) and/or had a temporary use of oxygen during the study (3 patients). As there is no mentioning of oxygen therapy at the end of the study, it is assumed that no patient became dependent of oxygen.

Outcomes

DLCO

The first primary endpoint for improvement of % predicted DLco (change from BL to week 52) was met. Using MMRM during PAP in the mITT population, the LS mean percentage change in % predicted DLco from baseline to Week 52 was greater in the olipudase alfa group (22%) compared to the placebo group (3%), a difference of 19% (p=0.0004). At week 104 (end of ETP), when patients previous on placebo crossed to olipudase alfa, the LS mean in percentage change from baseline in % predicted DLco improved by 25% and 22% in the placebo/olipudase alfa group (n=10) and the olipudase alfa/olipudase alfa group (n=17), respectively, using the original baseline. The results are consistent with the results of the PAP. Sensitivity and supportive results showed similar results.

There were 5 DLco responders (change from baseline on % predicted DLCO \geq 15% at Week 52) in the olipudase alfa group and none in the placebo group. At Week 104, a post hoc analysis showed that 8/15 in the placebo/olipudase alfa group and 7/15 patients in the olipudase alfa/olipudase alfa group were responders. This is indicative that more patients achieve the goal of a \geq 15% improvement from BL under continued treatment. Beyond week 104, DLco seems to remain stable; however, no firm conclusions can be drawn given the limited number of patients. Nevertheless, improvement or stabilisation of DLco is considered a beneficial effect.

As the long-term follow-up of the pivotal study is ongoing, not all patients (6 out of 36) have reached the end of week 104 at data cut-off. Between week 156 and week 208, 11 out of 36 patients received treatment. Four patients received olipudase alfa for more than 208 weeks. The final study report is awaited in due time.

The decline in DLco observed at Week 184 in the olipudase alfa/olipudase alfa group is explained by 1 patient who missed 6 consecutive infusions from Week 174 to Week 184. This patient lives in a COVID-19 hotspot, and was considered to be a high-risk patient due to severe pulmonary manifestations of ASMD. In addition, it can also be observed that when treatment is ceased, the lung function capacity rapidly declines but restores after treatment is reinitiated. However, based on the data of 12 patients, sporadic treatment interruptions of olipudase alfa do not have a major impact on the efficacy of olipudase alfa. As expected, lyso-sphingomyelin, a PD biomarker, increased but did not have clinical consequences with respect to DLco, spleen and liver volume, and platelets. It is agreed that no specific wording on temporary ceasing treatment and deterioration of disease symptoms in the SmPC is required.

Spleen volume

The second primary endpoint of reduction of spleen volume (change from BL to week 52) was met as well. The LS mean percentage change showed a reduction in the olipudase alfa group (39%) compared to an increase in the placebo group (0.5%). At Week 104, the LS mean percentage change in spleen volume from baseline in the placebo/olipudase alfa group patients (n=11) was reduced by 35.9% and by 47.0% in the olipudase alfa/olipudase alfa group (n=14).

The prespecified responder analysis - a $\geq 30\%$ reduction from baseline in spleen volume at 52 weeks - showed that in the treatment group, 17/18 patients were responders. In contrast, there were no responders in the placebo group. In line with the improvement of the spleen, improvement in platelet counts is seen, which is also beneficial.

Liver Volume

In the PAP, a reduction from baseline to week 52 of 28% in liver volume was observed in the treated group compared to placebo. An early clinical relevant response was already observed at week 26. The results from the PAP were sustained in the long-term follow-up. A similar reduction in liver volume was observed in patients switched from placebo to olipudase alfa. In general, normalisation of liver volume can be considered beneficial in patients with a lysosomal storage disease.

Further evidence of efficacy is supported by liver biopsies showing sphingomyelin reduction after 52 weeks of treatment. Similar results were shown when placebo patients crossed over to olipudase alfa in the ETP. The biopsy results are in line with the results of liver volume reduction. The change from baseline for liver function tests (e.g. ALT, AST, bilirubin) and lipid profiles (LDL, HDL) also showed consistent improvements indicative of liver function improvement. In the placebo group, the liver function did only change marginally.

Quality of life and dyspnoea

In literature (e.g., Jones *et al.*, 2020), DLco is described as predictive for mortality and morbidity, which may hold true for other diseases, but whether this also applies to ASMD is unknown. Low DLco seems to be associated with low QoL scores. The literature mentions that most ASMD patients report dyspnoea and recurrent respiratory infections (Cox *et al.*, 2018). It is anticipated that under olipudase alfa treatment, dyspnoea will either resolve or at least show some improvement.

The data show that in both the treated and placebo groups the improvement for the FACIT-dyspnoea score is similar.

In addition, in the Patient global impression of change scale (PGIC), there is an item on the shortness of breath. Only for this item a difference between the 2 groups was observed. Patients in the olipudase alfa group (n=17) reported greater improvement (LS mean = 1.11) than the placebo group (n = 16, LS mean = 0.30). For the shortness of breath item, the responder rate in the olipudase alfa group was higher than in the placebo group (61% versus 28%). The treatment groups were not different from

other PGIC items at Week 52. Similar trends were observed on the PGIC items during the long term follow-up when placebo patients crossed over to olipudase alfa treatment. The observations made for dyspnoea and shortness of breath can be explained the fact that dyspnoea is a subjective symptom, per the European Respiratory Society (Laviolette *et al.*, 2014), and can be confounded by changes in other emotional symptoms such as high anxiety/depression. Patients can adapt their behaviour to high anxiety/depression. A patient's perception of his/her illness can influence dyspnoea; those with higher neuroticism and lower conscientiousness were more likely to have dyspnoea, regardless of COPD status (Terracciano *et al.*, 2017). These observations particularly apply to the ASMD patient population in DFI12712 ASCEND. The majority of these patients have been living with ASMD for many years (age at diagnosis and age at baseline trial entry). Therefore, they may have adapted their lifestyles to become more sedentary. Hence, such measures in a patient population that has learned to adapt to their disease burden may be less relevant. Measurement of QoL parameters can thus be challenging in adult ASMD patients. Nevertheless, the observation that in the treated group patients showed a greater improvement over placebo adds to the overall beneficial effects of olipudase alfa treatment. Data of the prospective NHC study MSC12804 shows a difference in baseline value for DLco for dyspnoeic on non-dyspnoeic patients. Subgroup analyses showed that the treatment effect in the patients being dyspnoeic or non-dyspnoeic at baseline was similar. This was also observed when accounting for baseline ILD severity.

Other lung function tests

In line with the observed improvement in DLco, the other pulmonary tests (FVC, FEV₁ and TLC) - tertiary endpoints - showed relevant improvements in the PAP. In the ETP, these results were sustained. Results were confirmed when the patients crossed over from placebo to olipudase alfa, and these improvements were also sustained. It should be noted that the measurements of FEV₁, FVC are measurements that could be influenced by the muscle strength.

The applicant also investigated the lungs by, amongst others, high-resolution CT scans, showing improvements from baseline.

These differences in the pulmonary tests are reflected in the treadmill test, another tertiary endpoint (see below).

Ergometry

A post-hoc analysis on treadmill ergometry (CPET) was also performed. Overall the results indicate a difference between olipudase alfa and placebo patients in favour of olipudase alfa (change from baseline to week 52). After placebo patients crossed over to olipudase alfa, all parameters improved in the placebo/olipudase alfa group. This may also be indicative of some improvement in lung function. Notably, baseline O₂ saturation in both groups was in the normal ranges with no difference between the two groups (~97%). The values stated in the line listing for ergometry (O₂ saturation, etc.) are measured when the patient is at rest. The applicant confirmed that data on exercise values are not available.

In summary, the lung function data, including DLco, and the reduced reporting of shortness of breath indicates improvement of lung function in ASMD patients.

Other efficacy data

Several tertiary endpoints were evaluated amongst other liver function tests (e.g. ALT, AST, bilirubin). The liver function test showed consistent improvements in line with the improvements of the liver (reduction of liver volume). A similar trend was observed for the lipid profile, which showed improvements in the treated group but not in the placebo arm.

Paediatric study DFI13803

The efficacy results (e.g., reduction of spleen and liver volume, improvement of DLco (3 out of 4 adolescents and 6 out of 9 children showed improvements in DLco), improvement of platelet counts, improvement of liver-related enzymes and lipid profiles) observed in paediatrics are in line with the efficacy results observed in adults (e.g. pivotal study). The data is indicative of improvement. Given the limited number of patients (n=20) and the uncontrolled, open-label nature of the study, no firm conclusions can be drawn.

In contrast to the adult data, an improvement on different QoL measures is observed in paediatric patients. The primary objective of the study was to assess safety, therefore, no clear conclusions regarding the efficacy of the product in the paediatric population can be drawn.

The paediatric data was compared to data from a prospective NHC study (see further below) showing improvement in spleen and liver volume, but the results for DLco did not show any large differences. It may be that disease progression is yet not too advanced in these paediatric patients, and thus more time is required to show an effect on DLco.

As in the pivotal study, ergometry (cycle) was also performed in some patients (3 adolescents; 2 children). In the 5 patients who performed the test, a trend towards improvement on cycle ergometry was observed; however, given the limited number of patients and the lack of control arm, no firm conclusion can be drawn. Additional submitted data on the percent predicted oxygen uptake (parameter to measure an individual's capacity to perform aerobic exercise, but is dependent of the effort) showed that in 4 of 5 patients in DFI13803 Peds this improved after 52 weeks of olipudase alfa treatment. This indicates a functional improvement in paediatric ASMD patients. Notably, all patients showed simultaneous improvement in one or more of the following lung function parameters: % predicted DLco, % predicted FEV₁, % predicted FVC and/or % predicted TLC. Although the numbers are limited, the data are indicative of improved lung function under continued olipudase alfa treatment.

In addition, the quality of life among paediatric patients in DFI13803 Peds was measured using the PedsQL™ Generic Core Scales questionnaire. One of the four scales in this questionnaire is Physical Functioning, which includes questions that measure how difficult certain activities of daily living (walking, running, play sports or exercise, etc.) are for the patient either from the patient's or parent's perspective. In addition to the trend toward improvement on ergometry measures, 4 out of 5 patients had an increase on their self-reported physical functioning scale score of the PedsQL™ assessment, while for three out of five patients, an increase in the parent-reported physical functioning scale score was observed.

Therefore, despite the limited number of patients under continued olipudase alfa treatment there is a trend in improvement in QoL besides the observed efficacy parameters on DLco, spleen and liver.

The paediatric patient's growth (height Z-score) and bone markers (BAP) were also investigated. Under continued olipudase alfa treatment, these children gained growth (height Z-score improved). The mean overall increase was 0.56 at Week 52, and 0.78 at the end of the study at Week 64. Improvements in height Z scores were generally similar across all age groups. Improvement in growth also reflects upon the child's general health status, which thus is supportive of clinical benefit.

