CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761261Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number	761261
Priority or standard	Priority
Submit date	11/3/2021
Received date	11/3/2021
PDUFA goal date	10/3/2022
Division/office	Division of Rare Diseases and Medical Genetics (DRDMG)
Review completion date	See electronic stamp date
Established/proper name	Olipudase alfa-rpcp
(Proposed) proprietary name	Xenpozyme
Pharmacologic class	Hydrolytic lysosomal sphingomyelin-specific enzyme
Code name	GZ402665
Applicant	Genzyme Corporation
Dosage form/formulation	20mg olipudase alfa as a lyophilized powder in a single-dose vial for reconstitution
Dosing regimen	Adults: A starting dose of 0.1 mg/kg, followed by a dose escalation regimen for 14 weeks to reach a maintenance dose of 3 mg/kg administered as an intravenous infusion every 2 weeks. Pediatrics: A starting dose of 0.03 mg/kg, followed by a dose escalation regimen for 16 weeks to reach a maintenance dose of 3 mg/kg administered as an intravenous infusion every 2 weeks. Use actual body weight for patients with a BMI less than or equal to 30. For patients with a BMI greater than 30, calculate adjusted body weight (kg) = (actual height in m)2 × 30
Applicant proposed indication/ populations	(b) (4) treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients
Proposed SNOMED indication	Niemann-Pick disease type B (39390005), Niemann-Pick disease type A (52165006)
Regulatory action	Approval
Approved dosage (if applicable)	Adults: A starting dose of 0.1 mg/kg, followed by a dose escalation regimen for 14 weeks to reach a maintenance dose of 3 mg/kg administered as an intravenous infusion every 2 weeks. Pediatrics: A starting dose of 0.03 mg/kg, followed by a dose escalation regimen for 16 weeks to reach a maintenance dose of 3 mg/kg administered as an intravenous infusion every 2 weeks. Use actual body weight for patients with a BMI less than or equal to 30. For patients with a BMI greater than 30, calculate adjusted body weight (kg) = (actual height in m)2 × 30
Approved indication(s)/ population(s) (if applicable)	Xenpozyme is a hydrolytic lysosomal sphingomyelin-specific enzyme indicated for treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.
Approved SNOMED term for indication (if applicable)	Niemann-Pick disease type B (39390005), Niemann-Pick disease type A (52165006)

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Glossary

ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APR	acute phase reaction
ASM	acid sphingomyelinase
ASMD	acid sphingomyelinase deficiency
ASMKO	acid sphingomyelinase knockout
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BWG	body weight gain
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRP	C-reactive protein
CRS	cytokine release syndrome
DL_{CO}	diffusion capacity for carbon monoxide
DLT	dose limiting toxicities
DP	drug product
DPH	diphenhydramine hydrochloride
DS	drug substance
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
EFD	embryo-fetal development
E-R	exposure-response
ERT	enzyme replacement therapy
ETP	extension treatment period
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FVC	forced vital capacity
G-CSF	granulocyte colony stimulating factor
GD	gestation day
GI	gastrointestinal
GLP	good laboratory practice
HCP	host cell protein
IAR	infusion-associated reaction
IC_{50}	half maximal inhibitory concentration
IL	interleukin

ILD	interstitial lung disease
IND	investigational new drug
IU	international units
IV	intravenous
KC	keratinocyte chemoattractant
LSM	least square mean
MAP	multi-analyte profile
MedDRA	Medical Dictionary for Regulatory Activities
MIP-1	macrophage inflammatory protein-1
mITT	modified intent-to-treat
MMRM	mixed models for repeated measures
MN	multiples of normal
MRHD	maximum recommended human dosage
MRI	magnetic resonance imaging
NO	nitric oxide
NOAEL	no observed adverse effect level
NPD	Niemann-Pick disease
OPQ	Office of Pharmaceutical Quality
PAP	primary analysis period
PD	pharmacodynamic
PK	pharmacokinetic
PND	postnatal day
PPND	pre- and postnatal development
PRO	patient-reported outcome
PT	preferred term
Q2W	once every two weeks
rhASM	recombinant human acid sphingomyelinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SPM	sphingomyelin
SRS	splenomegaly related score
TBW	terminal body weight
TEAE	treatment-emergent adverse event
TK	toxicokinetic
TNF	tumor necrosis factor
ULN	upper limit of normal
WRS	working reference standard
WT	wild type

I. Executive Summary

1. Summary of Regulatory Action

Genzyme (Applicant) submitted this biologics license application (BLA) for olipudase alfa-rpcp (tradename Xenpozyme), seeking approval of this product as enzyme replacement therapy (ERT) for acid sphingomyelinase deficiency (ASMD), a rare autosomal recessive lysosomal disorder that includes Nieman-Pick type A, type B, and type A/B. Patients with ASMD have an enzyme deficiency that leads to sphingomyelin accumulation in liver, spleen, lung, and the brain, among others; olipudase alfa provides an exogenous source of ASM to metabolize sphingomyelin accumulated in the cells. Currently, there is no approved therapy for ASMD.

Substantial evidence of effectiveness for olipudase alfa in ASMD patients was established with one adequate and well-controlled trial with confirmatory evidence. This trial in 31 adults with ASMD (type B) showed a clinically meaningful and statistically significant improvement in lung function and spleen size, and also liver size, for patients randomized to olipudase alfa compared to those treated with placebo. Confirmatory evidence providing strong mechanistic support includes the well-established etiology of the disease, the mechanism of action of olipudase alfa, and pharmacodynamic biomarker data showing reductions in plasma ceramide and lysosphingomyelin, metabolites of sphingomyelin. Evidence of effectiveness for pediatric patients is based on partial extrapolation from the adequate and well-controlled trial in adults, given the similar pathogenesis of ASMD between pediatric and adult patients and mechanism of action of olipudase alfa; and comparable efficacy results (change from baseline) between adult and pediatric patients observed in an open-label, single arm study of eight pediatric patients (type B, type A/B). Drug efficacy for the treatment of non-CNS manifestations of ASMD in ASMD type A was extrapolated from the evidence in type B and type A/B ASMD patients, as the underlying etiology for non-CNS disease and mechanism of action of olipudase alfa are the same among these three types of ASMD.

The safety profile for olipudase alfa is acceptable for its intended use. Clinically important adverse reactions will be addressed mitigated via labeling. These include a Boxed Warning for hypersensitivity reactions, including anaphylaxis, and recommendations for periodic monitoring of laboratory tests for elevated liver enzymes. Exencephaly, occurring in the first trimester, was seen in a mouse study of embryo-fetal development with olipudase alfa. Published literature identified that a metabolite of sphingomyelin (ceramide) can produce exencephaly in chicks and mice. Therefore, labeling will state that dosage initiation or escalation at any time during pregnancy is not recommended as it may lead to elevated metabolite levels which may increase the risk of fetal malformations. This recommendation also takes into consideration the risk of serious hypersensitivity reactions with treatment start/dose escalation with the potential resultant adverse impact on the pregnancy. All the identified risks for olipudase alfa can be adequately mitigated through labeling and routine pharmacovigilance.

There was very limited safety information in patients younger than 2 years old and in ASMD type A patients; two cases of anaphylaxis occurred in these 2 groups of patients. The Applicant will be required to conduct a postmarket 5-year observational study to evaluate the long-term

safety of olipudase alfa in these two groups of patients. In addition, the Applicant committed to additional chemistry, manufacturing, and controls postmarket studies.

Each scientific discipline and the clinical teams recommend approval of olipudase alfa for the treatment of non–central nervous system manifestations of ASMD in adult and pediatric patients. The CDTL, division director, and signatory authority concur with this recommendation.

APPEARS THIS WAY ON ORIGINAL

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal disease that results in deficient activity of acid sphingomyelinase (ASM), an enzyme that metabolizes sphingomyelin into ceramide and phosphocholine. ASMD encompasses Neiman-Pick type A, type B, and type A/B. • ASM deficiency leads to the accumuation of sphingomyelin affecting organ systems such as the central nervous system (CNS), liver, spleen, lymph nodes, adrenal cortex, lung airways, and bone marrow. • Patients with ASMD type A have the most severe form of the disease, exhibit hepatosplenomegaly, pathologic alterations in the lungs in infancy, and profound CNS involvement, and rarely survive beyond two to three years of age. • Patients with ASMD type B have less severe disease, but also have hepatosplenomegaly and pathologic alterations of their lungs, however, there is no CNS involvement. Most patients can survive into adulthood. • Patients with ASMD type A/B have symptoms that are intermediate between type A and type B. The disease presentation and progression rate vary greatly in type A/B patients, but all are characterized by the presence of some CNS manifestations. • Patients have noted that organ enlargement can cause pain, vomiting, feeding difficulties and falls. (Section 4) • The estimated incidence is 0.4 to 0.6 per 100,000 births.	• ASMD is a rare and serious disease manifested by deterioration in liver function, splenomegaly, and interstitial lung disease caused by storage of sphingomyelin in pulmonary macrophages that results in frequent respiratory infections and eventual respiratory failure.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no approved therapies for the treatment of ASMD; the mainstay of therapy is supportive care. • Hematopoietic stem cell transplantation has been evaluated with variable results.	• There is an unmet need for the treatment of ASMD as there are no approved therapies.
Benefit	• Olipudase alfa is a recombinant human ASM which provides exogenous source of ASM to metabolize sphingomyelin accumulated in the cells. • Olipudase alfa does not cross the blood brain barrier and is not expected to treat CNS manifestations. <u>Adult Subjects:</u> • The efficacy of olipudase alfa was evaluated in an adequate and well-controlled trial DFI12712 (ASCEND) in 31 adults patients with ASMD type B (13 in treatment group, 18 in placebo group) of 52 weeks duration. The changes in DL_{CO} and spleen volume in combination with splenomegaly related score (SRS), the primary efficacy measurements, were compared between patients after 52 weeks treatment (dose escalation to a target olipudase alfa dose of 3 mg/kg or placebo). • The mean % change in % predicated DL_{CO} from baseline to Week 52 was higher in the active treatment group compared to the placebo group (24.2% versus 3.1%, p<0.0001). The mean % change in spleen volume in multiples of normal (MN) was also higher in the active treatment group than in placebo (-38.8% versus 0.4%, p<0.0001), but the mean change in SRS score (a patient reported outcomes [PRO] measure) was not statistically different between the two groups (-5.3 in the active treatment group versus -9.8 in the placebo; lower score is associated with fewer symptoms). Improvement was also observed on % predicted forced vital capacity (FVC), forced expiratory volume, and total lung capacity, as well as liver volume, and hematologic and hepatic laboratory values. <u>Pediatric Subjects</u>: • The safety and exploratory efficacy of olipudase alfa was evaluated in 8 pediatric subjects with type B or type A/B in	• The diffusion capacity for carbon monoxide (DL_{CO}) primary endpoint and spleen volume showed a statistically significant advantage for adult subjects treated with olipudase alfa over placebo. • The magnitude of treatment effect seen in % predicted DL_{CO} in the DFI12712 (ASCEND) trial was larger than that seen in many of the other pivotal trials for approved interstitial lung disease (ILD) therapies. This is noteworthy as the evaluation of DL_{CO} for ILD programs have focused on reduction in decline rather than improvement, in part, because these approved therapies have yet to demonstrate an improvement in DLco • Other pulmonary endpoints (% predicted forced vital capacity [FVC], FVC in mL, high-resolution computed tomography ground glass scores, high-resolution computed tomography interstitial scores, chest x-ray (interstitial scores) provided similarly favorable results. Compared to placebo, improvements in liver volume and hematological and hepatic laboratory values were also observed. • The results from the ASCEND-Peds trial largely mirrored the ASCEND trial. Although the ASCEND-Peds trial was an open label trial without a comparator, the endpoints assessed were objective and unlikely to be influenced by the unblinded nature of the trial. • The SRS component of the combination endpoint shows similar improvements in both the treatment and placebo arms, suggesting an insensitive PRO. Of notehe SRS has not been validated in the ASMD population as it was derived from an assessment of subject perception of splenomegaly symptoms in myelofibrosis, a significantly different patient population than ASMD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	an open-label single arm trial DFI13803 (ASCEND-Peds). Subjects received 64 weeks of olipudase alfa (dose escalation to the target dose of 3 mg/kg). • The mean percentage reduction in spleen and liver volumes from baseline to Week 52 was 46.7% and 37.3% (n=8 for both), respectively. The mean percentage increase in % predicted DL_{CO} from baseline to Week 52 was 50.6% (n=3). • Only one patient less than 2 years of age was enrolled in the pediatric trial. • No patients with ASMD type A were enrolled in the clinical trials.	• The key drivers of disease burden in ASMD are expected to be similar across age groups. Mechanistically, olipudase alfa would be expected to have a similar effect in patients regardless of the age group. Therefore, the clinical response of olipudase alfa in patients <2 years of age would be expected to be similar to those >2 years of age. • While the neurological manifestations differ among ASMD type A, B, and A/B, similar somatic manifestations are observed in all these disease phenotypes. Due to the mechanism of action of olipudase alfa, similar improvements in lung function and liver volume are expected across phenotypes. This therapy is expected to provide non-CNSclinical benefit to patients with ASMD type A as no other treatment currently is available in this devastating disease.
Risk and Risk Management	• Safety was assessed in a total of 38 treatment naïve subjects with ASMD type B or type A/B. This included 30 adult subjects with a median (range) olipudase alfa exposure of 3.0 (1.4 – 4.7) years and 8 pediatric subjects with a median expousure of 2.7 (2.5 – 3.1) years. • Treatment emergent serious adverse events (SAEs) were reported in 33.3% (10/30) adult subjects and in 50% (4/8) pediatric subjects. Treatment related SAEs included anaphylactic reaction; these SAEs were reported in pediatric subjects. • The most common adverse events (AEs) occuring in ≥10% adults that were considered related to olipudase alfa included headache, cough, diarrhea, hypotension, and ocular hyperemia. Common AEs occuring in ≥25% of pediatric subjects included pyrexia, cough, diarrhea, rhinitis, vomiting, abdominal pain, headache, urticaria, nausea rash, arthralgia, pruritus, fatigue, and pharyngitis. • Mild to moderate treatment related hypersensitivity AEs were reported in 33% (10/30) of adult and in 50% (4/8) of pediatric subjects. Hypersensitivity reactions occurred in adults were pruritus, urticaria, erythema, rash, rash erythematous, eczema, angioedema, and erythema	• The safety database was adequate for the safety assessment of olipudase for the proposed indication, patient population, dosage regimen, and duration. • Safety risks of hypersensitivity, including anaphylaxis and infusion-associated reactions, are known risks to enzyme replacement therapies (ERT). These risks can be addressed through labeling with a boxed warning specifically for hypersensitivity including anaphylaxis. • As the IARs were considered mild to moderate with no discontinuations, they can be addressed within warnings and precautions and does not require a boxed warning. • The dose-escalation regimen provides a gradual debulking of sphingomyelin and gradual release of ceramide decreasing the inflammatory response. • However, there are minimal safety data in patients with Type A ASMD and those under the age of 2, therefore a PMR is advised to further evaluate safety in those patients. • Due to the elevation of ceramide seen during the dose escalation phase, the labeling will advise that dosage initiation or escalation, at anytime during pregancy, should not occur as it may lead to elevated metabolite levels that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	nodosum. Hypersensitivity reactions in pediatric subjects were urticaria, pruritus, rash, erythema, and localized edema. All hypersensitivity reactions were of mild to moderate intesity and resolved with dose interruption or temporarily treatment discontinuation. • One severe anaphylactic reaction occurred in a 1.5-year-old subject. Olipudase alfa was temporarily discontinued and was restarted with a densensitization protocol, and the subject reached the maintainence dosage. • 50% (15/30) of adult subjects and 75% (6/8) of pediatric subjects reported infusion-associated reactions (IARs). IARs that occurred in ≥10% of adult subjects included headache, pruritus, urticaria, and vomiting. IARs reported in ≥10% of pediatric subjects were urticaria, erythema, headache, nausea, pyrexia, vomiting, abdominal pain anaphylactic reaction, increased in blood alkaline phosphatase, total bilirubin, and C-reactive protein (CRP), muscle edema, rash, and skin mass. • Ten events of acute phase reactions (APRs) were identified in 3.3% (1/30) of adult subjects and 12.5% (1/8) of pediatric subjects. Most of the APRs occurred at 48 hours post infusion during the dose escalation period. Clinical symptoms commonly associated with APRs were pyrexia and vomiting. All APRs resolved over time by repeating or reducing olipudase alfa at the subsequent infusion. • Exencephaly was observed in 5 fetuses of 2 pregnant mice treated with 10 and 30 mg/kg of olipudase alfa in a study of embryo-fetal development in pregnant mice. This malformation was not seen when olipudase alfa (3, 10, or 30 mg/kg) was administered to rabbits daily from gestation day 6 to 19. These data are consistent with literature reports that brief embryonic exposure to sphingomyelin metabolite (ceramide) or the S1P agonist fingolimod produces neural tube defects, including exencephaly, in chicks and mice; another sphingomyelin metabolite is sphingosine 1 phosphate (S1P). In addition, the drug class	may increase the risk of fetal malformations. This recommendation also takes into consideration the risk of serious hypersensitivity reactions associated with dose start/escalation and the potential resultant adverse impact on the pregnancy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of S1P agonists is associated with embryo-lethality and increased incidences of fetal malformations.	

2.2. Conclusions Regarding Benefit-Risk

Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal disease caused by biallelic pathogenic variants in the SPMD1 gene, which leads to a deficiency in the enzyme acid sphingomyelinase (ASM) that catabolizes sphingomyelin (SPM) into ceramide and phosphocholine. Organ systems affected include the central nervous system (CNS), liver, spleen, lymph nodes, adrenal cortex, lung airways, and bone marrow. There are no approved therapies for the treatment of ASMD.

Olipudase alfa is a recombinant human ASM being developed as enzyme replacement therapy for the treatment of non-CNS manifestations of ASMD in pediatric and adult patients. Olipudase alfa does not cross the blood brain barrier and is not expected to treat the CNS manifestations of the disease.

The efficacy of olipudase alfa was evaluated in an adequate and well-controlled trial DFI12712 (ASCEND) in 13 adult patients with ASMD type B on treatment compared to 18 patients on placebo. The changes in diffusion capacity for carbon monoxide (DL_{CO}) and spleen volume in combination with splenomegaly related score (SRS), as primary efficacy measurements, were compared between patients after 52 weeks of treatment at a target olipudase alfa dose of 3 mg/kg or placebo.

The DL_{CO} primary endpoint showed a statistically significant advantage for subjects treated with olipudase alfa over placebo. By Week 52, the percentage increase from baseline was found to be 3.08% for placebo versus 24.3% on treatment. Regarding spleen volume, the percentage decrease from baseline to Week 52 was -0.4% for placebo versus 38.8% on treatment.

Efficacy in the pediatric population relies upon partial extrapolation of efficacy from the adequate and well-controlled study in adults (ASCEND), given the similarity in disease pathogenesis and anticipated response to therapy between adults and pediatric subjects with ASMD. Supportive evidence of efficacy in the pediatric population was seen in the findings of the exploratory efficacy endpoints in the open-label single arm trial in 8 pediatric subjects with type B or type A/B (ASCEND-peds). Pediatric subjects received 64 weeks of olipudase alfa at the target dose of 3 mg/kg. The mean percentage reduction in spleen and liver volumes from baseline to Week 52 was 46.7% and 37.3% (n=8 for both), respectively. The mean percentage increase in % predicted DL_{CO} from baseline to Week 52 was 50.6% (n=3). Of note, ASCEND-peds assessed the same endpoints as the ASCEND trial and included subjects with more severe baseline values than the treatment arm of the ASCEND trial; and showed a greater percentage improvement from baseline at Week 52 to those in the treatment arm of ASCEND trial.