BAP is correlated with bone growth in children. At BL, the BAP mean values are below the normal values for healthy peers. The mean BAP increased from baseline to Week 52 in all age groups except for the adolescent cohort. This increase may be due to treatment, but it cannot be excluded that it is also attributed to the growing child. The reduction of BAP in adolescence is also a normal observation.

Comparative study for paediatric data

The comparison between paediatric populations in both MSC12840, a natural history study, and DFI13803 Peds showed a relevant decrease in spleen volume (46%), liver volume (48%), and platelet

count (46%), HRCT (both GG and ILD), and height Z score, consistent with the results of study DFI12712. However, for % predicted DLco, in the MSC12840 group, the standard deviation of percentage change (50.9) is much higher than that in DFI13803 Peds group (29.1). The applicant explained that at the time of the comparison of data from both studies, the same formula was used for the calculation of the % predicted DLco (i.e., % predicted values from MSC12840 had to be recalculated for that purpose), potential differences in data collection may have occurred that could explain differences in SD. The applicant suggests that this difference in data collection may be attributed to the difference in study design. Study MSC12840 was a prospective, multicenter, multinational natural history study in patients with Niemann-Pick type B disease of varying severity, while study DFI13803 Peds study was 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 paediatric patients. Although there is a difference in collection, a standardised execution of lung function measurements would not impact the results of a test. Therefore, it is more likely that the recalculation would explain the large difference in SD for the % change from BL. Although the large SD indicates a less precise measurement of baseline DLco, it can be accepted for the comparisons of the studies.

Long term follow-up study LTS13632

In line with the results observed in the preceding studies, the improvements in spleen and liver volume were maintained in the LTFU (up to the cut off 1 March 2021). DLco further improved; however one adolescent patient deteriorated after 18 months of treatment. Based on additional submitted data which pertained to a single female patient who had anaemia, it is considered possible that due to a combination of anaemia (likely due to the onset of puberty with menorrhagia) and normalization of height, as demonstrated by the Height Z Score improvement, the % predicted DLco adjusted for haemoglobin decreased in this patient. For the other efficacy parameters, no deterioration was observed. Although the data are very limited, further improvement in ergometry values from baseline was observed.

For the 5 adults original started in study DF13412, 78 weeks data is available. For the paediatric patients initially started in study DFI13803, about 62 weeks of data is available.

The clinical relevance of the PedsQL Generic Core Scales and the PedsQL Multidimensional Fatigue Scale was further substantiated.

The positive changes from baseline to Week 52 were compared to MCID estimates derived from the published literature and the DFI13803 Peds dataset. The published MCID thresholds are based on child- and parent-reported PedQL Generic Core data from 10,241 families in the United States. The MCID threshold was calculated in that sample as 1 standard error of measurement (SEM) to reflect the amount of improvement required to exceed changes that may occur due to measurement error alone. Published thresholds for the Multidimensional Fatigue Scales are not available. Additionally, the distributions of the baseline PedsQL scores in the DFI13803Peds study were examined to estimate an MCID; 0.5 standard deviation of the baseline values for all scales was used as the MCID estimate. Based on these MCIDs the number of responders was scored. For example, for the domain fatigue score when self-reporting 92% of the patients was considered responders above the MCID.

For both measures, it was shown that the size effects are considered relevant. Given the limited number of patients available (n=13) no firm conclusion can be drawn, however, it is noted that for most of the score items, a positive effect is observed. This is indicative of additional beneficial effects noted by the patients and/or caregivers.

2.6.7. Conclusions on the clinical efficacy

It is considered demonstrated that under continued olipudase alfa treatment, spleen and liver volume are reduced. These reductions are clinically meaningful. It is also considered demonstrated that DLco improves or stabilises under continued treatment. The observed improvements of DLco are also considered clinically relevant. Results in adults and paediatrics are comparable, and the extrapolation of adult data to paediatrics is sufficiently substantiated and justified. In addition to the observed improvements in organomegaly, improvements in pharmacodynamic parameters, other lung function parameters, improvement of dyspnoea and improvement in QoL were noted.

The indication in type A/B and B ASMD patients is acceptable. As the youngest patients were diagnosed around birth and some patients treated in the first months of life, no age restriction has to be included in the indication.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Seventy-two (72) patients divided over 5 studies (some of the patients participated in more than 1 study) received olipudase alfa. Of them, 11 received a single dose and are not included in the pooled safety database. Of the remaining 61 patients, there are 41 adults and 20 children. Follow up varied from 26 weeks up to 9 years.

Table 22. Summary of subject disposition - All enrolled patients

Subject Disposition	Paediatric	Adult	Overall
Enrolled/randomized patients, n	20	41	61
Enrolled/randomized but untreated patients, n	0	1	1
Enrolled/randomized and treated patients, n	20	40	60
Safety set, n	20	40	60
Ongoing in the study, n(%)	20 (100%)	37 (92.5%)	57 (95.0%)
Discontinued study treatment, n (%)	0	3 (7.5%)	3 (5.0%)
Reason for treatment discontinuation, n (%)			
Adverse event	0	0	0
Non-compliant	0	0	0
Wishes to withdraw	0	1 (2.5%)	1 (1.7%)
Lost to follow-up	0	0	0
Screen failure	0	0	0
Other	0	2 (5.0%)	2 (3.3%)
Related to COVID-19	0	1 (2.5%)	1 (1.7%)
Not related to COVID-19	0	1 (2.5%)	1 (1.7%)
Percentages are based on the number of safety set in each group. For patients from DFI13412 and DFI13803 Peds, the number of patients completed study treatment refers to the study treatment during LTS13632 study. Treated patients only referred as patients who are treated with olipudase alfa.			

Of the 59 patients, 55 (20 paediatric patients and 35/39 adults) achieved a dose of 3.0 mg/kg at the time of the data cut-off.

Four adult patients were not receiving the 3.0 mg/kg dose at the data cut-off. Two patients had not reached the 3.0 mg/kg dose due to TEAEs. Two patients (placebo/olipudase alfa in DFI12712 ASCEND) had not reached the 3.0 mg/kg dose due to reasons other than TEAEs. In one patient, the data cut-off occurred before dose escalation in the ETP was completed, and the other patient had missed doses.

Table 23. Summary of treatment exposure - olipudase alfa safety set.

Extent of Treatment Exposure	Paediatric (N = 20)	Adult (N = 40)	Overall (N = 60)
Cumulative duration of olipudase alfa exposure (patient-years)	80.29	135.78	216.08
Duration on olipudase alfa (years)			
Number of patients with value	20	40	60
Mean (SD)	4.01 (1.195)	3.39 (1.868)	3.60 (1.689)
Median	4.15	2.95	3.11
Min : Max	2.5 : 5.7	0.4 : 7.8	0.4 : 7.8

Percentages are based on the number of safety set in each group.

Initial dose escalation period is the first time when patient reached the 3 mg/kg; or if a patient never reached 3 mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.

2.6.8.2. Adverse events

The most reported TEAEs in adults were: headache (n=26, 65.0%), nausea (n=17, 42.5%), nasopharyngitis (n=17, 42.5%), upper respiratory tract infection (n=16, 40.0%), back pain and abdominal pain (n=14 each, 35.0%), and arthralgia (n=13, 32.5%). In children the most reported AE were: pyrexia (n=18, 90.0%), cough (n=16, 80.0%), nasopharyngitis (n=14, 70.0%), diarrhoea, vomiting, and headache (n=13 each, 65.0%).

For the most frequently reported TEAEs, a higher proportion of paediatric than adult patients experienced TEAEs potentially reflecting the common cold (e.g., nasopharyngitis, cough, upper respiratory tract infection). Paediatric patients were also more likely to report pyrexia, diarrhoea, vomiting, and abdominal pain.

Most adverse events can be related to infusion reactions (high temperature, rash and erythema like cutaneous manifestations) or treatment failure.

An overview of TEAEs is provided in Table 24.

All 60 patients (100.0%) had at least one TEAE; 43 (71.7%) patients had treatment related TEAEs; 14 (23.3%) patients had at least 1 severe TEAE; and 11 (18.3%) had a TEAE leading to dose reduction. No patient permanently discontinued treatment.

When compared with placebo, no clear pattern of AE's could be identified related to the study drug.

Table 24. Overview of treatment-emergent adverse events - olipudase alfa safety set.

	Paediatric (N=20)			Adult (N=40)			Overall (N=60)		
	n (%)	Events	EAIR (PY)	n (%)	Events	EAIR (PY)	n (%)	Events	EAIR (PY)
Any TEAEs	20 (100%)	1436	1722.88 (1.2)	40 (100%)	2692	1323.37 (3.0)	60 (100%)	4128	1434.23 (4.2)
Treatment-emergent AEs by severity									
Severe	7 (35.0%)	9	11.47 (61.0)	7 (17.5%)	13	5.93 (118.1)	14 (23.3%)	22	7.82 (179.1)
Moderate	17 (85.0%)	148	91.60 (18.6)	28 (70.0%)	219	54.55 (51.3)	45 (75.0%)	367	64.39 (69.9)
Mild	20 (100%)	1279	1537.89 (1.3)	40 (100%)	2459	876.42 (4.6)	60 (100%)	3738	1023.11 (5.9)
Any treatment-emergent serious adverse events	9 (45.0%)	20	16.12 (55.8)	13 (32.5%)	23	12.18 (106.7)	22 (36.7%)	43	13.53 (162.6)
Any treatment-emergent serious adverse events potentially related to study treatment	4 (20.0%)	7	5.86 (68.3)	1 (2.5%)	1	0.74 (134.2)	5 (8.3%)	8	2.47 (202.5)
Any TEAEs potentially related to study treatment	15 (75.0%)	155	59.11 (25.4)	28 (70.0%)	831	71.97 (38.9)	43 (71.7%)	986	66.89 (64.3)
Any TEAEs leading to death	0	0	0 (80.3)	0	0	0 (135.8)	0	0	0 (216.1)
Any TEAEs leading to treatment interruption	5 (25.0%)	33	7.33 (68.2)	13 (32.5%)	54	11.13 (116.8)	18 (30.0%)	87	9.73 (185.0)
Any TEAEs leading to permanent treatment discontinuation	0	0	0 (80.3)	0	0	0 (135.8)	0	0	0 (216.1)
Any TEAEs leading to dose reduction	7 (35.0%)	24	12.86 (54.4)	4 (10.0%)	25	3.31 (120.9)	11 (18.3%)	49	6.27 (175.3)
Any TEAEs leading to dose increase	0	0	0 (80.3)	0	0	0 (135.8)	0	0	0 (216.1)
<p><i>N = Number of patients treated within each group, n (%) = number and % of patients with at least one event in the category, Events = number of events in the category, EAIR = exposure adjusted incidence rate, PY = Patient Year, AE = Adverse event, TEAE = treatment-emergent adverse event</i></p> <p><i>For patients with event, the patient year is calculated as time from first olipudase alfa infusion to the time of first event; for patients without event, it is calculated as the total duration of olipudase alfa exposure. EAIR = 100 x n/PY.</i></p> <p><i>TEAEs potentially related to study treatment include TEAEs that are identified by the investigator as related or possibly related to the study treatment.</i></p> <p><i>Any TEAE leading to treatment interruption is based on AE eCRF page where 'Action Taken = Drug Interrupted' from DFI12712, DFI13412 and LTS13632, as well as based on AE eCRF page where 'Action Taken = Drug Interrupted or Drug withdrawn' from DFI13803.</i></p> <p><i>In DFI13803, 'Drug withdrawn' is filled for any TEAE for which the infusion was interrupted at that visit and not completed. 'Drug Interrupted' is filled for any TEAE for which the infusion was paused until event resolution, and then completed.</i></p>									

The percentage of patients with treatment-related TEAEs was similar in adult and paediatric patients (69.2% and 70.0%, respectively).

Treatment-related AEs were experienced by 43 (71.7%) of all patients (N=60), and the percentage of patients with treatment-related TEAEs was similar in adult and paediatric patients (70.0% [28/40] and 75.0% [15/20], respectively).

Headache (31.7%), Pyrexia (25.0%), Nausea (20.0%), Abdominal pain (15.0%), Vomiting (16.7%), Myalgia (11.7%), Pruritus (10.0%), Urticaria (21.7%), and C-reactive protein increased (10.0%) were the treatment related adverse events most reported.

2.6.8.3. Deaths

As of the data cut-off date (15 March 2021 for DFI12712 ASCEND, and 01 March 2021 for LTS13632), no deaths were reported.

2.6.8.4. Serious adverse event

There were 22 (36.7%) patients who had 43 treatment-emergent SAEs. The treatment-emergent SAEs were most frequently in the SOC infections and infestations (7 patients, 11.7%).

Most frequently reported serious adverse events considered infections in 7 patients (3 adults and 4 children). In the adults, the infections are considered COVID, urinary tract infection and 1 case of gastritis. In the children, 2 cases of gastritis and one of pharyngitis are reported; further, one case of pneumonia was reported. In addition, three SAE were reported more than once: one event of loss of consciousness each in 2 adult patients; one event of gastroenteritis each in 2 paediatric patients; and 2 events of hypersensitivity in 1 paediatric patient.

The percentage of patients with SAEs was higher in paediatric than adult patients (45.0% versus 32.5%, respectively), as were related SAEs (20.0% versus 2.5%) and severe TEAEs (35.0% versus 17.5%).

The higher incidence of SAEs, dose reductions and severe TEAEs in paediatric patients, compared to adults, did not impact the paediatric populations attaining maintenance-level dosing with olipudase alfa.

When compared with placebo no SAE could be identified to be related to the study drug.

2.6.8.5. Laboratory findings

2.6.8.5.1. Haematology

Sporadic fluctuations were observed in mean changes from baseline for haematology parameters in adult and paediatric patients. In general, fluctuations were transient and observed at later timepoints when the number of patients in the analyses was reduced.

2.6.8.5.2. Clinical chemistry

Overall, among those patients with normal lab values for chemistry values at baseline, the most frequently observed divergent values during treatment were high creatinine in 20 (33.3%) patients,

hypoglycaemia in 18 (30.0%) patients and elevated BUN in 14 (23.3%) patients.

For adults, the most frequently observed divergent values during treatment were glucose ≤ 3.9 mmol/L and $< LLN$ in 15 (38.5%) and glucose unfasted ≥ 11.1 mmol/L and fasted > 7 mmol/L in 7 (17.5%) patients.

For children the most frequently observed divergent values during treatment were BUN ≥ 6.4 mmol/L or 18 mg/dL reported in 14 (70.0%) patients and potassium ≤ 3.5 mmol/L in 3 (15.0%) patients.

In general, the fluctuations observed were transient.

2.6.8.5.3. Liver function and coagulation

Overall, there was a decrease in the numbers of adult and paediatric patients with elevated LFT (alkaline phosphate, ALT, AST, direct bilirubin, total bilirubin) values, indicating improved liver function. The transaminase elevations were particularly observed in patients with liver function tests $> 2 \times ULN$ at baseline and during the dose-escalation phase and are likely associated with the initially increased breakdown of accumulated sphingomyelin stored in the liver. Transaminase elevations were no longer or less likely observed during the dose maintenance period. In patients with liver function tests $< 2 \times ULN$ post infusion elevations in AST or ALT were observed in a few patients.

There were no clinically meaningful changes from baseline in coagulation parameters in adult or paediatric patients.

2.6.8.5.4. Urinalysis

There were no clinically meaningful changes in urine pH.

2.6.8.5.5. Vital signs

Overall, there were no meaningful changes in mean vital sign parameters. However changes in vital signs were more often reported in children.

2.6.8.5.6. Electrocardiogram

According to the newly updated ICH E14 guideline, a prolongation of QTc > 500 ms during therapy is a threshold of particular concern in clinical trials. However, as none of the adult patients had an increase ≥ 500 ms in QTc and none of the following clinical events indicative for a QT prolongation were reported: Torsade de Pointes, sudden death, ventricular tachycardia or ventricular fibrillation and flutter, it can be assumed that olipudase alfa treatment does not induce a clinically relevant QT prolongation.

2.6.8.6. Treatment discontinuation

According to the applicant, none of the AEs led to permanent treatment discontinuation during the first 104 weeks of treatment.

Temporary treatment interruption was mostly due to adverse events related to IAR (infusion associated reactions). Other adverse events leading to temporary treatment interruption are considered chance findings (COVID-19 and pneumothorax) or related to the underlying disease (tonsillitis, upper respiratory tract infection, nasopharyngitis and conjunctivitis).

Dose reduction was mainly due to treatment-related pyrexia, liver function disturbances or vomiting.

2.6.8.7. Infusion-associated reactions

IARs occurred in 53.8% of adult patients. The most frequent IARs were headache, nausea, urticaria, pyrexia, and arthralgia. All IARs were mild or moderate, and headache was the most frequently reported moderate IAR. More adult patients had IARs during dose escalation than after.

IARs occurred in 60.0% of paediatric patients. The most frequent IARs were pyrexia, urticaria, vomiting, headache, nausea, C-reactive protein increased, serum ferritin increased, and rash. Three paediatric patients had a serious IAR, anaphylactic reaction (n=1), urticaria and rash (n=1), and hypersensitivity reactions (n=1), respectively. The percentage of paediatric patients with IARs was similar during and after dose escalation.

Overall, 15 (25.4%) patients had 61 hypersensitivity related IARs, including 7 (17.9%) adult patients and 8 (40.0%) paediatric patients. The more than 2-fold higher proportion of paediatric patients suggests that children with ASMD may have a higher risk of hypersensitivity IARs associated with olipudase alfa treatment.

2.6.8.7.1. TEAEs by place of infusion (site or home) in Study LTS13632

Of the 24 patients in Study LTS13632 who had data collected by the CSR cut-off date (10 December 2019), 14 patients (5 adult and 9 paediatric) had home infusions. No TEAEs during the home infusion period were serious, resulted in treatment interruption, discontinuation, or dose reduction.

2.6.8.7.2. TEAEs and infusion-associated reaction analyses by the manufacturing process

There was no consistent association of TEAEs with either process in either group, which suggests that exposure to olipudase alfa from either process did not impact the safety profile of olipudase alfa.

2.6.8.7.3. TEAEs by ADA status

These are discussed under the secondary pharmacology paragraph above.

2.6.8.7.4. ADA-positivity and ADA association with hypersensitivity IARS

In the olipudase alfa safety set, hypersensitivity IARs were reported more frequently in ADA positive patients compared to ADA negative patients respectively, both in adults, 5 (38.5%) versus 2 (7.7%) patients and in paediatric patients 7 (58.3%) versus 1 (12.5%) patients.

Comparing patients who developed ADA with those who did not, respectively, treatment-emergent SAEs were reported in 4 (30.8%) versus 5 (19.2%) adult patients and in 6 (50.0%) versus 3 (37.5%) paediatric patients. For adults, each of the SAE PTs represented a singular event, and no patterns could be identified. In paediatric patients, 3 of 6 ADA positive patients with SAEs had hypersensitivity IARs.

In either adults or paediatric patients, rash, pruritis, and urticaria were the only hypersensitivity IARs reported in more than one ADA positive patient.

2.6.8.7.5. Pre-treatment

Pretreatments for prophylactic management of IARs were not to be used systematically. In patients who experienced moderate to severe or recurrent IARs with evidence of hypersensitivity, pretreatment regimens (eg, antihistamines, antipyretics, glucocorticoids) could be prescribed by the Investigator as per clinical judgment.

2.6.8.8. TEAE and IAR analyses by manufacturing process

The applicant provided data on subject disposition and exposure across manufacturing process.

2.6.8.9. TEAEs by process

By-process results for both adult and paediatric patients appear not very different. Safety in special populations.

2.6.8.9.1. Gender

No trends were observed between male and female patients for the most frequently reported types of TEAEs.

2.6.8.9.2. Age

A higher proportion of infants/early children patients experiencing SAEs, compared to the other 2 age cohorts, and a lower proportion of adolescent patients experiencing IARs, compared to the other 2 age cohorts, no trends among age cohorts were observed for the most frequently reported types of TEAEs.

2.6.8.9.3. Race

No trends were observed between racial or ethnic groups for the most frequently reported types of TEAEs. The limited number of patients in certain racial or ethnic groups makes comparisons between groups difficult to interpret.

2.6.8.10. Safety related to drug-drug interactions and other interactions

See PD assessment.

2.6.8.11. Post marketing experience

At the time of the data cut-off dates, olipudase alfa is not marketed in any country. Expanded access safety experience prior to the data cut-off dates is described below.

One paediatric patient received olipudase alfa as part of an eIND application to prepare planned gene therapy. The patient experienced 2 anaphylactic reactions; treatment was discontinued given the much lower anticipated benefit of gene therapy following the delay of its start and the patient's overall condition.

As of the cut-off dates, 7 patients (6 paediatric and 1 adult patient) have been enrolled in the individual compassionate use programs, and 3 patients (1 paediatric and 2 adult patients) were enrolled in the temporary authorization for use program. Of the 10 patients, one paediatric patient from the US had an SAE. This patient (aged 12 months) also had several events of emesis during infusion and an overnight stay following the infusion, which was part of the patient's baseline medical history. The patient had a feeding tube, and the treating physician did not think the frequency or severity of the emesis had changed compared to baseline.