Confirmatory evidence is derived from the (1) well-established etiology of the disease, (2) the mechanism of action of the therapy, and (3) PD biomarker data from olipudase alfa clinical trials in adult and pediatric subjects with ASMD. Specifically, ASMD is a lysosomal disease caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene that result in deficient activity of the enzyme acid sphingomyelinase (ASM). ASM catalyzes the hydrolysis of SPM to ceramide and phosphocholine. The deficiency in ASM causes an intracellular accumulation of SPM as well as cholesterol and other cell membrane lipids in various tissues, including the spleen, liver, and lungs. Olipudase alfa (a recombinant human ASM) provides an exogenous source of ASM. Plasma ceramide and lysosphingomyelin (or lyso-SPM, a deacylated

form of SPM) were used as PD biomarkers to assess the pharmacological effect of olipudase alfa in subjects with ASMD. Reductions of plasma ceramide and lyso-SPM were consistently observed in subjects with ASMD treated with olipudase alfa across the clinical trials in the BLA.

Safety was assessed in a total of 38 treatment naïve subjects with ASMD type B or type A/B. This included 30 adult subjects with a median (range) olipudase alfa exposure of 3.0 (1.4 – 4.7) years and 8 pediatric subjects with a median exposure of 2.7 (2.5 – 3.1) years. The occurrences of AEs were higher in pediatric subjects than in adults. SAEs and AEs leading to dose modification occurred in 4 (50% versus 32.3% in adults) and 5 (62.5% versus 40% in adults) pediatric patients, respectively. Dose interruption and reduction were reported in 4 (50%) and 2 (25%) pediatric patients, respectively, compared to 11 (36.7%) and 2 (6.7%) adult patients, respectively. The most common adverse reactions (ADRs) occurring in ≥10% adults were headache, cough, diarrhea, hypotension, and ocular hyperemia. Treatment related serious adverse events (SAEs) included anaphylactic reaction, rash, and urticaria; all these SAEs were reported in pediatric subjects. Treatment related hypersensitivity adverse events (AEs) were reported in 33% (10/30) adult subjects and in 50% (4/8) pediatric subjects. Hypersensitivity reactions occurred in adults were pruritus, urticaria, erythema, rash, rash erythematous, eczema, angioedema, and erythema nodosum. Hypersensitivity reactions in pediatric subjects were urticaria, pruritus, rash, erythema, localized edema, and anaphylactic reaction. With the exception of a severe anaphylactic reaction occurred in a 1.5-year-old subject, all hypersensitivity reactions were of mild to moderate intensity and resolved with dose interruption or temporarily treatment discontinuation. Infusion-associated reactions (IARs) were reported in 50% (15/30) of adult subjects and 75% (6/8) of pediatric subjects and were considered mild to moderate and requiring no discontinuation of treatment. Acute phase reactions (APRs), transient elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were also observed after infusions. These risks can be addressed through labeling and routine pharmacovigilance. The label also includes a dose-escalation regimen when starting treatment to provide a gradual debulking of SPM and gradual release of ceramide decreasing the inflammatory response. A modified-dose escalation regimen is also included in the label for restarting treatment after missed doses.

An embryo-fetal development study in mice treated with olipudase alfa showed exencephaly, a neural tube defect in the first trimester of pregnancy. Olipudase is not expected to cross the placenta. However, published literature has reported that early embryonic exposure to the sphingomyelin metabolite (ceramide) can produce exencephaly in chicks and mice. Since, elevated metabolite levels occur during the dose escalation phase, and there is an elevated risk of serious hypersensitivity reactions and the potential resultant adverse impact on the pregnancy with dose start/escalation, it will be recommended to not initiate treatment or escalate treatment at any time during pregnancy.

No patients with ASMD type A and only one patient under the age of 2 were enrolled in the clinical trials. While neurological manifestations differ among the different subtypes of ASMD, the somatic manifestations are observed in all disease phenotypes and age groups. Due to the mechanism of action of olipudase alfa, similar improvements in lung functions, spleen volume and liver function are expected regardless of age or subtype. However, minimal safety data is known in patients with Type A and those under the age of 2 and therefore the applicant will be required to conduct a postmarket 5-year observational study to evaluate the long-term safety of olipudase alfa in these two groups of patients.

In summary, the randomized, double-blind, placebo-controlled trial showing scientifically valid, statistically significant, and clinically meaningful improvements in lung function and spleen size. The review team concluded on the basis of this evidence, plus confirmatory evidence from biomarkers and understanding of ASMD etiology and olipudase alfa mechanism of action, that there was substantial evidence of effectiveness. Given the patient perspective, the significant unmet need, the compelling scientific evidence of effectiveness from the randomized trial and confirmatory biomarker data, and adequate risk mitigation can be addressed with labeling, including the dose escalation regimen, boxed warning for hypersensitivity including anaphylaxis and that the principal risks of therapy are reversible with treatment discontinuation, the review team concluded that the benefits of olipudase alfa therapy outweigh the risks for adult and pediatric patients with ASMD when used according to the agreed-upon labeling. The availability of olipudase alfa will provide the first available treatment for the non-CNS manifestations of patients with ASMD.

II. Interdisciplinary Assessment

3. Introduction

Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal disease caused by biallelic pathogenic variants in the *SPMD1* gene, which leads to a deficiency in the enzyme acid sphingomyelinase (ASM) that catabolizes sphingomyelin (SPM) into ceramide and phosphocholine. SPM is a major component of cell membranes and a principal phospholipid of the myelin sheath. Deficiency of ASM leads to the accumulation of SPM and secondary increases in cholesterol and other metabolically related lipids. Organ systems affected include the central nervous system (CNS), liver, spleen, lymph nodes, adrenal cortex, lung airways, and bone marrow. The estimated incidence of ASMD is 0.4 to 0.6 per 100,000 live births (April 2021).

Historically, ASMD is known as Niemann-Pick disease (NPD) type A or B. Type A (infantile neurovisceral ASMD) is an early onset severe disease. It is a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and rapidly progressive neurodegenerative course (Wasserstein and Schuchman 1993). Interstitial lung disease (ILD) caused by storage of SPM in pulmonary macrophages results in frequent respiratory infection and often respiratory failure. Most children succumb before the third year of life. Type B (chronic visceral ASMD) is a later onset disease, and the manifestations are less severe; it is also characterized by progressive hepatosplenomegaly, gradual deterioration in liver and pulmonary function, osteopenia, and an atherogenic lipid profile. No CNS manifestations occur in Type B ASMD. There is an intermediate form type A/B (chronic neurovisceral ASMD) with symptoms that are intermediate between type A and type B. The disease presentation and progression rate vary greatly in type A/B patients, but all are characterized by the presence of some CNS manifestations. Patients with type A/B have hepatosplenomegaly, ILD, dyslipidemia, osteopenia, and thrombocytopenia. Coarse facial features present in a subset of patients with type A/B. Most patients with type B and type A/B can survive into adulthood. Adults can have significant short stature because of abnormal linear growth and delayed skeletal maturation, which are common in children and adolescents with these two subtypes. Organ enlargement can cause pain, vomiting and feeding difficulties leading to a worsening quality of life (Cowie et al. 2022).

There are no approved therapies for the treatment of ASMD. Management of patients includes supportive therapies such as partial splenectomy for severe hypersplenism, supplemental oxygen for symptomatic pulmonary disease, physical and occupational therapies for progressive neurologic disease, and medications to manage dyslipidemia. Hematopoietic stem cell transplantation has been investigated with variable results; stabilization of the neurologic component following hematopoietic stem cell transplantation has not been reported.

Olipudase alfa is a recombinant human ASM being developed for the treatment of non-CNS manifestations of ASMD in pediatric and adult patients. Olipudase alfa does not cross the blood brain barrier and is not expected to treat the CNS manifestations of the disease. The clinical development program for olipudase alfa in ASMD included five clinical trials with olipudase alfa treatment and five non-interventional natural history studies without olipudase alfa treatment. Four of the five trials were multiple dose studies (DFI12712 ASCEND, DFI13803

ASCEND-Peds, LTS13632, and DFI13412); one of them was a single dose study (SPHINGO00605). The application includes all five clinical trials. The natural history studies are not included, as they are ongoing or did not provide additional relevant information on the disease.

During the clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process in the following order, referred to as Processes A, B, C (b) (4) and C (b) (4) In this review, Processes A, B, C (b) (4), and C (b) (4) refer to drug product (DP) manufactured by these manufacturing processes respectively. The clinical development was initiated with Process A which was only used in the single-dose study SPHINGO00605. Processes B, C (b) (4), and C (b) (4) were used in Trials DFI12712 (ASCEND), DFI13803 (ASCEND-Peds), LTS13632, and DFI13412. Subjects in the ongoing trials ASCEND extension treatment period (ETP) and LTS13632 were transitioned from Process C (b) (4) to Process (b) (4) treatment beginning in February 2020; hence, only subjects in two trials have received treatment with Process C (b) (4) Analytical comparability and/or nonclinical pharmacodynamic (PD) comparability were conducted for olipudase alfa DPs manufactured by Process B versus Process A, Process C (b) (4) versus Process B, and Process C (b) (4) versus Process C (b) (4) no dedicated clinical studies were conducted to demonstrate pharmacokinetic (PK) comparability between these DPs. PK comparability was assessed using data obtained from the clinical trials to supplement analytical and/or nonclinical PD comparability.

In terms of the product's regulatory history, the Applicant submitted the investigational new drug (IND) opening protocol (IND 012757) to the U.S. Food and Drug Administration (FDA) on October 26, 2005. The program was developed to evaluate olipudase alfa as an enzyme replacement therapy (ERT) for (b) (4) treatment of non-CNS manifestations of ASMD in pediatric and adult patients. Olipudase alfa was granted an Orphan Designation for the treatment of NPD type B on August 3, 2000; the product was subsequently granted an Orphan Designation Amendment for the treatment of ASMD (NPD) on December 18, 2007, to include all types of NPD. Olipudase alfa was granted a Fast-Track Designation for the treatment of ASMD on April 23, 2007, a Breakthrough Therapy Designation for non-neurological manifestations of ASMD on May 26, 2015, and a Rare Pediatric Disease Designation to treat pediatric patients with non-neurological manifestation of ASMD on October 17, 2018. A type B pre-biologics license application (BLA) meeting was held on March 24, 2021, and a rolling review submission request was granted. Part 1 of the Rolling BLA submission, which includes all nonclinical documents, was submitted on September 8, 2021. Part 2 of the Rolling BLA submission, which includes all administrative, clinical, and chemistry, manufacturing, and controls (CMC) documents, was submitted on November 3, 2021. The application met the criteria for a priority review because olipudase alfa represents a treatment for ASMD, a serious condition with no approved therapy and unmet medical need.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Evidence of Effectiveness in Adults and Pediatric Subjects

3.1.1.2. Confirmatory Evidence

3.1.1.3. Youngest Age Limit for Pediatric Indication

3.1.1.4. Inclusion of ASMD Type A Patients in Indication

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Exencephaly Seen in Mouse Embryo-Fetal Studies

3.1.2.2. Elevated Levels of Host Cell Proteins (HCP) Seen in Process C (b) (4) and Process C (b) (4)

3.1.2.3. Boxed Warning for Hypersensitivity Including Anaphylaxis

3.2. Approach to the Review

Clinical data from four different trials in subjects with ASMD type B or type A/B were submitted to support the efficacy and safety of olipudase alfa; subjects with type A were excluded from enrollment as described by the eligibility criteria of the clinical trials. The four trials provide clinical data for 40 adult subjects and 20 pediatric subjects from different age groups (four older children and adolescents aged 12 to 17 years old, 15 pediatric subjects aged 2 to 11 years old, and one subject <2 years old). The trials also include clinical data from olipudase alfa products with different manufacturing processes, namely Process B, Process C (b) (4) and Process C (b) (4) Because Process B was found not to be analytically comparable to Process C, the primary efficacy and safety analyses were evaluated based on clinical data from subjects who had only received the to-be-marketed DP i.e., Process C. This excludes nine adults and 12 pediatric subjects who had ever received Process B and includes 31 adults and 8 pediatric subjects (seven children aged 2 to 11 years old and one subjects <2 years old) who started an received treatment only with Process C.

Efficacy Assessment

The efficacy of olipudase alfa in adult subjects was assessed using placebo-controlled clinical data from the primary analysis period (PAP) of ASCEND. Of the 36 adult subjects in ASCEND, 13 subjects in the active treatment group and 18 subjects in the placebo group were evaluated in the primary analyses (see Table 3).

The two primary efficacy endpoints i.e., diffusion capacity for carbon monoxide (DL_{CO}) and spleen volume in combination with splenomegaly related score (SRS), were evaluated for their statistical significance as well as clinical benefit in terms of percent change from baseline to Week 52 as specified in the statistical analysis plan (SAP). The absolute change from baseline to Week 52 in these two endpoints and percent change in other secondary endpoints (e.g., forced vital capacity [FVC], forced expiratory volume, etc.) were also evaluated. Because there was only one adequate and well-controlled trial in adults, confirmatory evidence for effectiveness including mechanistic evidence and PD biomarker data from clinical trials were also evaluated.

The pediatric trial ASCEND-peds was a single arm open-label study, and the effectiveness of olipudase alfa in pediatric subjects will be assessed in the framework of partial extrapolation. Eight subjects who received Process C were included in the primary analyses (see Table 3). Additionally, the Applicant has performed analysis of efficacy measures (spleen and liver volumes, platelet count, percent predicated DL_{CO}, ILD as assessed by chest X-ray and high-resolution computed tomography, and height Z-score) in pediatric subjects in ASCEND-Peds. These analyses will be evaluated as supportive analysis for olipudase alfa efficacy in pediatric patients.

Table 3. Number of Subjects of DFI12712 (ASCEND) Adult Study and DFI13803 (ASCEND-Peds) Pediatric Study by Olipudase Alfa Manufacturing Process

Primary Efficacy	Process B ± Process C	Process C only	Placebo
ASCEND (N=36; N=18 active, N=18 placebo)	5	13	18
ASCEND Peds (N=20 all on active treatment)	12	8	0

Source: reviewer
Abbreviations: N, number of subjects.

Safety Evaluation

Safety data from three trials (ASCEND, ASCEND-peds, and LTS13632) were evaluated to determine the safety of olipudase alfa in patients with ASMD; data from the ASCEND trial in adults were analyzed separately from the pooled data from ASCEND-peds and LTS13632 in pediatric subjects because of different safety profile between the adult population and pediatric population. Data from DFI13412 were excluded because all subjects in this trial started treatment with Process B. The primary analysis to support the safety of olipudase alfa includes comparisons of safety data between the active treatment group and the placebo group in ASCEND PAP. Further analysis was performed to assess safety in all adult subjects after initiation of olipudase alfa treatment in ASCEND, including subjects who were randomized to olipudase alfa during PAP and continued with active treatment during the ETP and subjects randomized to placebo during PAP and initiated olipudase alfa during ETP. In the pediatric population, the safety of olipudase alfa was assessed based on the following age groups (12 to 17 years old, 2 to 11 years old, and <2 years old), rather than the age groups proposed by the

Applicant (12 to 17 years, 6 to 11 years, and <6 years old). Of note, the four adolescent subjects who received Process B and were not included in the primary analyses. Clinical data from pediatric subjects were compared to adult subjects as well. With regard to the safety evaluation of DPs with different manufacturing processes, the comparison of Process B and Process C (b) (4) was performed primarily using clinical data from ASCEND-Peds. Because only subjects in ASCEND ETP and LTS13632 had received the intended commercial product [i.e., Process C (b) (4)] and treatment durations on Process C (b) (4) and Process C (b) (4) were variable in these subjects, exposure adjusted incidence rate (EAIR) of adverse events (AEs) were compared between Process C (b) (4) and Process C (b) (4)

The assessment of AEs, laboratory evaluations, vital signs, and electrocardiograms (ECGs) was performed based on descriptive summaries and tables provided by the Applicant and Clinical Data Scientists from the FDA. Subject narratives were reviewed for death, treatment discontinuation, serious adverse events (SAEs), and adverse event of special interest. Clinical trial data were independently analyzed using JMP and JMP Clinical as appropriate. All safety assessments and conclusions were those of the clinical review team unless otherwise specified.

Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Olipudase Alfa

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
DFI12712 ASCEND	Adult patients with ASMD type B	Control type: Placebo controlled Randomization: Randomized Blinding: Double-blind Biomarkers: Yes Innovative design features: None	Drug: Olipudase alfa Dosage: 0.1, 0.3, 0.3, 0.6, 0.6, 1, 2, and 3 mg/kg IV Q2W within the first 14 weeks, followed by maintenance dose at 3 mg/kg or maximum tolerated dose (MTD) IV Q2W Choose unit. Number treated: 18 olipudase alfa in PAP and ETP; 18 placebo in PAP followed by olipudase alfa in ETP Duration (quantity and units): 52 wk PAP; up to 4 years and 3 months in the ongoing ETP	Primary: % change in % predicted DLco from baseline to W52; % change in spleen volume in MN combined with change in splenomegaly related score (SRS) from baseline to W52 Secondary: % change in liver volume in MN and platelet counts from baseline to W52; change from baseline to W52 in fatigue and pain severity as measured by item 3 of the BFI and BPI-SF scale, respectively; change from baseline to W52 in dyspnea severity as measured by FACIT dyspnea tool	36 planned; 36 randomized	24 centers in 18 countries

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
DFI13803 ASCEND-Peds	Pediatric patients with ASMD without acute or rapidly progressive neurological abnormalities	Control type: NA Randomization: NA Blinding: NA Biomarkers: Yes, for safety and exploratory efficacy Innovative design features: None	Drug: Olipudase alfa Dosage: 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1, 2, and 3 mg/kg IV Q2W within the first 16 weeks, followed by maintenance dose at 3 mg/kg or maximum tolerated dose (MTD) IV Q2W Choose unit. Number treated: 20 Duration (quantity and units): 64 wk	Primary: Safety assessments of AEs/TEAEs including IARs and AESI, physical exam, neurological exam, clinical lab evaluations, vital signs, ECG, doppler ECG, liver ultrasound doppler, safety biomarkers, immune response assessment. Secondary: PK measurements, exploratory efficacy assessment of spleen and liver volumes by MRI, pulmonary function tests and imaging, chest X-ray, bone age, cycle ergometry, physicians' global assessment of change, serum and bone biomarkers, lipid profile, health outcome questionnaires, cognitive and adaptive function	20 planned; 20 treated	6 centers in 6 countries

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
LTS13632	Adult and pediatric patients with ASMD who previously received olipudase alfa treatment in DFI12712 (ASCEND) or DFI13803 (ASCEND-Peds), respectively	Control type: NA Randomization: NA Blinding: NA Biomarkers: Yes, safety and efficacy Innovative design features: None	Drug: Olipudase alfa Dosage: 3 mg/kg or MTD IV Q2W Choose unit. Number treated: 25 (5 adults and 20 pediatric subjects Duration (quantity and units): Up to 9 y and is ongoing	Primary: Safety assessments of AEs/TEAEs including IARs and AESI, physical exam, extended neurological exam, abbreviated physical exam, weight/heigh (peds only), vital signs, clinical laboratory test, ECG, ECHO, safety biomarkers, liver biopsy (DFI13412 only), liver ultrasound with doppler (DFI13803 [ASCEND-Peds] only), immune response assessments. Secondary: Spleen and liver volumes, pulmonary function tests and imaging, hemoglobin and platelet count, lipid profile, X-ray, Tanner staging, height Z-score, adult and pediatric health outcome questionnaires, biomarker concentrations, and PK	25 planned; 25 treated	8 centers in 8 countries

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
DFI13412	Adult patients with non-neuronopathic ASMD	Control type: NA Randomization: NA Blinding: NA Biomarkers: Yes Innovative design features: None	Drug: Olipudase alfa Dosage: 0.03, 0.1, 0.3, 0.3, 0.6, 1, 2, and 3 mg/kg IV Q2W within the first 12 weeks, followed by maintenance dose at 3 mg/kg or maximum tolerated dose (MTD) IV Q2W Choose unit. Number treated: 5 Duration (quantity and units): 26 wk	Primary: Safety assessments of AEs/TEAEs including IARs, hematology and blood chemistry, physical exam, vital signs, ECGs, ECHO with doppler, biomarkers, immunogenicity testing, and additional testing for cytokine release syndrome Secondary: PK, tissue and blood/plasma biomarker concentrations, spleen and liver volumes, pulmonary function tests and imaging, health outcome measures, fasting lipid profile	6 planned; 5 treated	2 centers in 2 countries

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: ASMD, acid sphingomyelinase deficiency; BID, twice daily; DB, double-blind; ECG, electrocardiogram; LTE, long-term extension study; MC, multi-center; MTD, maximum tolerated dose; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; Q2W; every 2 weeks; R, randomized; TEAE, treatment emergent adverse event.