2.6.8.12. COVID-19

The COVID-19 pandemic did not appear to have an impact on the adverse events (and efficacy; see ancillary assessment) observed in both adult and paediatric patients.

2.6.9. Discussion on clinical safety

The olipudase alfa safety data from 4 clinical studies with multiple-dose regimens were pooled to form the olipudase alfa safety set. The 4 clinical studies include Phase 1b (DFI13412), Phase 1/2 (DFI13803 Peds), Phase 2/3 (DFI12712 ASCEND), and long term (LTS13632) studies. The Phase 1a clinical trial (SPHINGO00605) was not included in the pool because it is a single-dose study. As the safety information retrieved from the single-dose studies is limited, it is considered acceptable not to include this information in the safety database. Two (2) studies (DFI13412, DFI13803 Peds) are completed. The data cut-off dates for the 2 ongoing studies DFI12712 ASCEND and LTS13632 are 15 March 2021 and 01 March 2021, respectively.

The safety database consists of 61 patients. Eleven (11) received a single dose and are not included in the pooled safety. Of the 61 patients included, there are 41 adults and 20 children. Of them, 57 (20 children and 37 adult patients) are still under treatment. Follow up varied from 26 weeks up to 9 years.

Three patients discontinued during the DFI12712 ASCEND ETP (all adults). Two patients in the olipudase alfa/olipudase alfa group (one withdrew consent and the second per patient's decision) the other patient in the placebo/ olipudase alfa group discontinued for reasons related to the COVID-19 pandemic. According to the applicant, there were no discontinuations due to AE by the cut-off date.

The low number of patients makes the pooled database limited and will not allow for robust conclusions, especially for the rarer adverse events. Although it is accepted that the limited database is the only information that can be used in the assessment, the applicant updated the safety information during the procedure. Further, it is considered that a more complete safety profile will emerge during treatment over the years following routine pharmacovigilance.

The majority of TEAEs in the overall safety set were mild or moderate in severity. Fourteen (23.3%) patients had 22 severe TEAEs; loss of consciousness was reported in 2 patients, and all other severe TEAEs were single events occurring in individual patients. As in the pre-clinical study, bradycardia was reported it should be ruled out that the loss of consciousness was due to cardiac conduction dysfunction (for discussion hereof, see below).

Treatment-related TEAEs were experienced by 43 (71.7%) of all patients (N=60), and the percentage of patients with treatment-related TEAEs was similar in adult and paediatric patients (70.0% and 75.0%, respectively). Headache (31.7%), pyrexia (25.0%), urticaria (21.7%), nausea (20.0%), vomiting (16.7%), abdominal pain (15.0%), myalgia (11.7%), pruritus (10.0%), and c-reactive protein increased (10.0%) were the treatment related adverse events most reported.

The most frequently reported TEAEs were reported by a higher proportion of paediatric than adult patients. TEAEs reflect the common cold (e.g., nasopharyngitis, cough, upper respiratory tract infection), infusion reactions (high temperature, rash and erythema like cutaneous manifestations) or failure of treatment. Nevertheless, in paediatric population the most frequently reported TEAEs were: pyrexia (n = 18, 90%), cough (n = 16, 80%), nasopharyngitis (n = 14, 70%), diarrhoea, vomiting, and headache (n = 13 each, 65%). No specific pre-treatment to mitigate the occurrence of pyrexia was stated. Antipyretics with paracetamol, being the most common antipyretic used, were the most frequently reported medications to treat the patients (16 patients received paracetamol, 1 patient received metamizole and paracetamol, 1 patient received paracetamol and salicylic acid). All events

except one were resolved. Therefore, it is agreed with the applicant that based on the data, no specific recommendation for pre-treatment is required. Routine symptom management and antipyretic therapy should be applied if needed.

The applicant was requested to discuss whether there were differences in the safety profile between responders and non-responders (responder was a patient meeting the $\geq 15\%$ improvement in DLco from BL). A comparable incidence of severe TEAEs was reported between both responders and non-responders. More moderate events were reported in the responder group compared to non-responders.

In 30.4% of patients from the responder group and 35.3% from the non-responder group, serious adverse events were reported. No relation between severity of disease at baseline and TEAEs reported was observed.

Diarrhoea, vomiting, and abdominal pain are signs and symptoms of the disease (especially in children) and might be indicative of treatment failure rather than a treatment-related AE. There were 22 (36.7%) patients who reported 43 SAEs. Most reports of serious adverse events considered infections (3 adults and 4 children). In the adults, the infections were COVID, urinary tract infection and 1 case of gastritis. In the children 2 cases of gastritis, 1 of pharyngitis and 1 case of pneumonia were reported. Three SAEs were reported more than once: one event of loss of consciousness each in 2 adult patients; one event of gastroenteritis each in 2 paediatric patients; and 2 events of hypersensitivity in 1 paediatric patient.

The percentage of patients with SAEs was higher in paediatric than adult patients (45.0% versus 32.5%, respectively), as were related SAEs (20.0% versus 2.5%) and severe TEAEs (35.0% versus 17.5%).

A higher proportion of paediatric patients experienced treatment-emergent ADA compared to adult patients. In both groups, hypersensitivity-related IARs occurred in a higher proportion of patients who developed treatment emergent ADA than those who did not.

The majority of the serious and severe events pertained to the SOC "Infections and infestations". However, no specific pattern was observed regarding the nature of these events in the paediatric population compared to the adult population as most of the events were isolated. The reported events do also not suggest that any of them were more often reported as severe or serious in children out of special concerns for that population. All patients recovered from all events cited above.

The effects of ADA and the relation to anaphylactic reactions, hypersensitivity reactions and IAR are depicted in the SmPC.

To date, no death occurred (cut off 15 March 2021).

Compared with placebo, no clear pattern of AE's related to the study drug could be identified.

ASMD patients are known for a high frequency of recurrent respiratory infections (42% of patients presented with a history of pulmonary infections and shortness of breath). Therefore a high frequency of respiratory infections is to be expected. However, the high frequency of infections (about 90%) reported appears higher than reported in the literature. This observation might reflect the different objectives and approach to data collection between clinical studies and natural history studies. The QoL results did not indicate that infections have a relevant detrimental influence on the QoL in children. Further, the infections did not result in aggravations of the underlying conditions.

Temporary treatment interruption was mostly due to IAR related adverse events. Other adverse events leading to temporary treatment interruption are considered chance findings (COVID-19 and

pneumothorax) or related to the underlying disease (tonsillitis, upper respiratory tract infection, nasopharyngitis, conjunctivitis). Dose reduction was mainly due to pyrexia, liver function disturbances or vomiting.

Overall 29 (48.3%) patients developed treatment-emergent ADA. ADA titers were predominantly low, 5 patients, 3 paediatric and 2 adults developed intermediate titers up to 3200. Some of the TEAEs associated with ADA also resemble IARs. Among all 61 patients, 1 (1.7%) paediatric patient had an anaphylactic reaction, the remaining IARs were assessed as mild (30 patients, 50.0%, 302 events) or moderate events (17 patients, 28.3%, 51 events). The most frequently reported IARs were urticaria (8 patients, 13.3%) and headache (6 patients, 10.0%). Mild and moderate IARs were manageable. Based on the evaluations during the clinical trials, the immunogenicity profile of olipudase alfa has been adequately characterized, and the development of ADA does not pose a clinical risk in the majority of patients. Based on the clinical data, no impact of ADAs was observed; from a safety perspective, ADA's did not influence the observed TEAEs. The TEAEs associated with treatment-emergent ADA (anaphylactic reaction, urticaria) resulted in temporary discontinuations of treatment in 2 patients. A higher incidence of treatment-emergent infusion-associated reactions (IARs) and hypersensitivity was seen in patients who developed treatment-emergent ADA versus those who did not. There was no general pattern suggesting a relationship to ADA status. ADA results are not used in the clinical management of patients having symptoms of IAR and hypersensitivity. Therefore, it is agreed with the applicant for all the reasons stated, routine ADA measurement does not provide additional clinical benefit and is not warranted post-authorization. For the moment, these patients will be treated in specialised centra. It is assumed that antibodies will be measured in those patients reporting immunogenetic related reactions. Therefore currently, no risk minimalization measures are deemed necessary.

There was a higher percentage of patients with treatment-emergent hypersensitivity-related IARs in patients who developed treatment-emergent ADA versus those who did not; a similar trend was also seen for IARs. The high frequency of IARs is of concern. The Applicant clarified the risk factors for the occurrence of infusion-related reactions. Overall, the most frequently reported IARs in the overall safety population were headache, nausea, pyrexia, urticaria, arthralgia, vomiting and abdominal pain. The most frequently reported IARs in paediatric patients were pyrexia, urticaria and vomiting.

12 patients meeting the high IAR group criterion were identified and 48 patients who reported less than 10 IAR events. In the paediatric population 4 and 16 patient who reported the high and low IAR were identified. It was shown that in the paediatric population, the high IAR group was younger (mean age 5.9 years) compared to the low IAR group (mean age 8.8 years).

With respect to the disease characteristics, mean age at ASMD diagnosis appeared to be lower in the high IAR group than in the low IAR group.

Overall, it cannot be excluded that age at diagnosis may be associated with a higher incidence of IARs.

With respect to the effectiveness of pre-treatment, no adult patient in study DFI12712 received any pre-treatment during the primary analysis period.

The analysis of the data in paediatric patients in study DFI13803 showed that about 10% of the infusions were associated with a medication to pre-treat or treat an IAR. 4 paediatric patients with pre-treatment were associated with 70 of the 102 IARs. In contrast, the remaining 7 paediatric patients who reported a total of 32 IARs did not receive any pre-treatment. Overall, the number of paediatric patients associated with pre-treatment was low. It is agreed with the applicant that the limited data do not support a general recommendation in the SmPC to administer pre-treatments for prophylactic management of IARs.

Besides the patients that reported anaphylaxis in the clinical studies, 1 paediatric patient-reported two anaphylactic reactions in the named-patient programme. The occurrence of anaphylaxis and desensitisation steps are reflected in the SmPC. Further pre-treatments for prophylactic management of IARs were not to be used systematically but could be prescribed by the Investigator as per clinical judgment. No analysis of the use of pretreatment was provided. The applicant elaborated that no specific pre-treatment to mitigate the occurrence of pyrexia was stated. Routine symptom management and antipyretic therapy should be applied if needed.

The reported loss of consciousness, syncope or presyncope were either isolated or widely separated in time. There was no evidence of QTc prolongation: no female patient had a QTcB or QTcF >470 ms and no male patient had a QTcB or QTcF >450 ms during the study. Further, the following clinical events indicative for a QT prolongation were not reported: Torsade de Pointes, sudden death, ventricular tachycardia or ventricular fibrillation and flutter. Based on the totality of these data, it can be assumed that olipudase alfa treatment does not induce clinically relevant QT prolongation.

Analysis of liver parameters identified no clear pattern of adverse events. As treatment is considered to improve liver parameters, this is not a surprise. However, some transaminase elevations were observed during the dose-escalation phase in patients with liver function tests >2xULN at baseline.

According to the applicant, this might be related to the initially increased breakdown of accumulated sphingomyelin stored in the liver. Transaminase elevations were no longer or less likely observed during the dose maintenance period.

Analysis of haematology identified no clear pattern of adverse events. The frequency of AEs related to thrombocyte function indicates that under treatment the number of reported haemorrhage TEAEs are decreasing. This, however, was not reflected in the changes in function coagulation parameters (Activated Partial Thromboplastin Time (sec), D-Dimer (mg/l), Prothrombin Intl. Normalized Ratio (RATIO), Prothrombin Time (sec)) in adult or paediatric patients nor in the improvement of the platelets (about 25% of the adults with normal platelet count at the start have a platelet count below normal after 1 year of treatment). Further analysis of the patients for whom haemorrhagic events were reported did not show abnormal platelet counts at the time of the event. It should also be noted that over 85% of the adverse events were reported as a bruise or contusion, and this was more commonly observed in paediatric patients than in adult patients, the improvement regarding haemorrhagic events may therefore not only be related to the platelet count and the coagulation parameters. The age distribution might be the confounding factor as adults are less prone to have bruises or contusions.

Experience with treatment in compassionate use programs did not reveal new or unexpected (S)AEs.

Although the duration of exposure in the at-home infusion setting was shorter than that of the at-site infusion setting, the fact that the proportion of patients with TEAEs in the at-home infusion setting is lower still indicates no increase of TEAEs after switching to at-home infusions.

The number of TEAE and IARs across manufacturing processes was considered comparable.

Additional expert consultation

N/A

Assessment of paediatric data on clinical safety

Is included in the general discussion on clinical safety, above.

2.6.1. Conclusions on the clinical safety

The adverse events profile is generally mild to moderate and is, in most cases, manageable. The majority of reported adverse events are related to infections, infusion-related reactions or gastro-intestinal complaints (disease signs and symptoms in children).

For the most frequently reported AEs, a higher proportion of paediatric than adult patients experienced AEs.

To date, no deaths occurred (cut off 15 March 2021).

There was no evidence of QTc prolongation: no female patient had a QTcB or QTcF >470 ms, and no male patient had a QTcB or QTcF >450 ms during the study.

The proportion of patients with TEAEs in the at-home infusion setting is lower, indicating no greater increase of TEAEs after switching to at-home infusions.

The number of TEAE and IARs across manufacturing process was considered comparable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	Immunogenicity: <ul style="list-style-type: none"> • Infusion associated reactions (IARs), • Systemic hypersensitivity including anaphylactic reactions, • Anti-Drug Antibody (ADA) mediated hypersensitivity reactions.
Important potential risks	Medication errors in home infusion setting Foetal toxicity
Missing information	Use in lactating women Long-term safety (beyond 2 years)

ADA: Anti-Drug Antibody; IAR: Infusion Associated Reaction.

2.7.2. Pharmacovigilance plan

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
LTS13632 - A long-term study to assess	To obtain data regarding the safety and efficacy of	<ul style="list-style-type: none"> • Immunogenicity: Infusion Associated Reactions (IARs), 	First patient First Visit:	04-Dec-2013

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
the ongoing safety and efficacy of olipudase alfa in patients with ASMD Ongoing	olipudase alfa in patients with ASMD who are exposed to long-term treatment with olipudase alfa. <u>Primary objective:</u> To assess the long-term safety of olipudase alfa in patients with ASMD. <u>Secondary objective:</u> To assess the maintenance of effect of olipudase alfa and to characterize the PDs and PKs following long-term administration.	systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. <ul style="list-style-type: none"> Medication errors in home infusion setting. Long-term safety (beyond 2 years). 	First Interim Report: Second Interim Report: Last patient Last Visit: Final study Report submission planned:	Cut-off date 10-Dec-2019 Cut-off date 01-Mar-2021 included in the initial MAA Anticipated Feb-2024 Aug-2024
DFI12712 ASCEND A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat-dose study to evaluate the efficacy, safety, PDs, and PKs of olipudase alfa in patients with ASMD Ongoing	To evaluate the efficacy, safety, PDs and PKs of olipudase alfa in adult patients with ASMD. <u>Primary objectives:</u> To evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD by assessing changes in: <ul style="list-style-type: none"> Spleen volume as measured by abdominal MRI. Infiltrative lung disease as measured by the pulmonary function test, diffusing capacity of the lung for carbon monoxide. <u>Secondary objectives:</u> <ul style="list-style-type: none"> To confirm the safety of olipudase alfa administered intravenously once every 2 weeks for 52 weeks. To characterize the effect of olipudase 	<ul style="list-style-type: none"> Immunogenicity: Infusion Associated Reactions (IARs), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions. Medication errors in home infusion setting. Long-term safety (beyond 2 years). 	First patient First visit: Last patient Last Visit for PAP: First Interim Report: Second Interim Report: Last patient last visit for ETP: Final study Report submission planned:	17-Dec-2015 17-Oct-2019 Cut-off date 17-Oct-2019 Cut-off date 15-Mar-2021 included in the initial MAA Anticipated Oct-2023 Jun-2024

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	<p>alfa on the patient perception related to spleen volume as measured by SRS after 52 weeks of study drug administration.</p> <ul style="list-style-type: none"> • To characterize the effect of olipudase alfa on the following endpoints assessed sequentially: <ul style="list-style-type: none"> - The effect of olipudase alfa on liver volume after 52 weeks of study drug administration - The effect of olipudase alfa on platelet count after 52 weeks of study drug administration - The effect of olipudase alfa after 52 weeks of study drug administration on fatigue - The effect of olipudase alfa after 52 weeks of study drug administration on pain - The effect of olipudase alfa after 52 weeks of study drug administration on dyspnea 			

ADA: Anti-Drug Antibody; ASMD: Acid Sphingomyelinase Deficiency; ETP: Extension Treatment Period; IAR: Infusion Associated Reaction; MAA: Marketing Authorization Application; MRI: Magnetic Resonance Imaging; PAP: Primary Analysis Period; PD: Pharmacodynamic; PK: Pharmacokinetic; SRS: Splenomegaly Related Score.

2.7.3. Risk minimisation measures

Safety concern	Risk minimization measures
<p>Immunogenicity:</p> <ul style="list-style-type: none"> • Infusion Associated Reactions (IAR), • Systemic hypersensitivity including anaphylactic reactions, 	<p>Routine risk minimization measures:</p> <p>Sections 4.2, 4.3, 4.4 and 4.8 of the SmPC.</p> <p>Sections 2, 3 and 4 of the PL.</p> <p>Legal Status: Restricted medical prescription.</p>

Safety concern	Risk minimization measures
<ul style="list-style-type: none"> • Anti-drug antibody (ADA) mediated hypersensitivity reactions 	<p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • A HCP Guide for HCPs in home infusion setting including nurses. • A Patient Card for patients/caregivers.
<p>Medication errors in home infusion setting</p>	<p>Routine risk minimization measures: Legal Status: Restricted medical prescription.</p> <p>Additional risk minimization measures: A HCP Guide for HCPs in home infusion setting including nurses.</p>
<p>Foetal toxicity</p>	<p>Routine risk minimization measures: Section 4.6 of the SmPC. Section 2 of the PL. Legal status: Restricted medical prescription.</p> <p>Additional risk minimization measures: A Patient Card for patients/caregivers.</p>
<p>Use in lactating women</p>	<p>Routine risk minimization measures: Section 4.6 of the SmPC. Section 2 of the PL. Legal status: Restricted medical prescription.</p> <p>Additional risk minimization measures: None</p>
<p>Long-term use (beyond 2 years)</p>	<p>Routine risk minimization measures: Section 4.8 of the SmPC. Legal status: Restricted medical prescription.</p> <p>Additional risk minimization measures: None</p>

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR

cycle with the international birth date (IBD). The IBD is 28.03.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.9.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant requesting to have English only for the outer carton together with the immediate labelling and the package leaflet in Sweden, Denmark, Finland and Norway. This request has been found acceptable by the QRD Group for the following reasons :

Xenpozyme is indicated for the treatment of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients. This is an orphan medicinal product. The main rationale for this request is the currently very small number of patients in need of treatment in the Nordic countries.

The treatment with Xenpozyme should only be initiated and supervised by a healthcare professional experienced in the management of ASMD. Local language versions of the package leaflet and SmPC; as well as local language versions of RMP stipulated risk minimisation materials (Healthcare professionals guide, Patient guide and Patient card) will also be available via the QR code/URL displayed on the outer packaging and the package leaflet for all EU country packs.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing information to Healthcare Professionals, patients and caregivers has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

Statutory information

- Approved regulatory information, including the patient information leaflet (PIL) and Summary of Product Characteristics (SmPC);
- Educational material as outlined in the Risk Management Plan (healthcare professionals guide and patient card);
- Access to the national reporting systems for adverse events websites;
- Contact numbers of the local representative of the MAH;

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xenpozyme (olipudase alfa) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Olipudase is being developed for the treatment of non-CNS manifestations of ASMD, a rare and potentially life-threatening hereditary lysosomal storage disorder that can affect vital organs (e.g., lung, liver, CNS) and which results from the insufficient activity of the lysosomal hydrolase ASM, caused by various mutations in the *smpd1* gene. The overall estimated incidence is 0.4 to 0.6 in 100,000 live births, and although ASMD is rare, this may be an underestimate of the true incidence due to under- or misdiagnosis.

Patients are presenting with a broad spectrum of disease manifestations, ranging from a rapidly progressive and fatal neurodegenerative disease course in patients with primary CNS involvement (ASMD type A) to more chronic manifestations with variable degrees of visceral organ and CNS involvement (ASMD types B and A/B). In patients with ASMD type B or type A/B, the disease burden, both with respect to morbidity and mortality, is primarily driven by the degree of impairment of lung and liver function and complications due to excessive enlargement of organs, with respiratory complications, liver failure and bleeding events being key drivers of early mortality, development delays and failure to thrive prominent in children.

3.1.2. Available therapies and unmet medical need

There is no disease-specific treatment that can modify the disease or slow the rate of progression. Patients can only be provided palliative and supportive care for managing symptomology. Complications of the disease, such as progressive respiratory impairment and recurrent respiratory infections, liver cirrhosis, or splenomegaly with increased risk of splenic rupture, may mandate invasive therapeutic interventions that by themselves are associated with substantial risks (e.g., total lung lavage, liver transplantation, splenectomy).