4. Patient Experience Data

One of the primary efficacy endpoints in ASCEND was percent change in spleen volume in multiples of normal (MN) in combination with SRS, which is a novel 5-item scale that was adapted from myelofibrosis measures and used for the first time in ASMD patients in ASCEND. SRS was to measure splenomegaly symptoms and impacts. General pain was measured using a modified version of Item 3 of the Brief Pain Inventory-Short Form. Fatigue was measured with a modified version of Item 3 of the Brief Fatigue Inventory. Dyspnea was measured with the Functional Assessment of Chronic Illness Therapy-Dyspnea measure.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Section 6.2.1
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☒	Perspectives shared at patient stakeholder meeting	Section 3, 4
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

The most important patient experience data are the results from the randomized, double-blind, placebo-controlled trial showing scientifically valid, statistically significant, and clinically meaningful improvements in lung function and spleen size. The review team concluded on the basis of this evidence, plus confirmatory evidence from biomarkers, that there was substantial evidence of effectiveness. The team further concluded that it was reasonable to extrapolate this evidence of effectiveness to include patients with ASMD Type A, and pediatric patients, because, although the disease progression rate varies in these patients, all are characterized by hepatosplenomegaly, lung disease, dyslipidemia, osteopenia, and thrombocytopenia due to accumulation of SPM and secondary increases in cholesterol and other metabolically related lipids.

Having reached this scientific conclusion, the team then turned to additional sources for the patient perspective to inform the overall benefit-risk determination, including the International

Niemann-Pick Disease Alliance webinar May 12, 2022, "Patient Reported Outcomes – Pediatric Experience with Olipudase alfa." (Cowie et al. 2022) Structured interviews were conducted with ten caregivers in February of 2022. Parents described how ASMD affected their children, and many spoke to the ways that enlarged abdominal organs led to pain, vomiting, eating difficulties, and falls:

- "Every day she said, yes, my belly hurts, I have pain"
- "He was hooked up to feeding pumps, because the pressure that was being put on his stomach, he was only able to tolerate small volumes at a time"
- "Due to the bigger belly, she had some stability problems and she really fell a lot"
- "He would vomit upwards of five times a day"
- "After he was finished eating, he would throw up, which it makes sense now, with everything being so enlarged"
- "No child wants to be throwing up five times a day"

Parents were clear that there is significant unmet need (8/10 endorsed great to moderate need) for effective therapy, and while most reported improvements in systemic symptoms with olipudase therapy, families acknowledged that treatments for the neurologic manifestations remain an area of unmet need.

The principle observed risks of therapy in human trials were anaphylaxis and infusion-associated reactions (IARs), and the review team concluded that, although these are serious, they are self-evident to patients and reversible with treatment discontinuation, such that clear labeling would be sufficient to support doctors and patients in making informed, individualized treatment decisions.

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5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The pharmacologic activity, PK, and clinical pharmacology of olipudase alfa that are relevant to the interpretation of benefit and risk are summarized in Table 6.

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	A hydrolytic lysosomal sphingomyelin-specific enzyme.
Mechanism of action	ASMD is a lysosomal disease that results from reduced activity of the enzyme acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene. ASM degrades sphingomyelin (SPM) to ceramide and phosphocholine. The deficiency of ASM causes an intra-lysosomal accumulation of SPM (as well as cholesterol and other cell membrane lipids) in various tissues. Olipudase alfa provides an exogenous source of ASM. Olipudase alfa is not expected to cross the brain-blood barrier or modulate the CNS manifestations of the disease.
Active moieties	Olipudase alfa is a hydrolytic lysosomal sphingomyelin-specific enzyme and is the active moiety. Olipudase alfa consists of 570 amino acids and has a molecular weight of approximately 76 kDa.
QT prolongation	Olipudase alfa is a glycoprotein with a molecular weight of approximately 76 kDa. No TQT studies have been performed to evaluate the QT internal prolongation potential for olipudase alfa.
General Information	
Bioanalysis	Plasma concentrations of olipudase alfa were determined using three independently validated assays: methods ITR-653-0813 and PDV0079 with a lower limit of quantitation (LLOQ) of 0.04 µg/mL and method ITR-432-0409 with a LLOQ of 0.125 µg/mL. These three methods were cross-validated.
Healthy subjects versus patients	The PK of olipudase alfa has not been assessed in healthy subjects.

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)</td><td>The PK of olipudase alfa in adult and pediatric subjects with ASMD are summarized in Table 7 and Table 8.

Table 7. Mean (CV%) of Olipudase Alfa PK Parameters for the Process C(b) (4) Product Following Administration of 3 mg/kg Q2W in Adult Subjects With ASMD
<table><tr><th>Parameter</th><th>Adults (N=49)</th></tr><tr><td>C_{max} (µg/mL)</td><td>30.2 (17)</td></tr><tr><td>$AUC_{0-\tau}$ (µg.h/mL)</td><td>607 (20)</td></tr></table>Abbreviations: AUC0-τ: area under the plasma concentration versus time curve over a dosing interval; C_{max}: maximum plasma concentration; CV%, coefficient of variation %; N: total number of subjects; Q2W, every two weeks.
Note: PK parameters were calculated based on post-hoc estimates from the popPK analysis (response to FDA IR, 12-May-2022).

Table 8. Mean (CV%) of Olipudase Alfa PK Parameters for the Process C(b) (4) Product Following Administration of 3 mg/kg Q2W in Pediatric Subjects With ASMD
<table><tr><th>Parameter</th><th>Pediatric (N=20)</th></tr><tr><td>C_{max} (µg/mL)</td><td>24.3 (11)</td></tr><tr><td>$AUC_{0-\tau}$ (µg.h/mL)</td><td>449 (16)</td></tr></table>Abbreviations: $AUC_{0-\tau}$: area under the plasma concentration versus time curve over a dosing interval; C_{max}: maximum plasma concentration; CV%, coefficient of variation %; N: total number of subjects; Q2W, every two weeks.
Note: PK parameters were calculated based on post-hoc estimates from the popPK analysis (response to FDA IR, 12-May-2022).</td></tr>
<tr><td>Range of effective dosage(s) or exposure</td><td>The recommended adult and pediatric dosages of olipudase alfa are based on body weight. For patients with a BMI less than or equal to 30, the dosage is based on actual body weight (kg). For patients with a BMI greater than 30, calculate an adjusted body weight (kg) based on height in meters as described below: Adjusted body weight (kg) = (actual height in m)^2 × 30.

<u>For Adult ASMD Patients (≥18 years old)</u>
The recommended starting dose is 0.1 mg/kg, and the dose should be escalated to a maintenance dose of 3 mg/kg. The dose escalation regimen includes 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg administered every two weeks (Q2W) over 14 weeks.

<u>For Pediatric ASMD Patients (<18 years old)</u>
The recommended starting dose is 0.03 mg/kg, and the dose should be escalated to a maintenance dose of 3 mg/kg. The dose escalation regimen includes 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg Q2W over 16 weeks.</td></tr>
<tr><td>Maximally tolerated dosage (MTD) or exposure</td><td>An MTD was not determined. The highest evaluated dosage was 3 mg/kg Q2W across the clinical trials in patients with ASMD.</td></tr>
<tr><td>Dosage proportionality</td><td>Following IV infusions of 0.3 to 3 mg/kg Q2W, exposures of olipudase alfa were approximately dose proportional.</td></tr>
<tr><td>Accumulation</td><td>No accumulation of olipudase alfa was observed following repeated administration of 3.0 mg/kg Q2W.</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Volume of distribution</td><td>The mean (SD) volume of distribution of olipudase alfa is 13 (2) L in adult patients with ASMD.</td></tr>
<tr><td>Plasma protein binding</td><td>Plasma protein binding has not been characterized for olipudase alfa.</td></tr>
</table>

Characteristic	Drug Information
Elimination	
Clearance	The mean (SD) clearance of olipudase alfa is 0.33 (0.07) L/h (22%) in adult patients with ASMD.
Terminal Half-life	The mean half-life ranged from 32 to 38 hours in adult patients with ASMD.
Metabolic pathway(s)	Metabolic pathway of olipudase alfa has not been characterized. Olipudase alfa is expected to be degraded into small peptides and amino acids via catabolic pathways.
Intrinsic Factors and Specific Populations	
Body weight	Body weight was identified as a significant covariate on clearance of olipudase alfa. Subjects with lower body weight (e.g., younger pediatric subjects) are predicted to have lower exposure compared to subjects with higher body weight (e.g., adults) at the same body weight-based dose (e.g., 3 mg/kg). A dose adjustment based on body weight is not needed.
Age	Based on population PK analysis, after consideration of the body weight effect age did not have clinically meaningful effects on the PK of olipudase alfa. A dose adjustment based on body weight is not needed.
Renal impairment	No dedicated trial of the impact of renal impairment on the PK of olipudase alfa has been conducted. Intact olipudase alfa (molecular weight of approximately 76 kDa) is unlikely to be filtered by kidney or excreted in urine.
Hepatic impairment	No dedicated trial of the impact of hepatic impairment on the PK of olipudase alfa has been conducted. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of therapeutic proteins such as olipudase alfa.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	No CYP450-mediated drug-drug interaction studies were conducted for olipudase alfa. As a therapeutic protein, olipudase alfa is unlikely to be involved in CYP450-mediated drug interactions.
Inhibition/induction of transporter systems	No transporter-mediated drug-drug interaction studies were conducted for olipudase alfa. As a therapeutic protein, olipudase alfa is unlikely to be involved in transporter-mediated drug interactions.
Immunogenicity (if applicable)	
Bioanalysis	The immunogenicity of olipudase alfa was assessed in adult subjects with ASMD from 3 studies (DFI13412, DFI12712/ASCEND, and LTS13632) and pediatric subjects with ASMD from 2 clinical studies (DFI13803/ASCEND-Peds, and LTS13632). A validated electrochemiluminescent assay was used to detect anti-olipudase alfa antibodies (total anti-drug antibody [ADA]) in plasma. An assay identical to the total ADA assay was used to detect cross-reactive anti-olipudase alfa antibodies by method bridging. Two validated assays were used to determine the neutralizing activity of ADA: (1) the inhibition of enzymatic activity and (2) the inhibition of cellular uptake. A validated assay was used to detect anti-olipudase alfa IgE antibodies.

Characteristic	Drug Information
Incidence	Following 0.4 to 3.7 years of treatment with olipudase alfa in adult subjects with ASMD (ASCEND), 9 out of 30 (30%) subjects developed anti-olipudase alfa antibodies (ADA). One out of these 9 adult subjects had neutralizing antibodies (NAb) that inhibited the olipudase alfa enzyme activity. None of the subjects developed NAb that inhibited the cellular uptake of olipudase alfa. Following 2.5 to 3.2 years of treatment with olipudase alfa in pediatric subjects with ASMD (ASCEND-Peds), 6 out of 8 (75%) subjects developed ADA. One out of the 6 pediatric subjects developed NAb that inhibited olipudase alfa enzyme activity. None of the subjects developed NAb that inhibited the cellular uptake of olipudase alfa. The one pediatric subject in ASCEND-Peds who experienced an anaphylactic reaction developed IgE ADA.
Clinical impact	There was no identified clinically significant effect of ADA on PK of olipudase alfa. Because of small number of patients receiving process C(b) (4) olipudase alfa in ASCEND and ASCEND-Peds, the effect of ADA on the PD and effectiveness of olipudase alfa is unknown. Following 52 weeks of treatment with olipudase alfa in adult subjects with ASMD, infusion-associated reactions (including hypersensitivity reactions) occurred in a higher percentage in olipudase alfa-treated patients who developed ADA compared to those who did not develop ADA (73% versus 44%). One olipudase alfa-treated pediatric patient (18-months old) experienced an anaphylactic reaction during the sixth infusion and developed IgE ADA and the highest IgG ADA titers (ADA peak titer 1,600) of among the pediatric patients in ASCEND-Peds.

5.1. Nonclinical Assessment of Potential Effectiveness

Nonclinical confirmatory evidence is limited to the demonstration that treatment of ASMKO mice with native ASM or rhASM achieved dose- and duration-dependent reductions in SPM accumulation – a surrogate endpoint - in liver, spleen, kidney, and lung. A single dose (5 mg/kg) of native ASM reduced SPM levels on days 1 to 7 in liver (maximum -95%, day 7); in spleen (maximum -80%, day 7); and in kidney (maximum -71%, day 7). Conversely, reductions in lung were of lower magnitude (-43% on day 7). SPM levels began to increase after day 7. These findings were confirmed and extended for the course of nonclinical testing, when recombinant human acid sphingomyelinase (rhASM) (olipudase), was administered to ASMKO mice in place of native ASM.

Three-month repeated dose studies in ASMKO mice were generally conducted without toxicokinetic (TK) analyses of olipudase alfa, and – with a single exception at doses ≤3 mg/kg, a dose associated with a sub-therapeutic (0.14) margin as assessed by plasma AUC values relative to the maximum recommended human dosage (MRHD) of olipudase in humans. Olipudase was administered intravenously every other week for 6 to 7 doses. Necropsies were conducted at the end of dosing and at the end of recovery; recoveries of 2 to 4 weeks were incorporated.

Survival in 3-month studies was unaffected at any dose, when compared to that of ASMKO mice treated with vehicle. Lung function, which deteriorates with SPM accumulation, was not directly assessed in ASMKO animals. That said, in one study (06031), histopathology at the end of dosing in control groups included observations of cytoplasmic vacuolization and foamy macrophages in visceral organs, consistent with the untreated phenotype; while observations of reduced incidence/severity of cytoplasmic vacuolization and the numbers/sizes of foamy macrophages were made in tissues and organs of mice from rhASM-treated groups (including liver, kidney, bone marrow, thymus, lymph nodes, adrenal gland, small intestine, spleen, stomach, trachea, pancreas, cervix, ovary, uterus, and epididymis).

Considered together, nonclinical confirmatory evidence is not robust and limited to rhASM-related reduction of SPM in the liver, kidney, and spleen. A survival benefit was not demonstrated in this animal model. Refer to Section 6.3.2 for a discussion of nonclinical confirmatory evidence.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. Proposed Olipudase Alfa Dosage

Olipudase alfa is a hydrolytic liposomal sphingomyelin-specific enzyme developed as an ERT for the treatment of patients with ASMD. Olipudase alfa is administered as an intravenous (IV) infusion. The proposed dosage regimens in patients with ASMD are described below:

- For adult patients (≥18 years old), the proposed starting dose is 0.1 mg/kg once every two weeks (Q2W) and subsequently the dose should be escalated to a maintenance dose of 3 mg/kg. The proposed dose escalation regimen includes 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg Q2W over 14 weeks.
- For pediatric patients (0 to <18 years old), the proposed starting dose is 0.03 mg/kg Q2W and subsequently the dose should be escalated to a maintenance dose of 3 mg/kg. The proposed dose escalation regimen includes 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg Q2W over 16 weeks.

The proposed adult and pediatric dosage regimens have been tested in pivotal clinical trials in adult subjects with ASMD (ASCEND trial) and pediatric subjects with ASMD (ASCEND-Peds trial).

6.1.2. Dose Selection for the Clinical Studies

In the first-in-human trial (SPHINGO00605), the tolerability and safety of olipudase alfa was evaluated after single, ascending doses of olipudase alfa in 11 adult subjects with ASMD. The initial dose of 0.03 mg/kg (3 subjects) was chosen based on a 10-fold safety factor in comparison to the ASMKO mouse's single-dose no adverse effect threshold (NOAEL). Doses were escalated to 0.1 mg/kg (3 subjects), 0.3 mg/kg (2 subjects), 0.6 mg/kg (2 subjects), and 1.0 mg/kg (1 subject) and then the trial was terminated by the Applicant due to hyperbilirubinemia and acute phase inflammatory reaction.

After the first-in-human trial, the Phase 1b multiple ascending dose trial (DFI13412) was designed to evaluate a gradual dose escalation strategy as a means of providing safe and tolerable repeat olipudase alfa doses to adult subjects with ASMD based on the dose-dependent reductions in tissue SPM and amelioration of toxicities observed with a gradual debulking regimen in the ASMKO mouse and the safety and tolerability profile of single-dose olipudase administration in trial SPHINGO00605. The initial dose of 0.1 mg/kg was chosen since it was the highest dose in SPHINGO00605 that was not linked with any treatment-related AEs. This dosage corresponds to the single-dose no observable-effect level, which is three times lower than the ASMKO mouse's single-dose NOAEL. The Q2W dosing frequency was determined based on nonclinical study results to maintain SPM reduction. Following the 0.1 mg/kg starting dose, the within-subject dose escalation was as follows: 0.1, 0.3, 0.3, 0.6, 1.0, 2.0, and 3.0 mg/kg Q2W. The maintenance dosage of 3.0 mg/kg Q2W was based on nonclinical results predicted to efficiently reduce SPM in the lungs in adult subjects with ASMD. The overall treatment duration was 26 weeks after

which the subjects were enrolled to clinical trial LTS13632. Adult subjects with ASMD tolerated the gradual, within-subject dosage escalation protocol well and no major or severe AEs or deaths were reported. Several efficacy endpoints showed improvements at the conclusion of the 26-week treatment period.

For the pivotal ASCEND trial in adult subjects with ASMD, the starting dose of 0.1 mg/kg and gradual within-subject dosage escalation to a target maintenance dose of 3.0 mg/kg Q2W were chosen based on the results of the Phase 1b trial DFI13412. The dose escalation regimen was the same as in DFI13412, with the exception of an additional second 0.6 mg/kg dose to provide an even more gradual within-subject debulking of SPM and subsequent release of ceramide in the first 48 hours post-dose. The dosing regimen was shown to be safe and effective.

The pediatric study (ASCEND-Peds) used the same within-subject dosage escalation method as the adult trials, with doses of 0.03, 0.1, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg administered Q2W. The pediatric trial used a lower starting dose of 0.03 mg/kg, and the dosage escalation plan included an extra dose escalation step (2 more weeks) to achieve the same maintenance dose of 3.0 mg/kg Q2W as the adult ASCEND trial. The overall treatment duration was 64 weeks. The dosing regimen was shown to be safe and effective.

6.1.3. PK/PD Relationship for Plasma Lyso-SPM

The relationship between the plasma Lyso-SPM concentrations and the plasma olipudase alfa concentrations over time was best characterized by a turnover response model 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 K_{out}), Imax, the maximum drug induced inhibitory effect and half maximal inhibitory concentration (IC_{50}), the olipudase alfa plasma concentration at 50% of maximum drug inhibitory effect. Time-varying bodyweight significantly influenced both I_{max} and IC_{50}., with a lower IC_{50} and a slightly higher I_{max} estimated in patients with lower bodyweight. In addition, age was identified to significantly influence the plasma Lyso-SPM turnover time (T_{turn}), with longer T_{turn} estimated in younger patients. Population PK/PD parameters are listed in Table 9.

Table 9. Population PK/PD Parameters for the Final Lyso-SPM Model

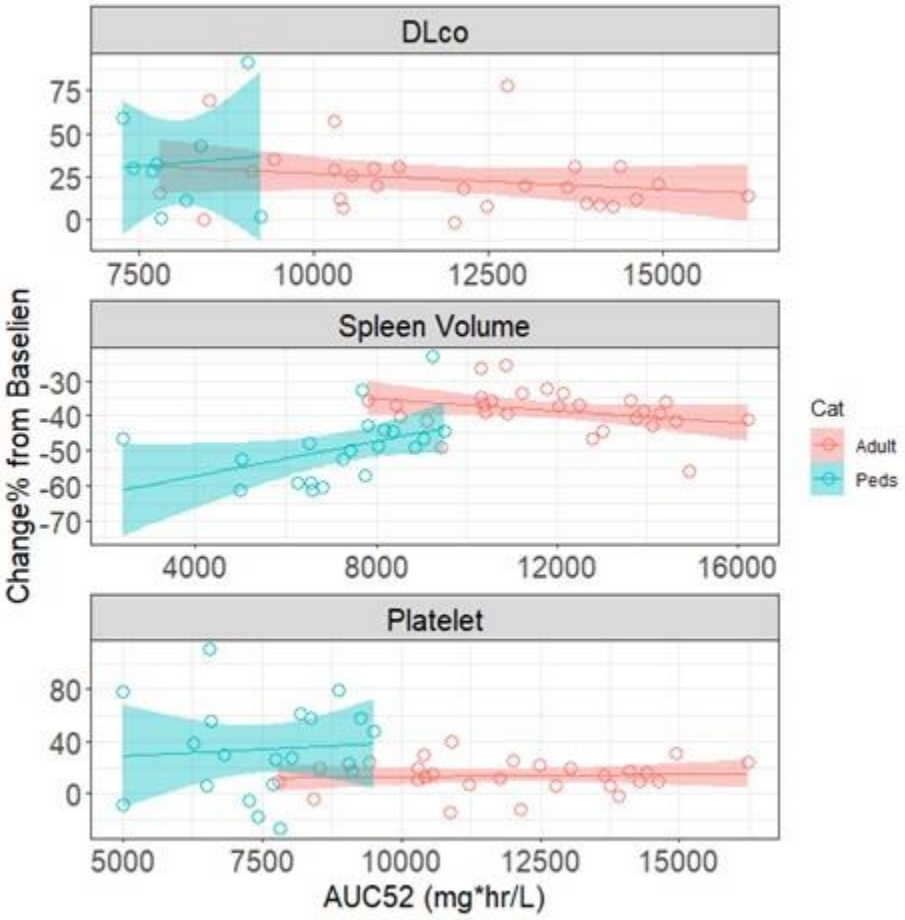
Parameter	Estimate (CV%)	% RSE	[95%CI] (Shrinkage %)
Typical value of Tturn (h)	828	6.07%	[727 ; 928]
Effect of AGE on Tturn	-16.5	10.9%	[-20.1 ; -12.9]
Typical value of Imax (θ2)	0.905	0.73%	[0.891 ; 0.918]
Effect of WT on Imax	-0.241	18.4%	[-0.33 ; -0.152]
Typical value of IC_{50} (θ3, mg/L)	0.00838	12.4%	[0.0063 ; 0.0105]
Effect of WT on IC_{50}	2.6	9.67%	[2.1 ; 3.11]
Inter-individual variability			
ω ² Tturn	0.234 (51.4%)	24.7%	[0.121 ; 0.348] (6.56%)
ω ² Imax	0.14 (38.8%)	41.8%	[0.0254 ; 0.254] (28.2%)
ω ² IC_{50}	2.43 (322%)	24.5%	[1.27 ; 3.6] (3.34%)
Residual variability			
Proportional term	0.035 (18.7%)	4.52%	[0.0319 ; 0.0381]
Additive term (ng/mL)²	48.0	21.5%	[27.8 ; 68.1]

Source: Table III of Applicant's Population PK/PD report.

6.1.4. Exposure-Response Relationships for Efficacy

As shown in Figure 1, there appeared to be no exposure-response (E-R) relationship for the 3 efficacy endpoints assessed in subjects with ASMD: DLco, spleen volume and platelet count. DLco and platelet count increased after olipudase alfa treatment, and the responses were similar between adult and pediatric subjects. Spleen volume decreased after olipudase alfa treatment, and the response in pediatric subjects appeared to be greater than in adult subjects.

Figure 1. Relationships Between Olipudase Alfa Exposure and Efficacy Endpoints

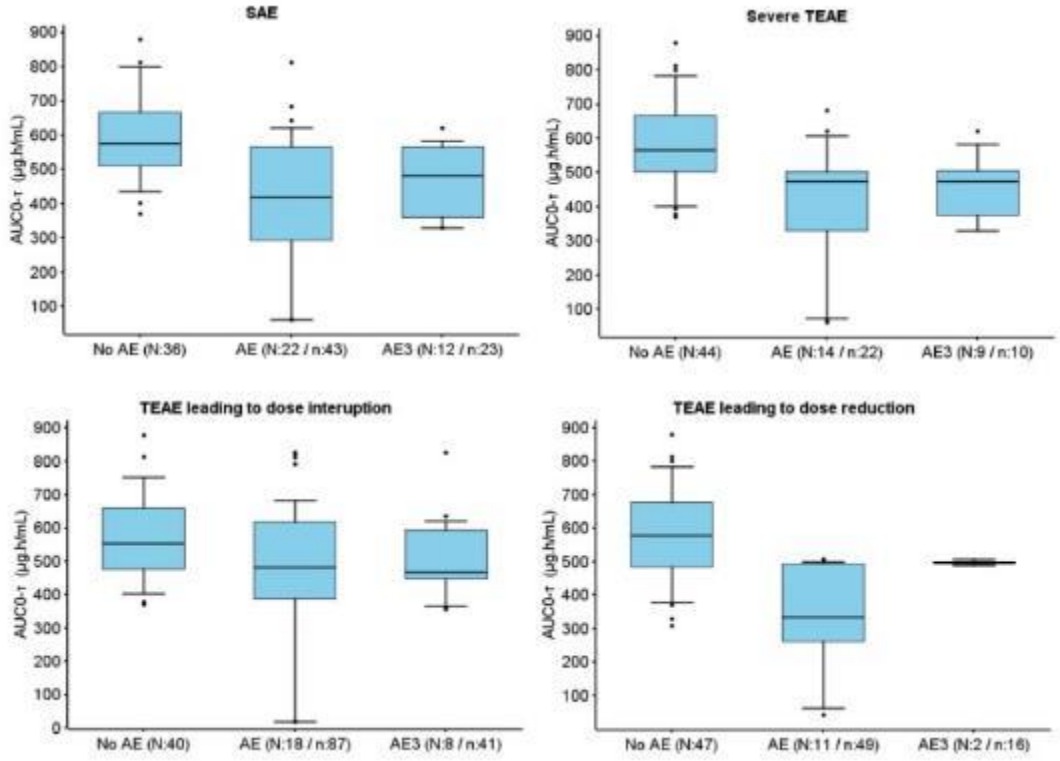


Source: FDA reviewer's analysis based on Applicant's datasets "dlco.xpt", "spleen.xpt", and "platelet.xpt".
Note: Olipudase alfa exposure metrics AUC52 is the cumulative AUC over the 52-week period per individual patient's actual olipudase alfa doses.

6.1.5. Exposure-Response Relationships for Safety

The exposure-safety analyses suggested no apparent E-R relationship for SAE, severe AE, treatment-emergent adverse event (TEAE) leading to dose interruption/reduction, and other AEs (Figure 2), where AUC0-τ is the area under the curve of plasma olipudase alfa concentration versus time profile in a dosing interval at steady-state (Weeks 50 to 52). Using the maximum olipudase alfa plasma concentration (C_{max}) at Week 50, the E-R plots showed similar flat relationship.

Figure 2. Relationship Between Olipudase Alfa Exposure and Safety Endpoints



Source: Figure 3 of Applicant's response to FDA request for exposure-safety analysis.
Note: The box represents the interquartile range of AUC0-τ at Week 52 and the whiskers represent 90% confidence interval. Lower and upper boundary of the box represents the 25th and 75th percentiles, respectively and the line within the box marks the median. No AE: olipudase alfa exposures at the maintenance dose of 3 mg/kg in patients with no AEs. AE: olipudase alfa exposures at the time of AE occurred at any dose in patients with AEs. AE3: olipudase alfa exposures at the time of AE occurred at 3 mg/kg in patients with AEs. N: the number of patients.
Note: AUC_{0-T} values were included for each individual AE.
Abbreviations: n, number of AEs

6.2. Clinical Trials Intended to Demonstrate Efficacy

Two main trials were run to assess efficacy. DFI12712 (ASCEND) was a Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat dose study trial, consisting of both a one-year PAP as well as an up-to-four-year open label ETP. Study DFI13803 (ASCEND-Peds) was a Phase 1/2, multi-center, open-label, ascending dose study, consisting of a 64-week treatment period, after which subjects were eligible to enroll in the Phase 2 long-term study, LTS13632, to continue receiving olipudase alfa.

6.2.1. DFI12712 (ASCEND)

6.2.1.1. Design, DFI12712 (ASCEND)

ASCEND was a Phase 2/3, multicenter, repeat-dose, clinical trial consisting of two consecutive major periods: (1) a 52-week randomized placebo-controlled, double-blind PAP followed by (2) an ETP. Subjects entered the ETP after completing the PAP. The primary objective of the trial

was to evaluate the efficacy of olipudase alfa by assessing changes from baseline to Week 52 in: (1) infiltrative lung disease as measured by DL_{CO} and (2) spleen volume as measured by magnetic resonance imaging (MRI) in association with subject perception related to spleen volume as measured by SRS. Thirty-six subjects were randomized 1:1 to receive an IV infusion of olipudase alfa or placebo Q2W in the PAP. Subjects who were randomized to the active treatment group in PAP underwent dose escalation of olipudase alfa from 0.1, 0.3, 0.3, 0.6, 0.6, 1, 2, and 3 mg/kg in the first 14 weeks and then maintained on 3 mg/kg (or maximum tolerated dose if the randomized dose was intolerable) thereafter into the ETP. Subjects who were randomized to the placebo group in the PAP crossed over to active treatment in the ETP and underwent dose escalation to a target dose of 3.0 mg/kg olipudase alfa. All subjects regardless of treatment assignment had dose escalation (true or mock) using the schedule above during both the PAP and ETP to maintain the double-blind, and treatment group allocation continued to be blinded for all subjects until the end of dose escalation portion in the ETP.

The protocol proposed to analyze two primary efficacy endpoints (one of which was a two-part combination endpoint):

- Percentage change in DL_{CO} at Week 52
- Combination endpoint:
  - Percentage change in spleen volume at Week 52
  - Change in splenomegaly-related score (SRS) at Week 52

These two endpoints comprise the three overall components of the primary efficacy analysis. In addition, five secondary endpoints and an array of additional endpoints were specified.

6.2.1.1.1. Primary Efficacy Endpoints

DL_{CO} Efficacy Endpoint

The first primary efficacy endpoint was the percentage change in DL_{CO}, as measured in percent predicted of normal and adjusted for hemoglobin and ambient barometric pressure, from baseline to Week 52. DL_{CO} measurements were taken as part of the pulmonary function tests which were performed during screening and approximately every six months thereafter.

The Combination Spleen Volume/SRS Endpoint

This endpoint consisted of two components:

- **Percentage Change in Spleen Volume (in MN):** Spleen volume was assessed with abdominal MRI at screening and approximately every 6 months thereafter.
- **Change in Splenomegaly-related Score (SRS):** This score was defined as the seven day mean of the daily sum of scores for the five symptom assessments of 1) abdominal pain, 2) abdominal discomfort, 3) early satiety, 4) abdominal body image, and 5) ability to bend down, which were taken from the Myelofibrosis-Symptom Assessment Form. Each of these 5 daily assessments represents a score from 0 (symptoms absent) to 10 (worst imaginable) for the previous 24 hours. Scores were collected from an eDiary prior to screening, the randomization visit, and quarterly thereafter.

The manner in which these two components are tested is detailed in Section 6.2.1.3.3.

6.2.1.1.2. Secondary Efficacy Endpoints

There were five secondary efficacy endpoints:

1. Percentage change in liver volume (in MN) from baseline to Week 522. Percentage change in platelet counts from baseline to Week 52
3. Week 52 change from baseline in fatigue severity as measured by item 3 of the Brief Fatigue Inventory scale
4. Week 52 change from baseline in pain severity as measured by item 3 of the Brief Pain Inventory scale
5. Week 52 change from baseline in dyspnea severity as measured by the Functional Assessment of Chronic Illness Therapy-Dyspnea tool

6.2.1.2. Eligibility Criteria, DFI12712 (ASCEND)

Inclusion Criteria

Male or female subjects aged 18 years or older who:

- Had a documented deficiency of ASM as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes, and a clinical diagnosis consistent with ASMD type B.
- Had a DL_{CO} ≤70% of the predicted normal value.
- Had a spleen volume ≥6 MN as measured by MRI; patients who have had partial splenectomy would be allowed if the procedure was performed ≥1 year before screening/baseline and the residual spleen volume was ≥6 MN.
- Had an SRS ≥5.
- Had a negative serum pregnancy test for β -human chorionic gonadotropin (for female patients of childbearing potential).
- Willing to practice true abstinence in line with their preferred and usual lifestyle, or use 2 acceptable, effective methods of contraception for up to 15 days following their last dose of study drug (for female patients of childbearing potential and male patients).

Exclusion Criteria

- Received an investigational drug within 30 days before study enrollment.
- Had a medical condition or any other serious medical condition that my preclude participation in the study.
- Had a platelet count <60 x $10^3/\mu L$ based on the average of two samples.
- Had an international normalized ratio >1.5.
- Had alanine aminotransferase (ALT) or AST >250 international units (IU)/L or total bilirubin >1.5 mg/dL (except for patients with Gilbert's syndrome).
- Had a major organ transplant.
- Were scheduled during the study for in-patient hospitalization including elective surgery and excluding the liver biopsies required per protocol.
- Were unable to adhere to the requirements of the study in the opinion of the investigator.
- Unwilling or unable to abstain from the use of alcohol for one day before and three days after each study drug infusion.

- Unwilling or unable to avoid 10 days before and 3 days after the protocol scheduled liver biopsies the use of medications or herbal supplements that are potentially hepatotoxic and/or may cause or prolong bleeding.
- Required medications that may decrease olipudase alfa activity.
- Required the use of invasive ventilatory support.
- Required the use of noninvasive ventilator support while awake for longer than 12 hours daily.
- Were breast-feeding.

6.2.1.3. Statistical Analysis Plan, DFI12712 (ASCEND)

The SAP was finalized on November 4, 2019. All efficacy endpoints were analyzed based on the modified intent-to-treat (mITT) population over the PAP, which spanned the period from baseline to Week 52. The mITT population was defined as all subjects who were randomized and received at least one (partial or total) infusion. The SAP also defined the mITT-C population as the mITT population, excluding those subjects who received process-B olipudase alfa. Missing data was not imputed in the mixed models for repeated measures (MMRM) analyses for the primary endpoints.

Reviewer's Comments: As mentioned in Section 3.2, five patients received process-B olipudase alfa in addition to process-C. Although the main efficacy analysis results based on the mITT and mITT-C populations are similar, the primary analysis in this review focuses on the mITT-C population because of the following reasons: (1) the processes B and C were determined analytically incomparable (see Section 7.7.2), (2) process C is the to-be-marketed version, and (3) the data from the process C treated patients are used to inform labeling .

6.2.1.3.1. Analyses for Efficacy Endpoint Components

The SAP-defined analyses for all three components of the two primary endpoints as well as the secondary endpoints used MMRM. Each model included baseline values for the variable of interest, baseline age, treatment arm, study visit, and a study visit-by-treatment arm interaction term as covariates. An unstructured covariance matrix was used to capture correlations among repeated measures within the same subject. Comparisons between treatment arms were made with least-square mean contrasts at the Week 52 visit, with denominator degrees of freedom estimated using the Kenward-Roger approximation. All endpoint values in the PAP were to be used, except for those taken after initiation of rescue therapy. (Ultimately no rescue therapy was required in this trial.)

6.2.1.3.2. Sensitivity and Supportive Analyses

Primary Endpoints

For each of the primary endpoint components, responder analyses were performed. Subjects were considered responders if they exhibited a percentage decrease in spleen volume ≥ 30%, an absolute improvement in DL_{CO} ≥15%, or an absolute decrease in SRS of ≥12.5 points, in the three respective analyses. Additionally, several sensitivity analyses were conducted which:

- Restricted the analysis to the per-protocol population;
- Restricted the analysis to the mITT-C population (i.e., excluded subjects who received Process B transfusions);
- Used a pattern mixture model to assess robustness to the missing at random assumption; and
- Used the Wilcoxon-Mann-Whitney test to test the normality assumption, where missing data were imputed using last observation carried forward.

For the DL_{CO} and spleen volume components, an additional supportive analysis analyzed the absolute – rather than percentage – change. For the SRS component, an additional supportive analysis analyzed the first three questions which pertain to symptoms, and the last two questions which pertain to subject impact, using separate models.

Secondary Endpoints

No sensitivity analyses were planned for secondary endpoints, but a supportive summary of the mITT-C population was to be provided.

6.2.1.3.3. Multiplicity Strategy for Primary and Secondary Endpoints

The following is the SAP-defined multiplicity testing strategy that incorporates the Hochberg method for the DLco and spleen volume endpoints:

The two-sided significance (p-value) for both the DL_{CO} endpoint and spleen volume endpoint component was assessed with separate MMRM.
The larger of these p-values was compared to 0.05:

- If the larger p-value was <0.05, both the DL_{CO} endpoint and the spleen volume component of the combination endpoint were considered significant.
- If the larger p-value was ≥0.05 but the smaller p-value was <0.025, then the larger was considered insignificant but the smaller significant.
- If the larger p-value was ≥0.05 and the smaller p-value was ≥0.025, then neither were considered significant.