Several attempts have been made to use cellular and solid organ transplantation as an indirect source of ASM replacement therapy. However, these interventions are also associated with substantial risks, and the experience to date with cell and organ transplantation is very limited.

Therefore, corrective treatment for ASMD remains an unmet medical need.

3.1.3. Main clinical studies

The main evidence to support the benefit-risk assessment for olipudase alfa is derived from three clinical trials in patients with ASMD:

- DFI12712 ASCEND, a randomized placebo-controlled pivotal trial in 36 adult patients with ASMD type B and type A/B, generated placebo-controlled data on the effects of olipudase alfa on pulmonary function and spleen size and several other parameters of organ impairment due to ASMD, as well as the safety and tolerability of olipudase alfa. The initial 52-week primary analysis period of this study included a dose escalation phase followed by maintenance therapy of olipudase alfa at 3 mg/kg every 2 weeks IV, or matching placebo. Thereafter, all patients were switched over to an ongoing ETP with open-label olipudase alfa for an additional 52 weeks. After week 104, patients could further receive olipudase alfa treatment in the long-term follow-up part of this pivotal study.
- DFI13803 Peds, a single-arm study in 20 paediatric patients (4 adolescents, 9 children, 7 infants/early child), is the major study to support the paediatric indication. This 64-week study deployed a similar olipudase alfa dosing regimen as DFI12712 ASCEND. While the main focus was on safety and pharmacokinetics, efficacy endpoints similar to those in DFI12712 ASCEND were assessed as well.
- An additional long-term follow-up study, LTS13632 addressed the safety and persistence of efficacy over a longer duration of olipudase alfa treatment at 3 mg/kg every 2 weeks IV in paediatric patients enrolled from DFI13803 Peds and 5 adult patients study DFI13412.

Overall, 5 clinical trials with olipudase alfa included a total of 67 patients with ASMD (47 adults, 20 paediatric patients). Three clinical trials (SPHINGO00605 (an early single-dose Ph1a study), DFI13412, and DFI13803 Peds) were completed, and 2 clinical trials (DFI12712 ASCEND and LTS13632) are currently ongoing. These clinical trials are complemented by two completed non-interventional natural history studies (NHC), MSC12840, a prospective, cross-sectional, natural history survey in 59 patients (29 adults, 30 paediatric patients) with ASMD, and SPHINGO00302, a retrospective natural history study of 100 patients (49 pre-pubertal) with ASMD. The two NHC studies (MSC12840 and SPHINGO00302) are used to compare the clinical data observed in the paediatric patients in study DFI13803. Further, the NHC studies will be helpful to inform on the disease course in ASMD patients.

3.2. Favourable effects

Pharmacodynamic

In the pivotal study, in adults (DFI12712; n=36), for the most important PD parameters (change from BL to week 52) the LS mean difference (SE) placebo (n=18) vs olipudase alfa (n=18) were for the % change in chitotriosidase (nmol/mL/h) -42.4 (10.1); % change in plasma lyso-sphingomyelin (lyso-SPM) (ug/L) -72.7 (5.8); and % change in plasma ceramide (mg/L) -36.1 (7.8). All changes between placebo and olipudase alfa were statistically significantly different. When placebo patients were crossed over at week 52 to olipudase alfa treatment similar reductions were observed. The reductions that were reached were maintained up to week 238, although patient numbers were limited. In the paediatric open-label single-arm study (DFI13803) similar results (change from baseline to week 52) for the PD parameters were seen.

Percentage predicted DLco

The LS mean % change from BL to week 52 in % predicted DLco (95% confidence interval (CI)) was 3.0 (-4.0, 10.0) and 22.0 (15.2, 28.8), for placebo and olipudase alfa respectively (p=0.0004). The primary endpoint was met.

A prespecified responder analysis for DLco in adults showed that 5/18 treated patients met the criterion of $\geq 15\%$ change from BL to week 52, while none of the placebo patients was a responder. After cross-over (week 52 to 104) in the placebo/olipudase alfa group, 8/15 patients were responders and 7/15 in the olipudase alfa/olipudase alfa group.

Reduction of spleen volume

The LS mean % change (BL to week 52) in spleen volume (CI) was 0.5 (-4.6, 5.6) and -39.5 (-44.3, -34.5), for placebo and olipudase alfa respectively (difference -39.9 (-47.1, -32.8), p<0.0001). This second primary endpoint was met.

Reduction of liver volume

The LS mean % change (BL to week 52) in liver volume (CI) was -1.5 (-6.6, 3.7) and -28.0 (-33.1, -23.0), for placebo and olipudase alfa respectively (p<0.0001).

Platelet count

The LS mean % change (BL to week 52) in platelet count (CI) was 2.5 (-6.0, 11.0) and 16.8 (8.8, 24.0), for placebo and olipudase alfa respectively (p<0.0001).

The results on DLco, spleen and liver volume, and platelet count observed in the pivotal study are repeated for the patients crossing over from placebo to olipudase alfa receiving 52 weeks of olipudase alfa treatment (week 52 to week 104). For the overall paediatric group (n=20), reductions similar to those observed in adults were seen.

Other pulmonary tests

In line with the observed improvement in DLco, the other pulmonary tests (FVC, FEV₁ and TLC) - tertiary - showed relevant improvements in the PAP. In the ETP these results were sustained. The data on the key pulmonary imaging parameters (change from baseline to week 52) in adults treated with olipudase alfa in study DFI12712 and DFI13803 suggest improvements in the lungs. Similar results were observed in paediatrics.

Quality of life

The Patient global impression of change scale (PGIC) in adults showed a difference for the item on the shortness of breath. Patients in the olipudase alfa group (n=17) reported greater improvement (LS mean = 1.11) than the placebo group (n = 16, LS mean = 0.30). In addition, for the shortness of breath item, the responder rate in the olipudase alfa group was higher than in the placebo group (61% versus 28%).

PedsQL Generic Core Scale and Multidimensional Fatigue Scale showed some improvements on the majority of subtests at Week 52 compared to baseline. The PedsQL Multidimensional Fatigue Scale showed positive changes at Week 52, in the overall group compared to baseline in 3 of 4 subtests in both child and parent reports. In addition, the Week 52 mean positive change from baseline on the Cognitive subscale showed improvements on the child reports, but not on the parent-reports (highest baseline mean).

Ergometry

The applicant conducted a post-hoc analysis on treadmill ergometry (CPET), which indicated a difference between olipudase alfa treated and placebo-treated patients in favour of olipudase alfa. When patients from placebo crossed over to olipudase alfa, results were repeated.

Cycle ergometry was performed in some paediatric patients (3 adolescents; 2 children). In the 5 patients who performed the test, a trend toward improvement on cycle ergometry was observed in the following parameters: mean maximum workload (+31.2 Watts overall at Week 52), mean percent predicted Maximum Workload (+3.4% absolute change overall at Week 52), mean working time (+2.8 min overall at Week 52), mean maximum O₂ Uptake (+691.8 mL/min overall at Week 52), and mean maximum CO₂ Output (+561.2 mL/min overall at Week 52).

Additional efficacy endpoints in paediatrics

Additional efficacy parameters were evaluated in paediatrics, e.g. height Z-score, one age (by hand X-Ray). The changes from baseline to week 52 showed improvement suggestive for growth catchup.

Further, paediatric data collected over 52 weeks in the prospective NHC study (MSC1284b0) was compared to the efficacy data – collected over 52 weeks – in paediatric patients from study DFI13803. It is noticed that the paediatric patients treated with olipudase alfa showed significant improvements in most efficacy parameters compared, including reduced spleen volume (mean difference 46.26%), reduced liver volume (48.22%), and increased platelet count (45.78%), and increased height z-score (0.64).

Long term follow-up study LTS13632

For the clinical parameters (reduction of spleen volume, percentage predicted DLco, reduction of liver volume and platelet count), the improvements reached during the preceding studies DFI13803 and DFI113412 were maintained up to month 60. In the different paediatric age cohorts, improvements were similar. When comparing the 5 adults with the overall paediatric group (n=20) improvements were similar as well.

Ergometry

By Month 54, the mean (SD) workload increased by 12.4 (31.9) Watts (range, -22 to 61) for the 5 adult patients. By Month 30, the mean (SD) workload increased by 87 (34) for 3 paediatric patients (range, 61 to 125), while the percent predicted workload improved by 10.7%, (SD= 21.8, range, -7% to 35%).

In both groups, further improvements in mean O₂ uptake and CO₂ output were seen.

3.3. Uncertainties and limitations about favourable effects

A total of 67 patients with ASMD (47 adults, 20 paediatric patients) were included in the studies; this number is limited. All patients were either ASMD type B, or ASMD type A/B. No patients with ASMD type A were included in the studies. ASMD type A patients are excluded from the indication, given that olipudase alfa does not cross the BBB, and the severe neurological problems cannot be treated.

Nine out of 60 patients developed neutralising antibodies (NAbs) that inhibited catalytic activity.

Pivotal study DFI12712 (adults only)

One patient in the placebo group did not complete the PAP due to poor compliance; therefore in the ETP 35 of 36 patients remained in the study. As the long-term follow-up of the pivotal study is ongoing, not all patients (29 out of 35 patients) have reached the end of week 104 at the data cut-off.

Between week 156 and week 208, 11 out of 35 patients received treatment. Four patients received olipudase alfa for more than 208 weeks.

The LS mean change (SE) for the FACIT Dyspnoea symptom score from baseline to Week 52 was not different between the olipudase alfa and placebo groups; -5.9 (1.7) versus -6.8 (1.9), respectively.

There were no differences observed for the other PGIC items except for dyspnoea at Week 52. Similar trends were observed on the PGIC items during the long term follow-up when placebo patients crossed over to olipudase alfa treatment.

The results for the other QoL questionnaires about dyspnoea showed contrasting results.

Paediatric study DFI13803

The paediatric study was an open-label study without a control arm in 20 patients. The primary objective of the study was to assess safety.

DLco is not measured in infants.

Long term follow-up study LTS13632

Only a limited number of patients were included in the long term follow-up; 5 adults patients from study DFI13413 and 20 paediatric patients from DFI13803.

During the LTF, further improvements in ergometry values from baseline were observed. However, data is available from 5 paediatric patients, which is too limited to draw firm conclusions.

In paediatric patients up to month 30, improvements in the PedsQL Multidimensional Fatigue Scale were observed (self- and caregiver reported). Beyond month 30, no relevant improvements were seen. The clinical relevance of the the PedsQL Multidimensional Fatigue Scale is unknown.

Comparative study for paediatric data

The efficacy data from BL to week 52 was compared to the data collected in the prospective NHC study MSC12840, which included 30 paediatric patients. The data from 4 paediatric patients and 10 adolescent patients in the MSC12840 study were compared with data from 11 paediatric patients and 4 adolescent patients in DFI13803. At BL there was a disbalance in age.