Assessing significance of the combination endpoint:

- If spleen volume was not significant in 2 above, then the combination endpoint was not considered significant.
- If the spleen volume was significant in 2 above, then the combination endpoint was significant if the SRS component p-value (as determined by the MMRM) was <0.15; but insignificant otherwise.

The trial was considered a "win" if either the DL_{CO} or combination endpoint were significant in the agreed SAP.

Testing of secondary endpoints only proceeded if both the DL_{CO} and combination endpoints were significant. In this case, the secondary endpoints would be tested sequentially in the order given in 6.2.1.1.2. Once a secondary endpoint failed to reach significance, that endpoint and all subsequent endpoints were deemed not significant.

Reviewer's Comment: According to the information in DARRTS, FDA agreed on the win criteria (IND12757 - Reference ID: 3897521).

6.2.1.3.4. Subgroup Analyses

Despite the small total sample size, both the DL_{CO} and spleen volume components had separate subgroup analyses based on whether subjects had "severe" versus "very severe" baseline DL_{CO} and spleen volume measurements. Additionally, all three primary endpoint components were evaluated within the subgroups: subjects with/without baseline ALT or aspartate aminotransferase (AST) abnormality and subjects with/without baseline total bilirubin abnormality. The spleen volume component was also examined for those with/without portal hypertension at baseline. These subgroup analyses used the MMRM model form used in the primary and secondary analyses, but with only the subjects in the relevant subgroup. Additionally, MMRM models were run with all subjects using subgroup and subgroup interactions as covariates.

6.2.1.4. Results of Analyses, DFI12712 (ASCEND)

This section presents subject disposition, baseline demographics, and results of the efficacy analyses for the primary endpoints. Section 6.2.1.4.2 describes the statistically significant improvement shown in the DL_{CO} endpoint between the olipudase alfa versus the placebo arm. Section 6.2.1.4.3 outlines the results from the combination endpoint component: the Spleen Volume component shows a statistically significant improvement in treatment over placebo; however, the SRS component shows no significant difference. As detailed in the multiplicity strategy (Section 6.2.1.3.3 above), this implies that the combination endpoint is not significant; however, the trial is deemed a success because one of the two primary endpoints passed.

6.2.1.4.1. Disposition and Baseline Demographics

Subject Disposition

Disposition information is presented in Table 10 and Table 11. A total of 62 subjects were screened for the trial; 36 of them were randomized to the treatment arms (18 to placebo; 18 to olipudase alfa). Of these, two subjects in each treatment arm discontinued the study.

Table 10. Subject Screening and Randomization, DFI12712 (ASCEND)

Disposition	Number of Subjects
Screened	62
Randomized	36

Source: Table 13 of the Clinical Study Report.

Table 11. Subject Disposition, DFI12712 (ASCEND)

Disposition Category	Placebo (N=18)	Received some process B (N=5)	Received process C only (N=13)	All patients treated with Olipudase alfa (process B or C) (N=18)
Subjects randomized	18 (100%)	5 (100%)	13 (100%)	18 (100%)
ITT/mITT population	18 (100%)	5 (100%)	13 (100%)	18 (100%)
Per protocol population	16 (89%)	5 (100%)	12 (92%)	17 (94%)
Safety population	18 (100%)	5 (100%)	13 (100%)	18 (100%)
Discontinued study drug	0 (0%)	0 (0%)	2 (15%)	2 (11%)
Adverse event	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lack of efficacy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patient decision	0 (0%)	0 (0%)	1 (8%)	1 (6%)
Poor compliance to protocol	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Withdrawal of consent	0 (0%)	0 (0%)	1 (8%)	1 (6%)
Discontinued study during PAP	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Discontinued study during PAP or ETP	2 (11%)	0 (0%)	2 (15%)	2 (11%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patient decisions	0 (0%)	0 (0%)	1 (8%)	1 (6%)
Poor compliance to protocol	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Withdrawal of consent	0 (0%)	0 (0%)	1 (8%)	1 (6%)
COVID-19 related	1 (6%)	0 (0%)	0 (0%)	0 (0%)

Source: May 6, 2022, Information Request.
Abbreviation: mITT, modified intention-to-treat; N, number of subjects; n, number of subjects with at least one event

Baseline Demographics

Subject demographic information is presented in Table 12. The mean ages in the placebo and olipudase alfa groups were 33.5 and 36.2 years respectively. Sex was somewhat imbalanced between the two arms, with 28% men in the placebo arm versus 50% men in the treatment arm. Race and ethnicity were well-balanced between the arms: 89% of each arm was made up of white subjects; 33% and 28% identified as Hispanic in the placebo and treatment arms.

Table 12. Baseline Demographic and Clinical Characteristics, Safety Population, DFI12712 (ASCEND)

Characteristic	Placebo (N=18)	Received some process B (N=5)	Received process C only (N=13)	All patients treated with Olipudase alfa (process B or C) (N=18)
Sex, n (%)				
Male	5 (28%)	1 (20%)	8 (62%)	9 (50%)
Female	13 (72%)	4 (80%)	5 (38%)	9 (50%)
Age, years				
Mean (SD)	33.5 (17.1)	38.8 (15.9)	35.1 (11.9)	36.2 (12.7)
Median (min, max)	24.1 (18.6, 65.9)	40.9 (18.8, 59.9)	34.2 (20.2, 58.7)	34.9 (18.8, 59.9)
Race, n (%)				
White	16 (89%)	5 (100%)	11 (85%)	16 (89%)
Asian	1 (6%)	0 (0%)	1 (8%)	1 (6%)
Other	1 (6%)	0 (0%)	1 (8%)	1 (6%)

Characteristic	Placebo (N=18)	Received some process B (N=5)	Received process C only (N=13)	All patients treated with Olipudase alfa (process B or C) (N=18)
Ethnicity, n (%)				
Hispanic	6 (33%)	1 (20%)	4 (31%)	5 (28%)
Non-Hispanic	12 (67%)	4 (80%)	8 (62%)	12 (67%)
Not Reported	0 (0%)	0 (0%)	1 (8%)	1 (6%)
Country of participation, n (%)				
Argentina	1 (6%)	0 (0%)	1 (8%)	1 (6%)
Australia	2 (11%)	0 (0%)	0 (0%)	0 (0%)
Brazil	2 (11%)	1 (20%)	1 (8%)	2 (11%)
Chile	2 (11%)	0 (0%)	1 (8%)	1 (6%)
France	1 (6%)	0 (0%)	1 (8%)	1 (6%)
Germany	2 (11%)	0 (0%)	1 (8%)	1 (6%)
Italy	2 (11%)	0 (0%)	0 (0%)	0 (0%)
Japan	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Netherlands	0 (0%)	2 (40%)	1 (8%)	3 (17%)
Spain	1 (6%)	1 (20%)	2 (15%)	3 (17%)
Turkey	1 (6%)	0 (0%)	1 (8%)	1 (6%)
United Kingdom	0 (0%)	1 (20%)	2 (15%)	3 (17%)
United States	3 (17%)	0 (0%)	2 (15%)	2 (11%)

Source: May 6, 2022, Information Request.
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic

6.2.1.4.2. Results for DL_{CO} Primary Efficacy Endpoint

The DL_{CO} primary endpoint showed a strong, statistically significant advantage for subjects treated with olipudase alfa over placebo. Table 13 show that baseline values for DL_{CO} were well matched between the placebo and treatments arms: the placebo arm had a mean % predicted DL_{CO} value of 48.5% with a standard deviation (SD) of 10.8%; the treatment arm had mean of 49.1% with a SD of 9.7%. By Week 26, the average percentage increase from baseline in the placebo arm was 1.41% versus 17.1% in the olipudase alfa arm. By Week 52 these percentage increases from baseline were 3.08% and 24.2%, respectively. These correspond to absolute, non-proportional increases of 1.2 and 10.8% predicted DL_{CO}. The MMRM shows the least square mean (LSM) difference of 21.1% which is highly significant (p-value<0.0001). This is reinforced with a model-free Wilcoxon-Mann-Whitney test, that gives a p-value of 0.0004 for the treatment difference.

Table 13. Absolute and Percentage Change in % Predicted DL_{CO} During PAP in mITT-C Population, DFI12712 (ASCEND)

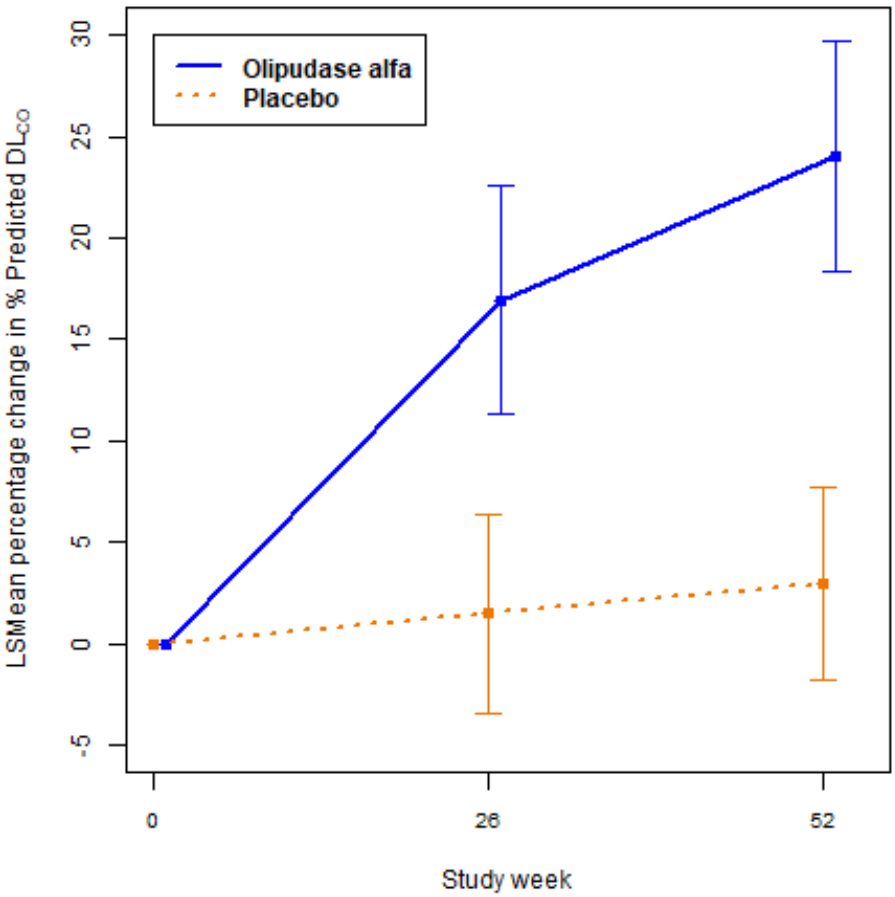
Change in % DL_{CO}	Placebo	Olipudase Alfa	Difference
Baseline values			
Number of subjects with value	18	13	
Mean (SD)	48.45 (10.77)	49.12 (9.69)	
Median (min:max)	46.87 (30.97:69.12)	49.23 (28.90:67.26)	
Week 26			
Number of subjects with value	16	12	

Change in % DL_{CO}	Placebo	Olipudase Alfa	Difference
Absolute change			
Mean (SD)	0.46 (4.51)	7.70 (5.21)	
LS Mean (95% CI)	0.52 (-1.29, 2.34)	7.59 (5.49, 9.69)	7.07 (4.29, 9.84)
P-value for difference between groups (MMRM)			<0.0001
P-value for difference between groups (WMW)			0.0008
Percentage change			
Mean (SD)	1.41 (9.72)	17.13 (16.21)	
LS Mean (95% CI)	1.45 (-3.43, 6.34)	16.93 (11.27, 22.59)	15.48 (7.99, 22.97)
P-value for difference between groups (MMRM)			0.0001
P-value for difference between groups (WMW)			0.0026
Week 52			
Number of subjects with value	17	12	
Absolute change			
Mean (SD)	1.21 (5.27)	10.76 (5.35)	
LS Mean (95% CI)	1.2 (-0.57, 2.96)	10.71 (8.61, 12.81)	9.51 (6.77, 12.25)
P-value for difference between groups (MMRM)			<0.0001
P-value for difference between groups (WMW)			0.0004
Percentage change			
Mean (SD)	3.08 (11.24)	24.19 (18.63)	
LS Mean (95% CI)	2.98 (-1.79, 7.74)	24.02 (18.37, 29.68)	**21.05 (13.65, 28.44)**
P-value for difference between groups (MMRM)			**<0.0001**
P-value for difference between groups (WMW)			0.0004

Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Numbers related to the primary endpoint are shown in bold.
Abbreviations: CI, confidence interval; DL_{CO}, diffusion capacity of carbon monoxide; max, maximum; min, minimum; MMRM, mixed model for repeated measures; SD, standard deviation; WMW, Wilcoxon-Mann-Whitney test, mITT-C, modified intent to treat excluding process-B subjects.

Figure 3 illustrates the mean (as determined by MMRM LSM) percentage change in % predicted DL_{CO} by treatment arm. The significant advantage in the olipudase alfa arm is shown by the well-separated LSM confidence intervals at Week 52. Figure 4 illustrates the progression of individual subjects during the PAP.

Figure 3. LSMeans of Percent Change in % Predicted DL_{CO} Among mITT-C Population During PAP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Error bars reflect the LSMeans confidence intervals from the MMRM.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period.

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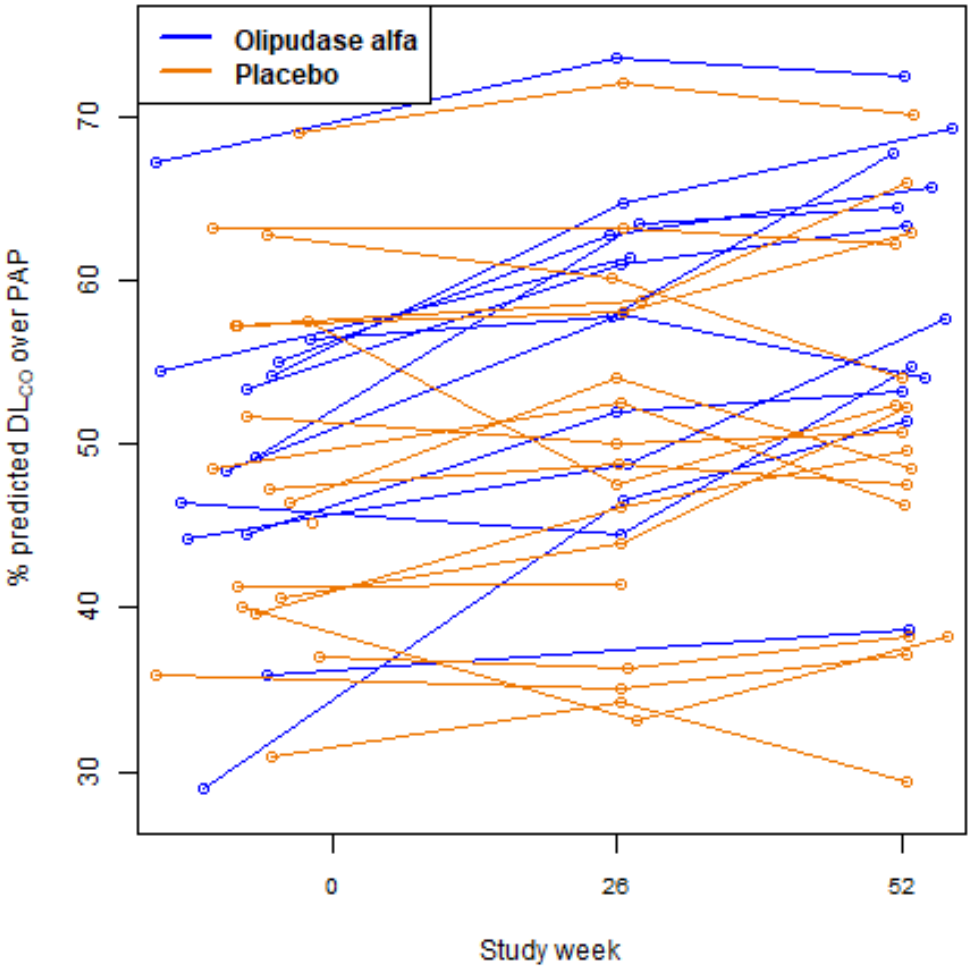
Figure 4. Individual Progression of % Predicted DL_{CO} Among mITT-C Population During PAP, DFI12712 (ASCEND)

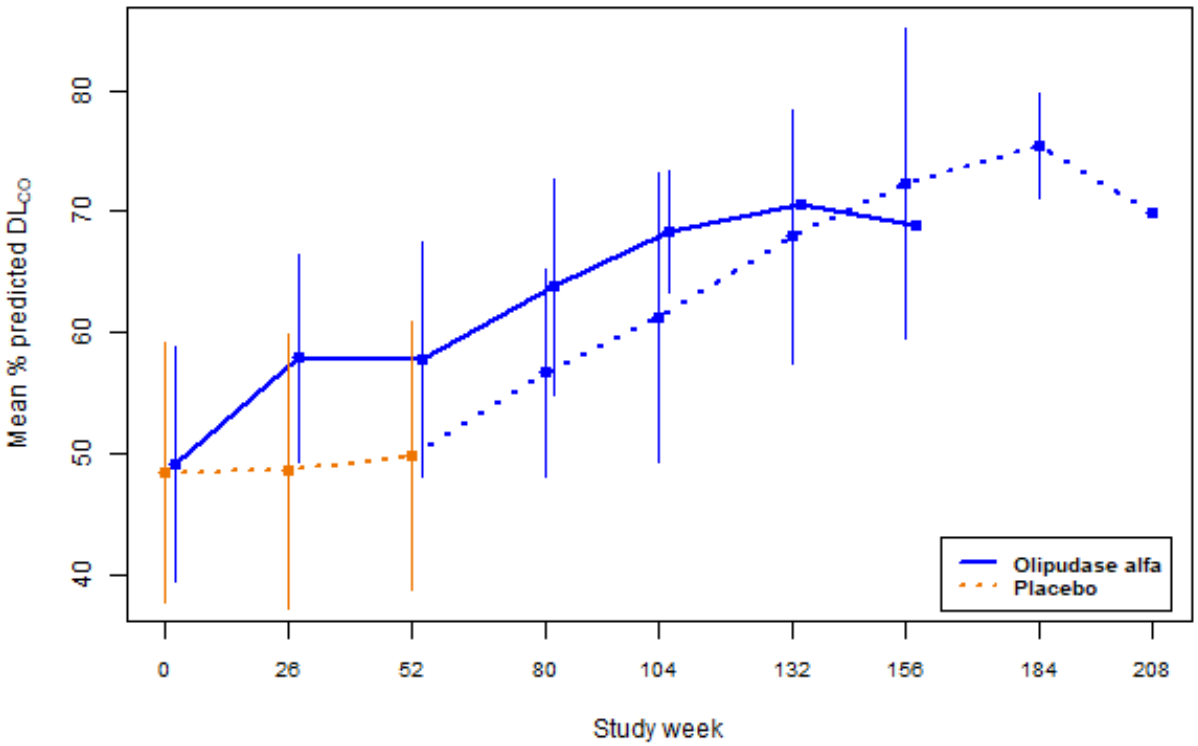


Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Blue is the treatment arm. Gold is the placebo.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period.

The responder analysis for DL_{CO} showed a clear advantage for the olipudase alfa arm, despite relatively few total responders. Four of the 12 subjects (33%) in the olipudase alfa arm showed an absolute increase in DL_{CO} from baseline ≥15%; the placebo arm showed none (0%).

Figure 5 shows the means of DL_{CO} over both the PAP and ETP, and Figure 6 shows the corresponding individual progressions. Once subjects were switched to olipudase alfa after placebo they demonstrated a similar increase in DL_{CO} to the original treated subjects. Finally, Figure 7 shows the progression in DL_{CO} over this period, with the most recently used treatment manufacturing process at each measurement point.

Figure 5. Observed Means (SD) of % Predicted DL_{CO}, Among mITT-C Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Error bars show the observed standard deviations, and not confidence intervals.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; ETP, extended treatment period; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period.

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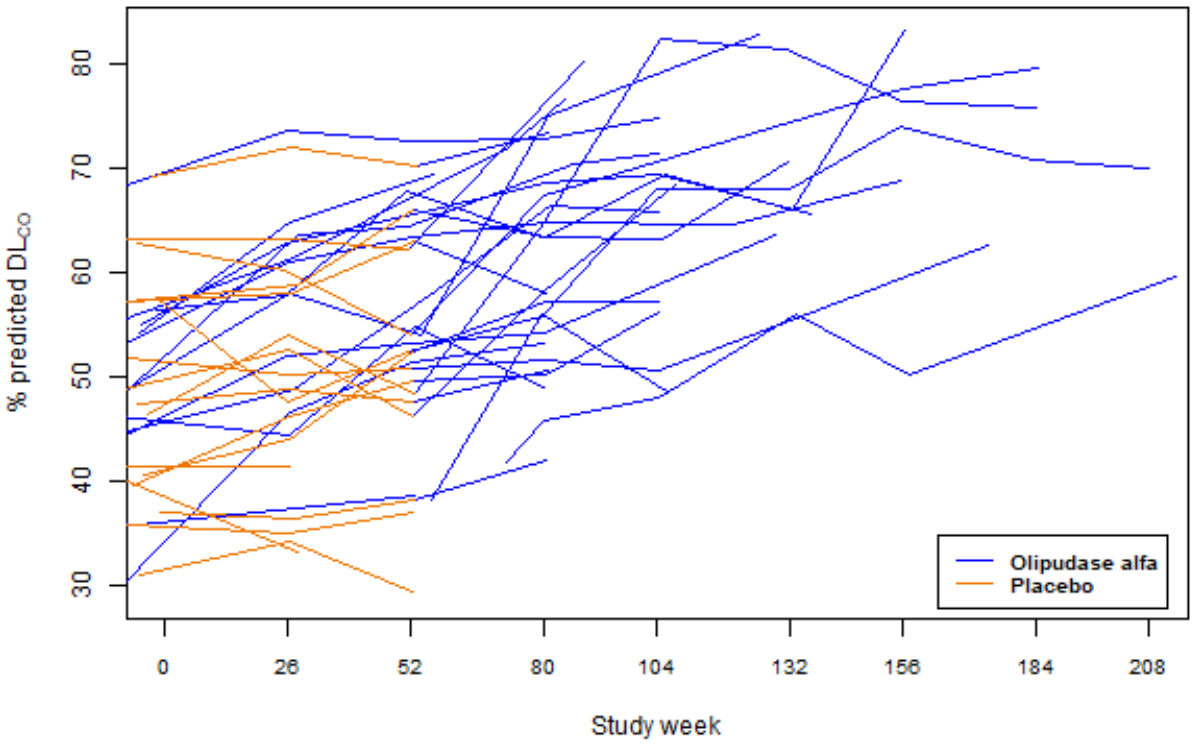
Figure 6. Observed Progressions of % Predicted DL_{CO} Among mITT-C Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; ETP, extended treatment period; PAP, primary analysis period; mITT-C, modified intent to treat excluding process-B subjects.

Treatments using manufacturing processes B and C (b) (4) were administered during the PAP; during the ETP processes C (b) (4) and C (b) (4) were administered (Figure 7). No obvious differences emerge between progress across manufacturing processes – however, it would be difficult to discern existing differences since the different processes were used sporadically.

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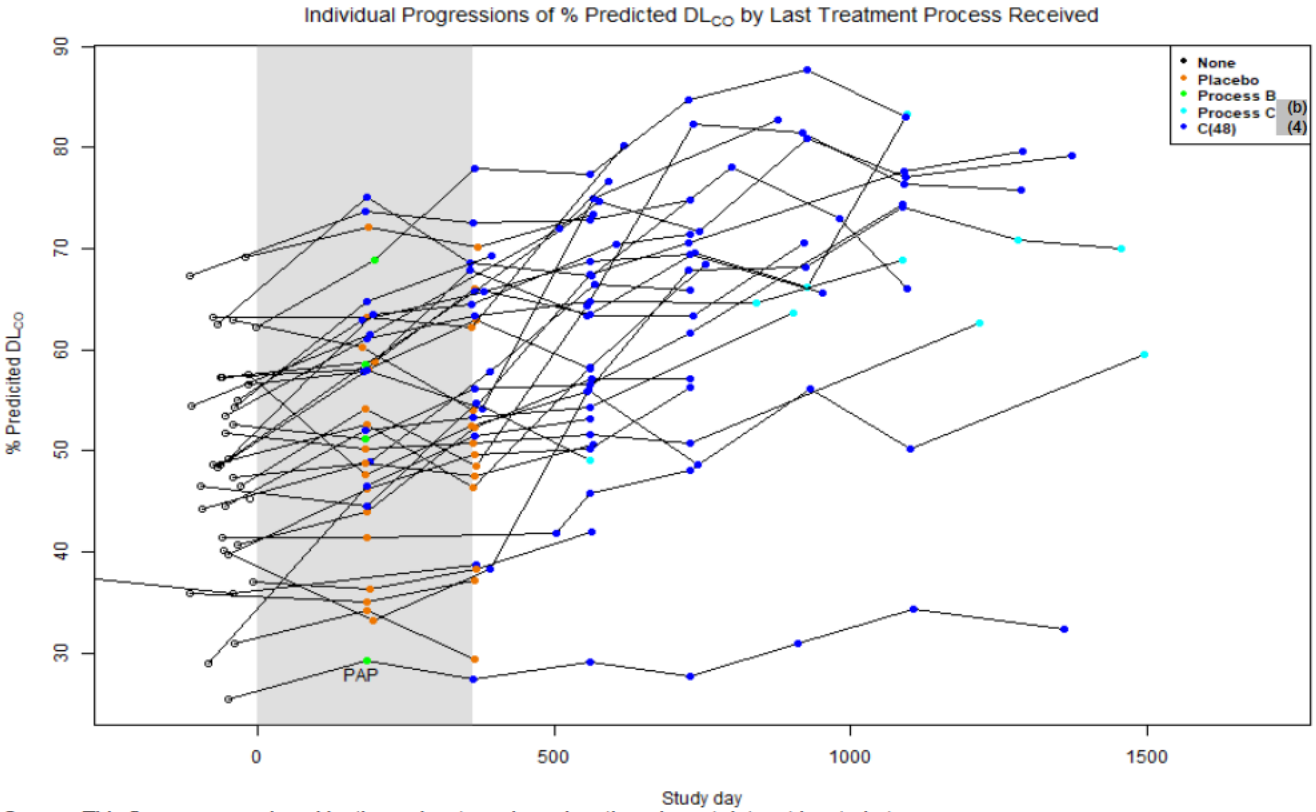
Figure 7. Observed Progressions of % Predicted DL_{CO} by Last Treatment Process Received, Among mITT Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: ETP, extended treatment period; mITT, modified intent to treat; PAP, primary analysis period.

Subgroup Analysis by Sex

The mITT-C population in the ASCEND study included 13 male and 18 female subjects. Table 14 provides the MMRM analysis for the DLco endpoint at Week 52 for the male and female subjects separately. In both the male and female cohorts, percentage and absolute change show statistically significant improvement for patients treated with olipudase alfa over placebo. The data show no marked difference in effect size between men and women. Of note, several subgroups have very small sample sizes (n=4 women received olipudase alfa and had data at Week 52; n=4 men received placebo and had data at Week 52).

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Table 14. Subgroup Analysis by Sex in % Predicted DL_{CO} at Week 52 in mITT-C Population, DFI12712 (ASCEND)

Subgroup Analysis	Placebo	Olipudase Alfa	Difference (95% CI)
N / Mean (SD)			
Baseline values			
Overall	18 / 48.5 (10.8)	13 / 49.1 (9.7)	
Male subjects	5 / 47.4 (9.4)	8 / 47.8 (8.7)	
Female subjects	13 / 48.9 (11.6)	5 / 51.3 (11.8)	
N / LSMean (95%CI)			
Absolute Change at Week 52			
Overall	17 / 1.20 (-0.57, 2.96)	12 / 10.7 (8.6, 12.8)	9.51 (6.77, 12.25), p<0.0001
Male subjects	4 / 2.53 (-1.51, 6.57)	8 / 12.1 (9.25, 14.9)	9.56 (4.62, 14.5), p=0.0004
Female subjects	13 / 0.78 (-0.87, 2.42)	4 / 7.95 (5.01, 10.9)	7.18 (3.80, 10.6), p=0.0001
Percentage Change at Week 52			
Overall	17 / 2.98 (-1.79, 7.74)	12 / 24.0 (18.4, 29.7)	21.1 (13.7, 28.4), p<0.0001
Male subjects	4 / 8.58 (-3.12, 20.3)	8 / 28.1 (19.9, 36.3)	19.6 (5.26, 33.9), p=0.0089
Female subjects	13 / 1.32 (-1.94, 4.57)	4 / 15.7 (9.88, 21.6)	14.2 (7.71, 21.1), p=0.0001

Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: CI, confidence interval; DL_{CO}; diffusion capacity for carbon monoxide; mITT-C, modified intent to treat excluding process-B subjects; N, total number of subjects; LSMean; least squares mean; SD, standard deviation

6.2.1.4.3. Results for Combination Primary Efficacy Endpoint

Percentage Change in Spleen Volume (in MN)

The spleen volume component of the combination primary endpoint also showed a strong, statistically significant advantage for subjects treated with olipudase alfa over placebo. Table 15 shows that baseline values for spleen volume (multiples of normal [MN]) were well matched between the placebo and treatments arms: the placebo arm had a mean value of 11.2 with a SD of 3.8; the treatment arm had a mean of 11.5 with a SD of 4.8. By Week 26, the average percentage decrease from baseline in the placebo arm was 2.4% versus 29.3% in the olipudase alfa arm. By Week 52 these percentage decreases from baseline had become -0.4% and 38.8%, respectively. These correspond to absolute, non-percentage decreases of -0.09 and 4.32. The MMRM shows a LSM difference of 39.2% which is highly significant (p-value<0.0001). This is reinforced with a Wilcoxon-Mann-Whitney test, that gives a p-value of <0.0001 for the treatment difference.

Figure 8 illustrates the mean (as determined by MMRM LSM) percentage change in spleen volume (MN) by treatment arm, and Figure 9 illustrates the progression of individual subjects during the PAP. The significant advantage in the olipudase alfa arm is again shown by the highly separated LSM confidence intervals (CIs) at Week 52.

Table 15. Absolute and Percentage Change in Spleen Volume (MN) During PAP in mITT-C Population, DFI12712 (ASCEND)

Change in Spleen Volume	Placebo	Olipudase Alfa	Difference
Baseline values			
Number of subjects with value	18	13	
Mean (SD)			
	11.21 (3.84)	11.51 (4.75)	
Median (min:max)			
	10.68 (6.05:18.06)	10.66 (6.30:20.49)	

Change in Spleen Volume	Placebo	Olipudase Alfa	Difference
Week 26			
Number of subjects with value	17	13	
Absolute change			
Mean (SD)	-0.13 (1.00)	-3.30 (1.50)	
LS Mean (95% CI)	-0.15 (-0.70, 0.40)	-3.29 (-3.84, -2.74)	-3.15 (-3.88, -2.42)
P-value for difference between groups (MMRM)			<0.0001
P-value for difference between groups (WMW)			<0.0001
Percentage change			
Mean (SD)	-2.43 (9.82)	-29.27 (8.93)	
LS Mean (95% CI)	-2.44 (-5.96, 1.07)	-29.29 (-33.44, -25.13)	-26.87 (-32.39, -21.36)
P-value for difference between groups (MMRM)			<0.0001
P-value for difference between groups (WMW)			<0.0001
Week 52			
Number of subjects with value	17	13	
Absolute change			
Mean (SD)	0.09 (1.06)	-4.32 (1.76)	
LS Mean (95% CI)	0.07 (-0.48, 0.63)	-4.31 (-4.85, -3.76)	-4.39 (-5.12, -3.66)
P-value for difference between groups (MMRM)			<0.0001
P-value for difference between groups (WMW)			<0.0001
Percentage change			
Mean (SD)	0.42 (11.99)	-38.77 (9.09)	
LS Mean (95% CI)	0.40 (-3.11, 3.92)	-38.78 (-42.94, -34.63)	**-39.22 (-44.73, -33.70)**
P-value for difference between groups (MMRM)			**<0.0001**
P-value for difference between groups (WMW)			<0.0001

Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Numbers related to the primary endpoint component are shown in bold.
Abbreviations: CI, confidence interval; DLCO, diffusion capacity of carbon monoxide; max, maximum; min, minimum; mITT-C, modified intent to treat excluding process-B subjects; MMRM, mixed model for repeated measures; SD, standard deviation; WMW, Wilcoxon-Mann-Whitney test.

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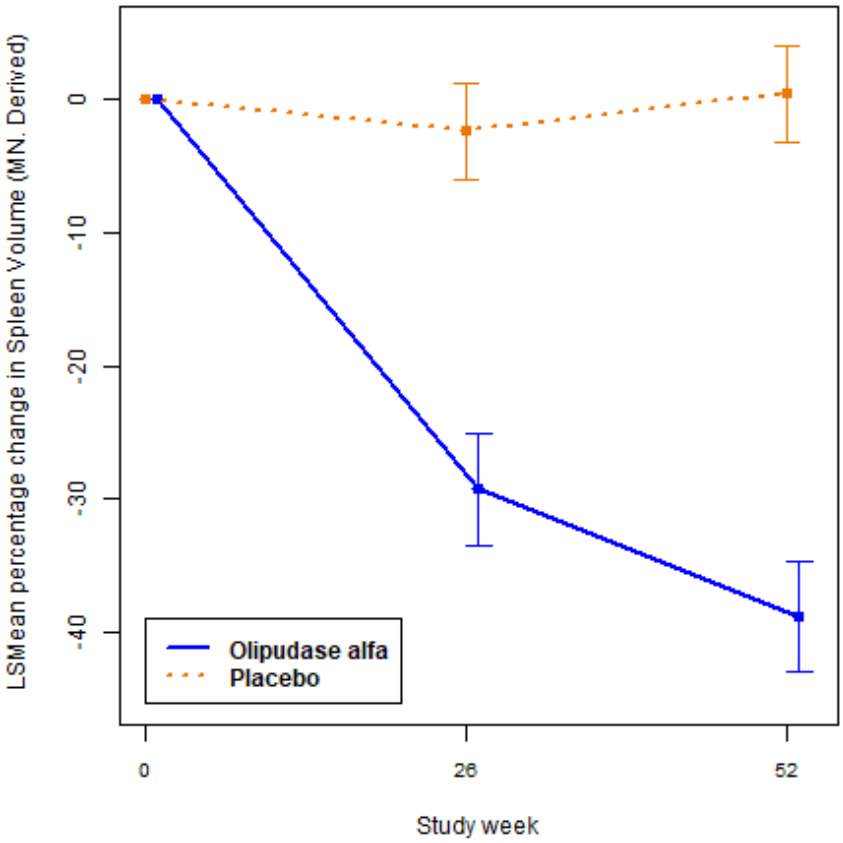
Figure 8. LSMeans of Percentage Change in Spleen Volume (MN) Among mITT-C Population During PAP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Error bars on the right reflect the LSMeans confidence intervals from the MMRM.
Abbreviations: LSMean, least squares means; PAP, primary analysis period; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal.

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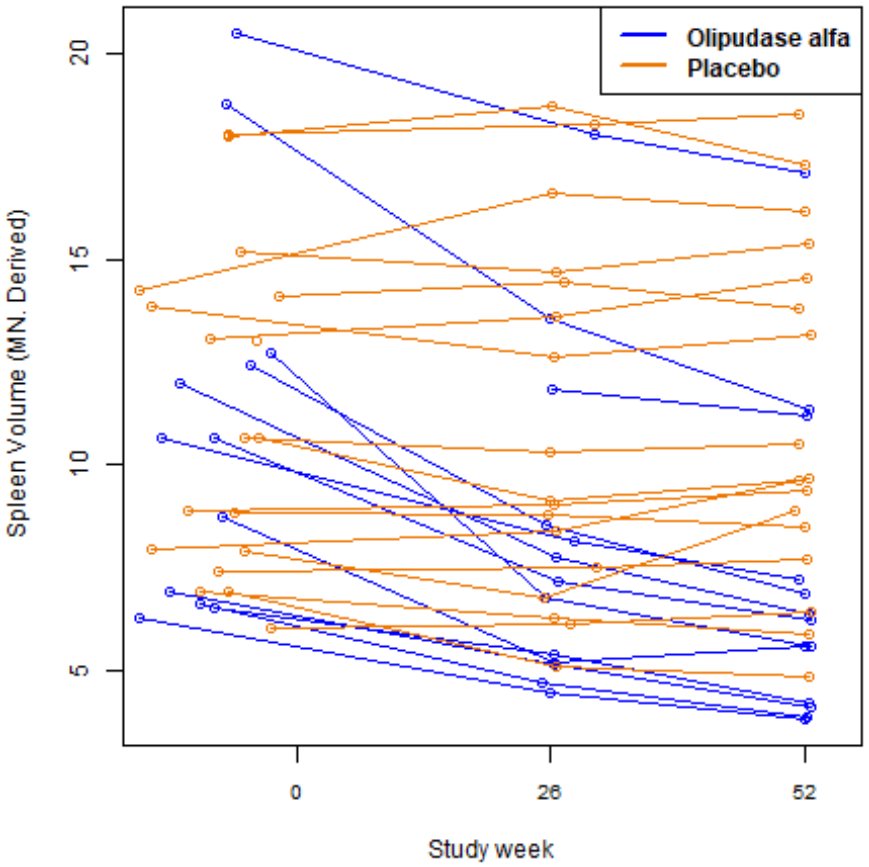
Figure 9. Individual Progressions of Spleen Volume (MN) Among mITT-C Population During PAP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Blue is the treatment arm. Gold is the placebo.
Abbreviations: mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal; PAP, primary analysis period.

The responder analysis for spleen volume shows clear improvement over placebo for subjects in the olipudase alfa arm. Twelve of the 13 (92%) olipudase alfa patients demonstrated a ≥ 30% percentage reduction in Spleen Volume at Week 52; whereas the placebo arm had none (0%).

Figure 10 shows the mean values by treatment arm of spleen volume over both the PAP and ETP, and Figure 11 shows the corresponding individual progressions. As with DL_{CO}, subjects that switch from placebo to olipudase alfa demonstrate roughly similar post-switch improvement to the original treated subjects.