No difference in DLco % predicted at baseline was observed in the two cohorts (MSC12840, ~52; DFI13803, ~54). The applicant mentioned that in the % change from BL for DLco the large difference in SD (study MSC12840 was 50.9 and in DFI13803 this was 29.1) might be explained by the differences in study design.

3.4. Unfavourable effects

The olipudase alfa safety data from 4 clinical studies (Phase 1b (DFI13412), Phase 1/2 (DFI13803), Phase 2/3 (DFI12712), and long-term study LTS13632) with multiple-dose regimens were pooled to form the olipudase alfa safety set. The Phase 1a clinical trial (SPHINGO00605) was not included in the safety pool.

The safety database consists of 61 patients. Eleven (11) received a single dose and are not included in the pooled safety. Of the 61 patients included, there are 41 adults and 20 children. Of them, 57 (20 children and 37 adult patients) are ongoing in clinical studies.

Three patients discontinued during the DFI12712 ETP (all adults).

Follow-up varied from 26 weeks up to 9 years.

The majority of TEAEs in the overall safety set were mild or moderate in severity. Fourteen (23.3%) patients had 22 severe TEAEs; severe loss of consciousness was reported in 2 patients, and all other severe TEAEs were single events occurring in individual patients.

Most frequently reported common AE for the overall population were: headache (65.0%), nasopharyngitis (51.7%), pyrexia (50.0%), cough (46.7%), upper respiratory tract infection (45.0%), nausea (43.3%), abdominal pain (41.7%), diarrhoea (40.0%), arthralgia (33.3%), abdominal pain upper (31.7%), back pain (31.7%), oropharyngeal pain (30.0%) and vomiting (30.0%).

Treatment-related TEAEs were experienced by 43 (71.7%) of all patients (N=60), and the percentage of patients with treatment-related TEAEs was similar in adult and paediatric patients (70.0% and 75.0%, respectively). Headache, pyrexia, urticaria, nausea, vomiting, abdominal pain, myalgia, pruritus, and C-reactive protein increased were the treatment-related adverse events most reported. For the most frequently reported TEAEs, a higher proportion of paediatric than adult patients experienced TEAEs potentially reflecting the common cold (e.g., nasopharyngitis, cough, upper respiratory tract infection). Paediatric patients were also more likely to report pyrexia, diarrhoea, vomiting, and abdominal pain.

Most adverse events can be related to infusion reactions (high temperature, rash and erythema like cutaneous manifestations) or treatment failure.

There were 22 (36.7%) patients who reported 43 SAEs. Most reports of serious adverse events considered infections in 7 patients (3 adults and 4 children). Three SAE were reported more than once: 1 event of loss of consciousness each in 2 adult patients; 1 event of gastroenteritis each in 2 paediatric patients; and 2 events of hypersensitivity in 1 paediatric patient.

The percentage of patients with SAEs was higher in paediatric than adult patients (45.0% versus 32.5%, respectively), as were related SAEs (20.0% versus 2.5%) and severe TEAEs (35.0% versus 17.5%).

To date, no death occurred (cut off 15 March 2021).

None of the AEs led to a permanent treatment discontinuation. Temporary treatment interruption was mostly due to IAR related adverse events. Other adverse events leading to temporary treatment interruption are considered chance findings (COVID-19 and pneumothorax) or related to the underlying disease (tonsillitis, upper respiratory tract infection, nasopharyngitis and conjunctivitis). Dose reductions were mainly due to pyrexia, liver function disturbances or vomiting.

Overall, 29 (48.3%) patients developed treatment-emergent ADA. ADA titers were predominantly low. Some of the TEAEs associated with ADA also resemble IARs. Among all 61 patients, 1 paediatric patient had an anaphylactic reaction; the remaining IARs were assessed as mild (30 patients, 50.0%, 302 events) or moderate events (17 patients, 28.3%, 51 events). The most frequently reported IARs were urticaria (8 patients, 13.3%) and headache (6 patients, 10.0%). From the named-patient program, another patient was reported with an anaphylactic reaction.

The reported loss of consciousness, syncope or presyncope were either isolated or widely separated in time. There was no evidence of QTc prolongation: no female patient had a QTcB or QTcF >470 ms, and no male patient had a QTcB or QTcF >450 ms during the study.

Analysis of liver function identified no clear pattern of adverse events. However, some transaminase elevations were observed during the dose-escalation phase in patients with liver function tests >2xULN at baseline. Transaminase elevations were no longer or less likely observed during the dose maintenance period.

Analysis of haematology identified no clear pattern of adverse events. The frequency of haemorrhage TEAEs is decreasing. The changes in function coagulation parameters (Activated Partial Thromboplastin Time (sec), D-Dimer (mg/l), Prothrombin Intl. Normalized Ratio (RATIO), Prothrombin Time (sec)) in adult or paediatric patients did not change nor did the platelet count; about 25% of the adults with normal platelet count at the start have a platelet count below normal after 1 year of treatment.

Experience with treatment in compassionate use programs did not reveal new or unexpected (S)AEs.

The proportion of patients with TEAEs in the at-home infusion setting is lower compared to in-clinic infusions.

The number of TEAE and IARs across manufacturing processes is considered comparable.

3.5. Uncertainties and limitations about unfavourable effects

The low number of patients makes the pooled database limited and will not allow for robust conclusions, especially for the rarer adverse events. Further, it is considered that a more complete safety profile will emerge during treatment over the years.

ASMD patients are known for a high frequency of recurrent respiratory infections (42% of patients presented with a history of pulmonary infections and shortness of breath). Although a high frequency of respiratory infections is to be expected, the reported frequency of infections (about 90%) is high when compared to the literature.

Besides the patients in the various studies reporting anaphylaxis, also in the name-patient programme 1 paediatric patient reported anaphylactic reactions (twice). The occurrence of anaphylaxis is reflected in the SmPC. Among the patients with anaphylaxis, 1 patient was desensitized. The desensitisation procedure for this patient required several steps, which were detailed by the applicant.

The frequency of haemorrhage TEAEs is decreasing during treatment. The changes in function coagulation parameters (Activated Partial Thromboplastin Time (sec), D-Dimer (mg/l), Prothrombin Intl. Normalized Ratio (RATIO), Prothrombin Time (sec)), however, did not change nor did the platelet count (about 25% of the adults with normal platelet count at start have a platelet count below normal after 1 year of treatment) these apparent contradictory results are not discussed or analysed.

Although the duration of exposure in the at-home infusion setting was shorter than that of the at-site infusion setting, the fact that the proportion of patients with TEAEs in the at-home infusion setting is lower might indicate no greater increase of TEAEs after switching to at-home infusions.

3.6. Effects Table

Table 25. Effects Table for Xenpozyme (data cut-off: 15 March 2021).

Effect	Short Description	Unit	statistics	Control	Treatment	Uncertainties/ Strength of evidence	References
Favourable Effects							
Change from BL to week 52 in DLco % predicted of normal	DLco	%	LS mean (CI)	3.0 (-4.0, 10.0)	22.0 (15.2, 28.8)	SoE: DB RCT PLC trial; primary EP met (p=0.0004); placebo patients who crossed over to olipudase alfa showed similar improvement in DLco (change wk 52 to 104); improvements in FVC (difference ^s 2.3 (95 CI 0.7, 9.9)), FEV ₁ (difference ^s 2.0 (95 CI -0.3, 8.1)), and chest x-rays were consistent with result of primary EP. Unc: -	Study DFI12712 (adults only)
				-	Overall population (n=9 ^a): 32.9 (13.4, 52.5)	SoE: difference from BL p=0.0053; improvements in other lung function tests (FVC, FEV ₁ , TLC) also showed improvements; pulmonary imaging showed improvements. Unc: open label study, no control arm.	Study DFI13803 (paediatrics)
Change from BL to week 52 in spleen volume	Spleen volume	MN	LS mean (CI)	0.5 (-4.6, 5.6)	-39.5 (-44.3, -34.5)	SoE: DB RCT PLC trial; primary EP met (p<0.0001); placebo patients who crossed over showed a similar reduction in spleen volume; change wk 52 to 104); other EPs (reduction of liver volume, improvements of platelets, reductions in sphingomyelin (PD) were all consistent with the primary EP. Unc: spleen reduction of 30% was borrowed from Gaucher disease; whether this is also relevant for ASMD is unknown.	Study DFI12712 (adults only)
				-	Overall population (n=20) -49.2 (-53.4,-45.0)	SoE: difference from BL p<0.0001; in the 3 age cohort the values for LS mean were similar to the overall group. Similar reductions were observed for liver volume, liver function test showed a relevant reduction, similar for PD parameters, platelet count improved. Unc: open label study, no control arm.	Study DFI13803 (paediatrics)
Change from BL to week 52 Patient global impression of change scale	PGIC	score	LS mean	0.3	1.1	SoE: placebo controlled study Unc: no other improvements in the PGIC items were observed; although some improvement in dyspnoea score was observed in the FACIT-dyspnoea score, the difference between treatment and placebo was similar. The clinical relevance of the scores is unknown.	Study DFI12712 (adults only)

Effect	Short Description	Unit	statistics	Control	Treatment	Uncertainties/ Strength of evidence	References
Change from BL to week 52 in PedsQL Multidimensional Fatigue Scale	PedsQL	score		-	+13.3	SoE: BL score 73.5 (a 100-point scale; higher indicates less problems; month 18 (12.0), month 36 (9.7). From month 30 to month 48 no difference was noted. A similar trend was observed in the parents/caregiver reports. Unc: -	Study DFI13803 (paediatrics) and long term study LTS13632
Unfavourable Effects							
Infections	Frequency of infections	%	descriptive	About 42%	About 90%	SoE: the frequency of the treated patients is based on the pooled safety population Unc: the reference is based on literature	Pooled safety population
anaphylaxis	Frequency per patient	N	descriptive	none	2	SoE: pooled safety population Unc: only reported in children	Pooled safety population
ADA's	frequency	%	descriptive	none	29 (48.3%)	SoE: pooled safety population Unc: effects on safety profile and PK are unknown	Pooled safety population

Abbreviations: BL, baseline; DB, double-blinded; CI, 95% confidence interval; DLco, diffusing capacity for carbon monoxide; EP, endpoint; MN, multiple levels of normal; PD, pharmacodynamic; PLC, placebo-controlled RCT, randomised clinical trial; SoE, Strength of evidence; Unc, uncertainty; wk, week
Notes: #) DCLO was only measured in the adolescents (n=4) and the child (n=6) cohort; \$) difference placebo versus olipudase alfa over 52 weeks

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is no disease-specific treatment that can modify the disease or slow the rate of progression in ASMD. Therefore, there is a high unmet medical need. Only 67 ASMD patients with type A/B and B were included in the clinical program. Given that ASMD is an orphan disease, this is acceptable.

The indication is restricted to the treatment of ASMD type A/B and B patients, which is agreed. The youngest patients were diagnosed around birth and some patients treated in the first months of life, hence no age restriction has to be included in the indication. Although olipudase alfa – as shown by the QSP model – can also be used to treat organomegaly in ASMD type A patients, it does not cross the BBB, and thus no large beneficial effects in survival for these type A patients are to be expected.

Plasma ceramide, a major catabolite of olipudase alfa-mediated metabolism of sphingomyelin, increased transiently following each olipudase alfa infusion in both adult and paediatric patients, signifying olipudase alfa bioactivity. A consistent decrease of mean plasma ceramide along with plasma Lyso-SPM, and other PD markers (chitotriosidase, CCL18, and ACE) was observed with olipudase alfa treatment over time. These reductions are consistent with the debulking of sphingomyelin from tissues which are evidenced by liver biopsies and add to the proof of concept.

In line with the observed reductions in PD parameters, under continued olipudase alfa treatment it was demonstrated that DLco % predicted improved, and spleen and liver volume decreased. Improvement in DLco % predicted ($\geq 15\%$ improvement from BL), and the reduction of spleen volume ($\geq 30\%$ reduction from BL) were both considered primary endpoints; both endpoints were met and the differences are clinically relevant and meaningful. At data cut-off, not all patients (only 29/35 patients) treated in the pivotal study reached week 104, i.e., the end of the ETP phase. One patient from the placebo group discontinued the PAP due to poor compliance, leaving 35 patients in the clinical program. Beyond week 156, data from 11/35 patients is available. Therefore, no firm conclusion on the long-term efficacy can be drawn; however, there is at least a positive trend which is reassuring that the treatment effect of olipudase alfa is maintained long term. Efficacy results in adults and paediatrics were similar. Despite the absence of a control arm and the limited number of paediatric patients, the PD and efficacy data is indicative of improvement; moreover, based on the literature and the natural history studies, no spontaneous improvement is observed in ASMD patients.

These positive results on PD parameters, organomegaly and lung function do not seem to have a large effect on the reported dyspnoea in these adult patients; the improvement is similar in both the treated and placebo groups. This observation might be explained by the fact that the majority of these patients have been living with ASMD for several years (age at diagnosis and age at baseline trial entry). Therefore, they may have adapted their lifestyles to become more sedentary. In paediatric patients, QoL and fatigue score results were more pronounced. Subgroup analyses based on the dyspnoea status at BL and baseline ILD severity showed no difference in treatment effect.

In both adults and paediatric patients under continued treatment, improvement in O₂ capacity (measured by ergometry) was observed, which indicates an increase in workload capacity. Improvements in ergometry were maintained long-term; the number of patients is limited.

Safety

The low number of patients, which is acceptable for such a rare disease, limits the safety database and will not allow for robust conclusions.

Based on the evaluations during the clinical trials, the immunogenicity profile of olipudase alfa has been adequately characterized and the development of ADA does not pose a clinical risk in the majority of patients. Based on the clinical data no impact of ADAs was observed, from a safety perspective ADA's did not have an influence on the observed TEAEs. The TEAEs associated with treatment emergent ADA (anaphylactic reaction, urticaria) resulted in temporary discontinuations of treatment in 2 patients. A higher incidence of treatment emergent infusion-associated reactions (IARs) and hypersensitivity was seen in patients who developed treatment emergent ADA versus those who did not. There was no general pattern suggesting a relationship to ADA status. ADA results are not used in the clinical management of patients having symptoms of IAR and hypersensitivity. Therefore, the routine measurement of ADA's is not required. A high percentage of anaphylaxis was reported with one patient following a successful desensitizing procedure. This desensitisation consisted of multiple specific steps. Given that desensitisation steps are specific, and remotely occurred, it is mentioned in the SmPC to contact the MAH in case of hypersensitivity. This is agreed.

The reported loss of consciousness, syncope or presyncope were either isolated or widely separated in time. There was no evidence of QTc prolongation. Further, the following clinical events indicative of a QT prolongation were not reported: Torsade de Pointes, sudden death, ventricular tachycardia, ventricular fibrillation, and flutter. Based on the totality of these data, it can be assumed that olipudase alfa treatment does not induce clinical relevant QT prolongation.

3.7.2. Balance of benefits and risks

The indication in ASMD type A/B and B patients is acceptable. Although the limited database precludes robust conclusions on all outcomes, the applicant has sufficiently demonstrated that under continued treatment with olipudase alfa, improvement of DLco and reduction of spleen and liver volume were obtained. The improvements and reductions are considered clinically relevant. Additional observations in improvements of other lung parameters, pharmacodynamic endpoints, and QoL contribute to the totality of clinical evidence. The adverse events profile is generally mild to moderate and manageable in most cases. Most reported adverse events are related to infections, infusion-related reactions or gastrointestinal complaints (disease signs and symptoms in children).

The benefit/risk for olipudase alfa is positive.

3.7.3. Additional considerations on the benefit-risk balance

The Applicant is applying for a full standard marketing authorisation conform Article 8.3 of Directive 2001/83/EC. By restricting the indication to ASMD type A/B and B patients, and based on the criteria below, it can be concluded that the clinical data submitted by the applicant is considered comprehensive. Therefore, Xenpozyme can be granted a full MAA conform Article 8.3 of Directive 2001/83/EC.

Regulatory options (e.g. criteria) for approval (standard marketing authorisation, conditional marketing authorisation, authorisation under exceptional circumstances).

1. Quality of evidence (including feasibility considerations)

From an internal validity perspective, one placebo-controlled study has been conducted in 36 patients comparing olipudase alfa to placebo (52 weeks of placebo or olipudase alfa followed by OLE of 52 weeks and LTF). Furthermore, a smaller single-arm paediatric study (n=20) and a dose-finding study in 5 adult patients, and an ongoing long-term extension study (includes the 20 paediatrics and 5 adults) were submitted. Safety information was available for 61 patients.

Given the rarity of the disease, this is considered reasonable. Therefore, it can be concluded that the "Quality of evidence" is as good as can be expected.

2. Efficacy: precision of effect size

Both the primary endpoints, e.g. change from baseline to week 52 for DLco % predicted, and spleen volume were met in a randomised placebo-controlled study in adult ASMD patients with type A/B or type B. Results were confirmed when patients previously on placebo were switched to active treatment. Similar results were also shown for paediatric patients who were treated in an open-label clinical study for 52 weeks.

3. Efficacy: clinical meaningfulness of the endpoint

The primary endpoint on DLco % predicted (e.g. $\geq 15\%$ improvement from BL to week 52) is considered clinically relevant and sufficiently substantiated. This is also applicable to the reduction in spleen volume ($\geq 30\%$ reduction from BL to week 52). In addition, liver volume, PD parameters and other lung function parameters also pointed in the same direction for improvement. Moreover, spontaneous improvement of disease symptoms has not been reported in the literature or was observed in natural history studies.

4. Efficacy: duration of efficacy

Under continued olipudase alfa treatment further improvements in both adult and paediatric patients were observed.

5. Safety: exposure

Safety information was available for 61 patients, with 72% exposed for more than one year. Given the rarity of the disease, this is considered reasonable. Of interest is the lower frequency of anaphylactic, hypersensitivity, and infusion-related reactions.

6. Safety: length of follow-up

Safety information was available for 61 patients. The mean follow-up is 3.6 years.

7. Target population vs. study population

The target population is all ASMD patients with type A/B or type B from birth. Type A/B and B were those patients included in the clinical program. Type A ASMD patients are not included in the labelling, as due to the severe neurological issues, life expectations are very limited; the applicant excluded the patients from the indication.

8. Pharmacological rationale

Olipudase alfa is an ERT intended to replace the faulty enzyme. Hence there is a strong pharmacological rationale.

9. Natural history/ course of the disease

Several natural history studies and case report series consistently demonstrate that ASMD is associated with significant pulmonary morbidity and mortality. The median life expectancy for the chronic visceral end of the ASMD spectrum (e.g. type B) has been reported as 17 years with a range of 1 to 72 years.

Conditional marketing authorisation

Not applicable.

Marketing authorisation under exceptional circumstances

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Xenpozyme is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xenpozyme is favourable in the following indication(s):

Xenpozyme is indicated 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

Prior to the launch of Xenpozyme in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at minimizing specific safety concerns.

The MAH shall ensure that in each member state where Xenpozyme is marketed, all healthcare professionals (HCPs) and patients/caregivers who are expected to prescribe, dispense, use Xenpozyme have access to/are provided with the following educational message to be disseminated through professional bodies:

1. HCP educational materials

2. Patient/caregiver educational materials

1. HCP educational materials:

1.1 HCP Guide for HCPs in home infusion setting including nurses:

The HCP guide includes the following key elements:

- On the front page, contact information of the prescribing/treating physician/centre that can be reached at any time,
- Reminder to read the summary of product characteristics (SmPC) prior to initiating treatment.
- To ensure awareness about the risk of immunogenicity, its monitoring and management, the guide includes the following:
 - Requirements that the home infusion HCPs/nurses should be trained for emergency measures and should have resuscitative equipment ready prior to initiating care.
 - Information on signs and symptoms of infusion-associated reactions (IARs), severe hypersensitivity or anaphylaxis and recommended actions for the management of adverse drug reactions (ADRs) if they occur.
 - Reminder to apply only maintenance dose (mg/kg) as prescribed by the treating/prescribing physician.
- Instruction to contact the prescribing/treating physician if the patient experienced signs/symptoms of IARs, hypersensitivity, anaphylaxis or if one or more infusions are missed or delayed.
- Medical evaluation of the patient prior to administration of the infusion at home.
- Requirements and organization of the home infusion including equipment, pre-treatment and emergency treatments.
- Details and instructions on the preparation, reconstitution, dilution and administration of the product to prevent the risk of medication errors.
- A calculation template to prepare the infusion solution based on prescribed maintenance dose and patient's body weight with instructions to record the calculation and infusion date.
- The calculation template can be used as a basis for recording infusion details in the patient's medical record.
- Reminder to check if additional supplies are required.

2. Patient educational materials:

2.1 Patient Card for patients/caregivers

The patient card includes the following elements:

- Instruction to the patients/caregivers to seek urgent medical attention if any signs and symptoms of IARs, severe hypersensitivity or anaphylaxis listed in the card appear or worsen during and after infusion and to report the event to the treating/prescribing physician.
- Contact information of the prescribing/treating physician/centre that can be reached at any time.
- Reminder to the women of childbearing potential (WOCBP) to discuss the need for contraceptive measures with the prescribing/treating physician.
- Reminder to the WOCBP to contact their prescribing/treating physician if they suspect they might be pregnant or plan pregnancy

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that olipudase alfa is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0459/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.