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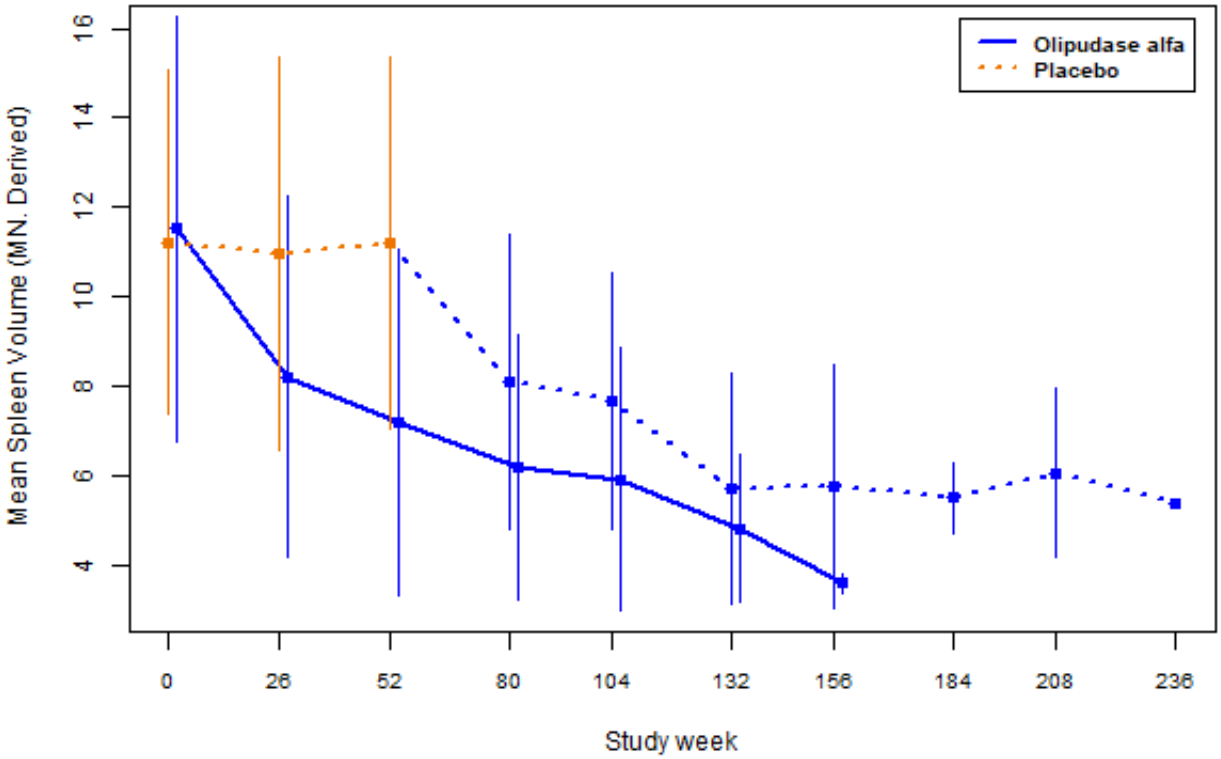
Figure 10. Observed Means of Spleen Volume (MN) Among mITT-C Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Error bars reflect the observed standard deviations, and not confidence intervals.
Abbreviations: ETP, extended treatment period; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal; PAP, primary analysis period.

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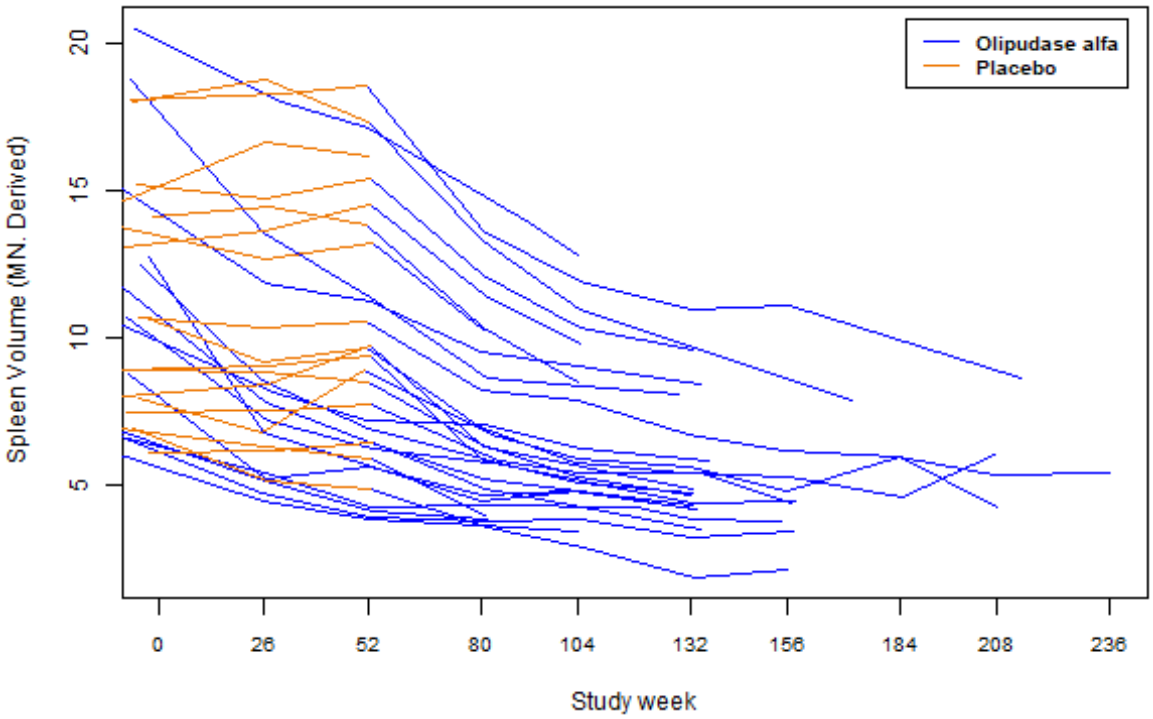
Figure 11. Observed Progressions of Spleen Volume (MN) Among mITT-C Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: ETP, extended treatment period; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal; PAP, primary analysis period.

Figure 12 shows the progression in spleen volume over this period, with the most recently used treatment manufacturing process at each measurement point. Treatments using manufacturing processes B and C (b) (4) were administered during the PAP; during the ETP processes C (b) (4) and C (b) (4) were administered. Again, no obvious differences emerge between manufacturing processes – however, discerning legitimate differences would be difficult since the different processes were used sporadically.

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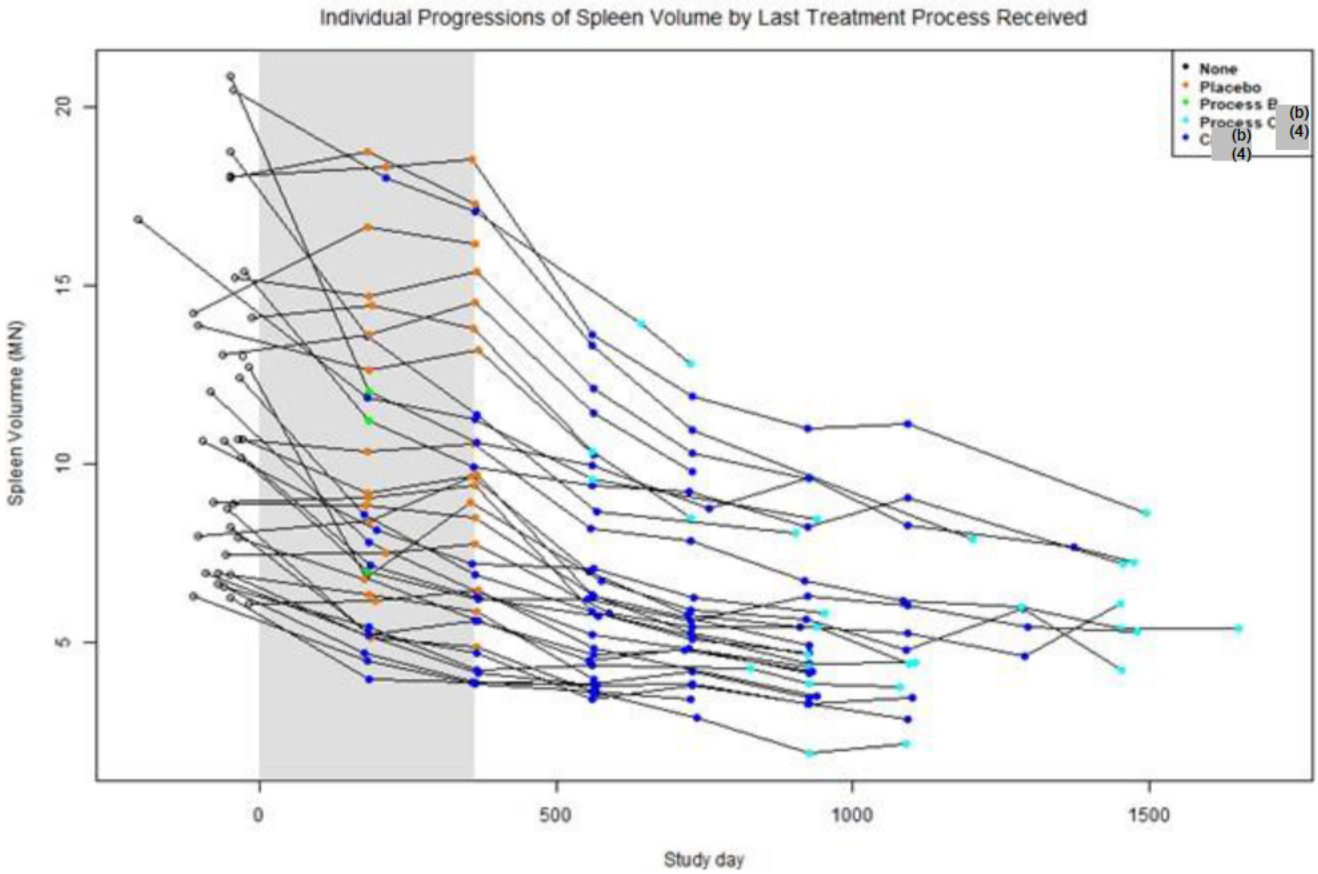
Figure 12. Observed Progressions of Spleen Volume (MN) by Last Treatment Process Received Among mITT Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: ETP, extended treatment period; mITT, modified intent to treat; MN, multiples of normal; PAP, primary analysis period.

Change in Splenomegaly-Related Score (SRS)

The splenomegaly-related score (SRS) component of the combination primary endpoint was the only primary endpoint that did not show an advantage for subjects treated with olipudase alfa over placebo. Because of this, according to the multiplicity scheme in 6.2.1.3.3, the primary combination endpoint is considered to have failed (despite a significant spleen volume component), and no secondary endpoints were tested as a result.

Table 16 shows that baseline values for SRS are somewhat evenly matched, with subjects in the placebo arm scoring higher (more severe initial symptoms): the placebo arm showed a mean value of 28.1 (scores can range from 0-50) with a SD of 10.6; the treatment arm showed a mean of 24.3 with a SD of 11.5. By Week 26, the average (absolute) decrease from baseline in the placebo arm was 7.07 versus 4.12 in the olipudase alfa arm. By Week 52 these decreases from baseline had become 9.81 and 5.32, respectively. Therefore, at both Week 26 and Week 52 the placebo arm showed slightly greater improvement, although the difference is insignificant using both the MMRM LSM as well as the Wilcoxon Mann-Whitney test at Week 52. These trends were broadly shared across all subdomains of the SRS.

Table 16. Absolute and Percentage Change in SRS During PAP in mITT-C Population, DFI12712 (ASCEND)

Change in SRS	Placebo	Olipudase Alfa	Difference
Baseline values			
Number of subjects with value	17	13	
Mean (SD)	28.05 (10.56)	24.31 (11.46)	
Median (min:max)	24.86 (10.17:48.00)	20.8 (9.00, 47.67)	
Week 26			
Number of subjects with value	15	12	
Absolute change			
Mean (SD)	-7.07 (8.66)	-4.12 (7.11)	
LS Mean (95% CI)	-6.76 (-10.09, -3.43)	-4.12 (-7.91, -0.32)	2.67 (-2.44, 7.77)
P-value for difference between groups (MMRM)			0.301
P-value for difference between groups (WMW)			0.6141
Percentage change			
Mean (SD)	-27.35 (35.54)	-16.12 (28.02)	
LS Mean (95% CI)	-27.53 (-41.05, -14.01)	-16.14 (-31.34, -0.94)	11.35 (-9.10, 31.79)
P-value for difference between groups (MMRM)			0.2723
P-value for difference between groups (WMW)			0.5806
Week 52			
Number of subjects with value	15	11	
Absolute change			
Mean (SD)	-9.81 (10.39)	-5.32 (9.59)	
LS Mean (95% CI)	-9.29 (-12.62, -5.96)	-5.55 (-9.48, -1.62)	**3.77 (-1.44, 8.98)**
P-value for difference between groups (MMRM)			**0.1533**
P-value for difference between groups (WMW)			0.3565
Percentage change			
Mean (SD)	-39.37 (40.98)	-22.23 (37.08)	
LS Mean (95% CI)	-38.44 (-51.94, -24.94)	-22.33 (-38.10, -6.55)	16.12 (-4.76, 36.99)
P-value for difference between groups (MMRM)			0.1283
P-value for difference between groups (WMW)			0.3302

Source: This figure was produced by the review team based on the adqs.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Numbers related to the primary endpoint component are shown in bold.
Abbreviations: CI, confidence interval; DL_{CO}, diffusion capacity of carbon monoxide; max, maximum; min, minimum; mITT-C, modified intent to treat excluding process-B subjects; MMRM, mixed model for repeated measures; SD, standard deviation; WMW, Wilcoxon-Mann-Whitney test.

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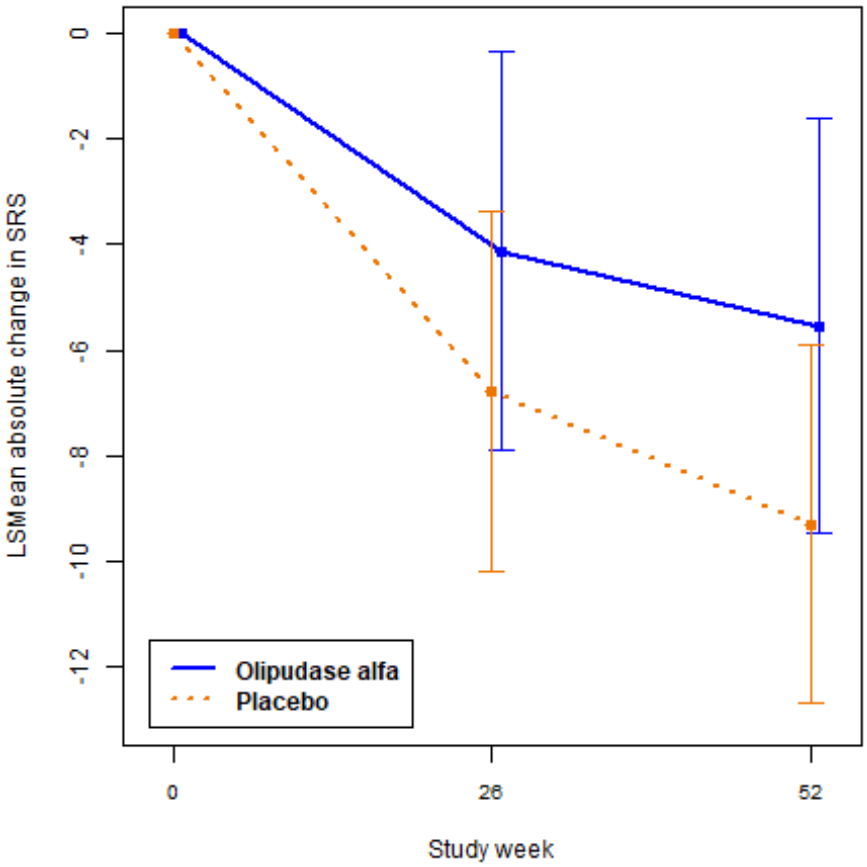
Figure 13. LSMeans of Change in SRS Among mITT-C Population During PAP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adqs.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Error bars on the right reflect the LSMeans confidence intervals from the MMRM.
Abbreviations: LSMeans, least squares means; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period; SRS, splenomegaly-related score.

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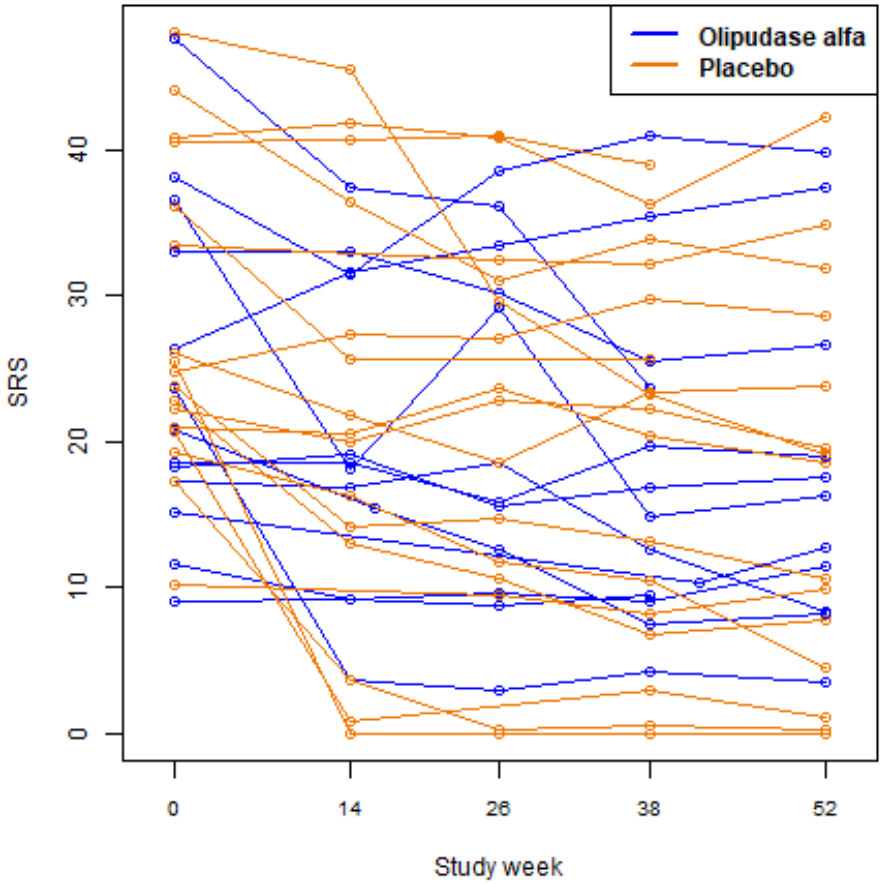
Figure 14. Individual Progressions of SRS Among mITT-C Population During PAP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adqs.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Blue is the treatment arm. Gold is the placebo.
Abbreviations: mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period; SRS, splenomegaly-related score.

The responder analysis for SRS showed little difference between the treatment arms. The primary and secondary responder thresholds were set at improvements of 12.5 and 18, respectively. For the primary threshold, the placebo arm had 7/15 (47%) responders; the olipudase alfa arm had 3/11 (27%). For the secondary analysis, the placebo arm had 3/15 (20%) responders; the treatment arm had 2/11 (18%).

Figure 15 shows the mean values of SRS over both the PAP and ETP, and Figure 16 shows the individual progressions.

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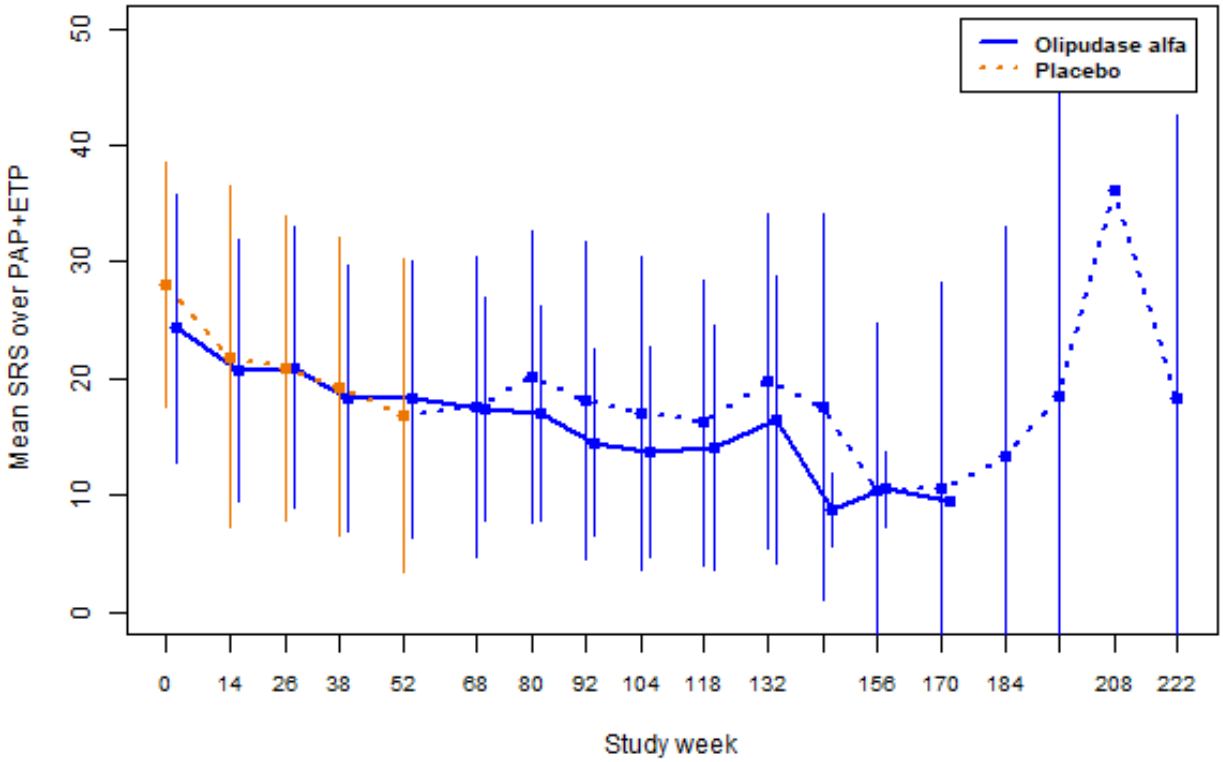
Figure 15. Observed Means of SRS Among mITT-C Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adqs.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Note: Error bars reflect the observed standard deviations, and not confidence intervals.
Abbreviations: ETP, extended treatment period; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period; SRS, splenomegaly-related score.

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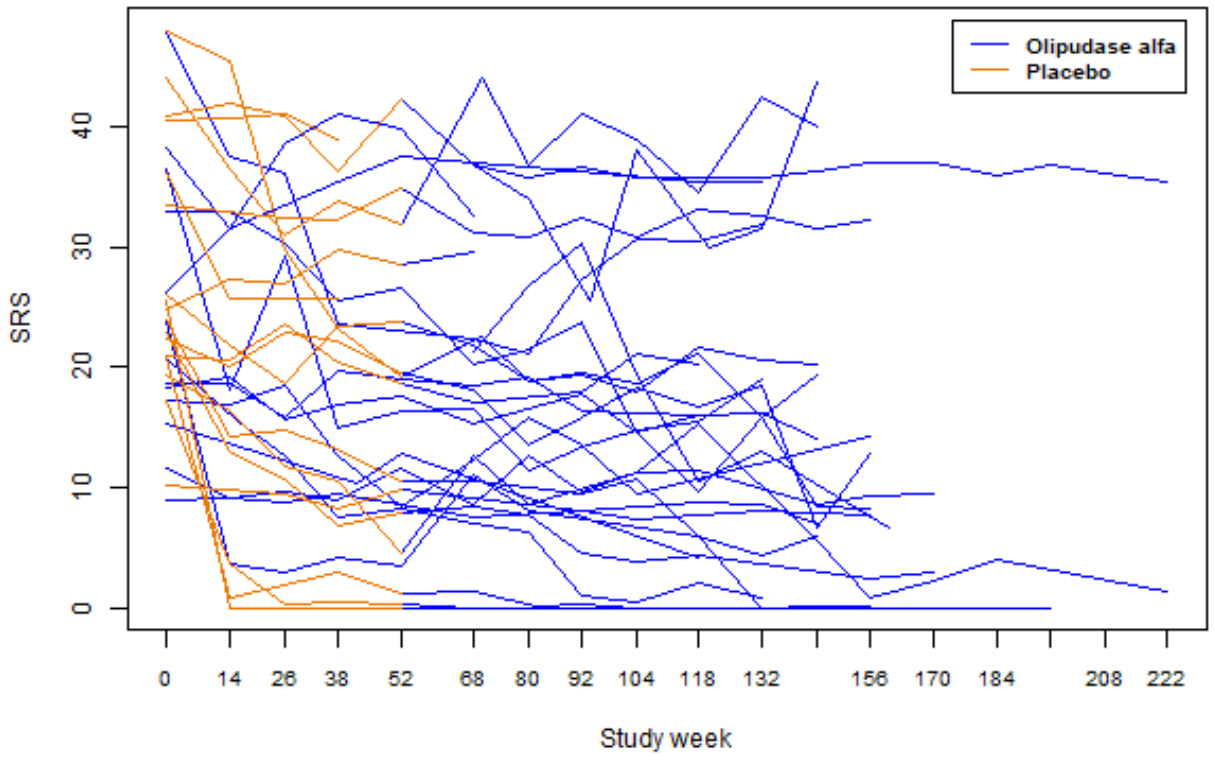
Figure 16. Observed Progressions of SRS Among mITT-C Population During PAP+ETP, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adqs.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: ETP, extended treatment period; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period; SRS, splenomegaly-related score.

6.2.1.4.4. Supportive Evidence from Other Endpoints

In addition to the significant advantage of olipudase alfa over placebo in the primary DL_{CO} endpoint, other key pulmonary endpoints showed positive results (Table 17). Percent predicted FVC, FVC (mL), high-resolution computed tomography interstitial scores, high-resolution computed tomography ground glass scores, and chest x-ray interstitial scores all showed numerical improvements in olipudase alfa over placebo. As per the SAP, none of these endpoints were tested because of the failure of the primary combination endpoint. These measurements show evidence of a positive drug effect on pulmonary function and support the ASCEND trial DL_{CO} findings.

Table 17. Key Pulmonary Endpoints During PAP in mITT-C Population, DFI12712 (ASCEND)

Baseline Mean (SD) and Change From Baseline [CI]	Placebo	Olipudase Alfa	Difference (95% CI)
% Predicted DL_{CO}	48.5 (10.8)	49.1 (9.69)	9.48 [5.67, 13.3],
	1.23 [-1.24, 3.69]	10.7 [7.81, 13.6]	p<0.0001
% Predicted FVC	83.1 (11.8)	77.8 (18.6)	3.22 [-1.32, 7.75],
	1.43 [-1.29, 4.15]	4.65 [1.05, 8.25]	p=0.1558
FVC (mL)	3,050 (598)	3,200 (910)	87.2 [-79.1, 253],
	69.2 [-31.9, 170]	156 [25.5, 287]	p=0.2893
HRCT ground glass scores	0.528 (0.643)	0.702 (0.824)	-0.738 (-1.268, -0.208),
	0.174 [-0.175, 0.523]	-0.564 [-0.963, -0.165]	p=0.0083
HRCT interstitial scores	2.13 (0.792)	1.89 (0.874)	-0.316 [-0.735, 0.103],
	0.099 [-0.175. 0.374]	-0.217 [-0.531, 0.097]	p=0.1331
CXR interstitial scores	1.78 (1.08)	1.92 (0.996)	-1.11 [-1.47, -0.746],
	0.260 [0.024, 0.496]	-0.847 [-1.12, -0.574]	p<0.0001

Source: This table was taken from the Information Request dated 19-Apr-2022.
Note: Units for numerical data are the same as the measure (e.g., % Predicted FVC difference is 8.950 percent predicted).
Abbreviations: CI, confidence interval; DL_{CO}, diffusion capacity of lung for carbon monoxide; FVC, forced vital capacity; HRCT, high resolution computed tomography; CXR, chest x-ray; LSMeans, least squares means; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period.

In addition, an array of other endpoints shows evidence of benefit from olipudase alfa over placebo. Table 18 shows that liver volume (MN), hemoglobin, platelet count, the lipid panel (HDL, LDL, VLDL, triglycerides), and liver function tests (AST, ALT, total bilirubin) all show numerical improvement. The improvements in hemoglobin level and platelet count demonstrate supportive evidence of benefit from olipudase alfa as a result of reducing the spleen volume. In addition, the positive impact of olipudase alfa on liver function is evidenced by the reductions in liver transaminase and total bilirubin levels, as well as the improvement in lipid profile.

Table 18. Key Endpoints During PAP in mITT-C Population, DFI12712 (ASCEND)

Baseline mean (SD) and Change From Baseline [CI]	Placebo	Olipudase Alfa	Difference (95% CI)
Liver Volume (MN)	1.62 (0.496)	1.41 (0.323)	-0.382 [-0.534, -0.230],
	-0.019 [-0.118, 0.079]	-0.401 [-0.515, -0.288]	p<0.0001
Hemoglobin (g/L)	129 (13.8)	139 (19.5)	5.98 [0.218, 11.7],
	-3.59 [-7.35, 0.173]	2.40 [-1.85, 6.64]	p=0.0425
Platelet count	116 (36.3)	109 (30.5)	13.5 [-0.173, 27.2],
	3.29 [-5.90, 12.5]	16.8 [6.67, 27.0]	p=0.0528
Lipid Panel (mmol/L)			
HDL	0.534 (0.253)	0.647 (0.241)	0.223 [0.124, 0.322],
	-0.011 [-0.076, 0.055]	0.213 [0.139, 0.286]	p<0.0001
LDL	4.01 (1.69)	3.58 (0.738)	-0.861 [-1.47, -0.258],
	-0.182 [-0.590, 0.226]	-1.04 [-1.48, -6.04]	p=0.0073
VLDL	1.07 (0.333)	0.840 (0.336)	-0.322 [-0.498, -0.146],
	-0.036 [-0.153, 0.081]	-0.358 [-0.485, -0.231]	p=0.0009
Triglycerides	2.50 (1.01)	1.84 (0.739)	-0.823 [-1.26, -0.388],
	-0.043 [-0.325, 0.238]	-0.866 [-1.19, -0.545]	p=0.0006

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Baseline mean (SD) and Change From Baseline [CI]	Placebo	Olipudase Alfa	Difference (95% CI)
Liver Function Tests			
AST	42.3 (30.2)	44.7 (34.2)	-16.3 [-26.7, -6.01],
	-1.78 [-8.55, 4.99]	-18.1 [-25.9, -10.3]	p=0.0039
ALT	44.7 (30.8)	39.8 (19.3)	-17.0 [-25.8, -8.22],
	-2.63 [-8.46, 3.21]	-19.7 [-26.2, -13.1]	p=0.0005
Total bilirubin	14.4 (6.36)	24.1 (22.4)	-5.98 [-10.5, -1.44],
	0.285 [-2.72, 3.29]	-5.69 [-9.06, -2.32]	p=0.0117

Source: This table was taken from the Information Request dated 19-Apr-2022.
Note: change from baseline is based on the LS means estimate, and CI is the 95% confidence interval.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal; PAP, primary analysis period; SD, standard deviation; VLDL, very low-density lipoprotein.

6.2.2. Trial DFI13803 (ASCEND-Peds)

6.2.2.1. Design, Trial DFI13803 (ASCEND-Peds)

ASCEND-Peds was a Phase 1/2, multi-center, open-label, repeated-dose study in pediatric subjects <18 years of age with non-CNS manifestations of ASMD. The primary objective was to evaluate the safety, tolerability, PK, PD, and exploratory efficacy of olipudase alfa. Twenty subjects were enrolled in a staggered fashion into three age cohorts: 4 to the adolescent cohort (12 to <18 years), 9 to the child cohort (6 to <12 years), and 7 to the infant/early child cohort (<6 years) and received IV infusions of olipudase alfa Q2W for a total of 64 weeks. However, for our analysis we use the more clinically relevant age cohorts: adolescent (12 to <18 years, 4 subjects), child (2 to <12 years, 15 subjects), and infant (<2 years, 1 subject). Of particular note, there was only one infant (<2 years of age) at initial infusion, and only one additional subject less than 3 years. Subjects underwent dose escalation of olipudase alfa from 0.03, 0.1, 0.3, 0.3, 0.6, 0.6, 1, 2, and 3 mg/kg within the first 16 weeks or longer and then maintained on 3 mg/kg (or maximum tolerated dose if the 3 mg/kg dose was intolerable) for the rest of the study. After completion of the 64-week treatment period, subjects were eligible to be enrolled in the long-term study, LTS13632. Subjects unable to tolerate two consecutive doses of 0.3 mg/kg olipudase alfa were replaced. Following enrollment in the youngest age cohort, the protocol was amended to enroll an additional eight subjects <12 years to received olipudase alfa manufactured with Process C (b) (4) These subjects were included in the appropriate age cohort (at least four subjects in the child cohort and at leave two in the infant/early child cohort) without staggering of enrollment.

Because the focus of ASCEND-Peds was to evaluate the safety and tolerability of olipudase alfa in pediatric subjects, all efficacy objectives were considered exploratory, and no primary or secondary endpoints were specified. For this reason, we focus on the primary endpoints components in the ASCEND trial: spleen volume (MN) and percent predicted DL_{CO}; and in addition, liver volume (MN).

6.2.2.2. Eligibility Criteria, ASCEND-Peds

Inclusion Criteria

Male or female patients <18 years of age who:

- Had a documented deficiency of ASM consistent with NPD, as measured in peripheral leukocytes, cultured fibroblasts, and/or lymphocytes.
- Had a spleen volume ≥5 MN as measured by 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.
- Had a height Z-score of -1 or lower.
- Had a negative serum pregnancy test for β-human chorionic gonadotropin (for female of childbearing potential).
- Were willing to practice true abstinence in line with their preferred and usual lifestyle or use two acceptable effective methods of contraception, a barrier method with spermicidal foam/gel/film/cream/suppository and an established non-barrier method, an intrauterine device, or intrauterine system for the duration of the study (for female patients of childbearing potential and male patients).

Exclusion Criteria

- Received an investigational drug within the 30 days before study enrollment.
- Had medical conditions and any other extenuating circumstance that could have significantly interfered with study compliance.
- Had acute or rapidly progressive neurological abnormalities.
- Were homozygous for *SMPD1* gene mutations R496L, L302P, and fs330 or any combination of these 3 mutations.
- Had delayed gross motor skills.
- Had a major organ transplant.
- Required the use of invasive ventilatory support.
- Required the use of noninvasive ventilatory support while awake and for >12 hours a day.
- Were unable to adhere to the requirements of the study in the investigator's opinion.
- Had a platelet count $<60 \times 10^3/\mu L$ (based on the average of 2 screening samples obtained greater than 24 hours apart).
- Had ALT or AST >250 IU/L or total bilirubin >1.5 mg/dL.
- Had an international normalized ratio >1.5.
- Were unwilling or unable to abstain from ingesting alcohol the day before through three days after each infusion of olipudase alfa during the treatment period.
- Were scheduled during the study for inpatient hospitalization including elective surgery.
- Required medication(s) that may decrease olipudase alfa activity.
- Were breast-feeding.

6.2.2.3. Statistical Analysis Plan, Trial DFI13803 (ASCEND-Peds)

The SAP was finalized on November 5, 2019. The SAP specified that, where appropriate, change from baseline may be modeled using analysis of covariance model with the baseline value as the sole covariate. Descriptive statistics were to be reported.

Similar to the ASCEND trial, the SAP-defined efficacy analysis population is the modified intent-to-treat population (mITT). For the purposes of this review, to be consistent with the ASCEND trial, we also define the mITT-C population as the members of the mITT population who received only Process C drugs.

Reviewer's Comments: As mentioned in Section 3.2, eight patients received exclusively process-C olipudase alfa (mITT-C population), while the remaining 12 patients received exclusively process-B olipudase alfa. Although the main efficacy results are similar for process-B and process-C drugs, the primary analysis in this review focuses on the 8 patients who received only process-C treatments because of the following reasons: (1) the processes B and C were determined analytically incomparable (see Section 7.7.2), (2) process C is the to-be-marketed version, and (3) the data from the process-C treated patients is used to inform labeling.

6.2.2.4. Results of Analyses, Trial DFI13803 (ASCEND-Peds)

Table 19 provides baseline characteristics for the 20 subjects, and Table 20 and Table 21 provides disposition and completion rates.

Table 19. Baseline Demographic and Clinical Characteristics, Safety Population, Trial ASCEND-Peds

Characteristic	Process B (N=12)	Process C (N=8)	Olipudase Alfa (Process B and C) (N=20)
Sex, n (%)			
Male	6 (50%)	4 (50%)	10 (50%)
Female	6 (50%)	4 (50%)	10 (50%)
Age, years			
Mean (SD)	8.7 (5.1)	6.0 (2.9)	7.6 (4.4)
Median (min, max)	8.0 (2:17)	6.0 (1:10)	7.5 (1, 17)
Age groups (years), n (%)			
<2	0 (0%)	1 (13%)	1 (5%)
≥2 to <12	8 (67%)	7 (88%)	15 (75%)
≥12 to <18	4 (33.%)	0 (0%)	4 (20%)
Race, n (%)			
White	9 (75%)	8 (100%)	17 (85%)
Asian	2 (17%)	0 (0%)	2 (10%)
Other	1 (8%)	0 (0%)	1 (5%)
Ethnicity, n (%)			
Hispanic	1 (8%)	0 (0%)	1 (5%)
Non-Hispanic	11 (92%)	8 (100%)	19 (95%)

Characteristic	Process B (N=12)	Process C (N=8)	Olipudase Alfa (Process B and C) (N=20)
Country of participation, n (%)			
United States	4 (33%)	2 (25%)	6 (30%)
Brazil	2 (17%)	0 (0%)	2 (10%)
United Kingdom	2 (17%)	0 (0%)	2 (10%)
Italy	3 (25%)	1 (13%)	4 (20%)
France	1 (8%)	1 (13%)	2 (10%)
Germany	0 (0%)	4 (50%)	4 (20%)

Source: May 6, 2022, Information Request
Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation.

Table 20. Subject Screening and Completion, Trial ASCEND-Peds

Disposition	Infant (<2)	Child (2 to <12)	Adolescent (12 to <18)	Total
No. subjects screened				23
No. subjects treated	1	15	4	20
No. subjects completed	1	15	4	20

Source: Table 8 of the Clinical Study Report.

Table 21. Subject Disposition, Trial ASCEND-Peds

Disposition Category	Process B (N=12)	Process C (N=8)	Olipudase Alfa (Process B and C) (N=20)
ITT/mITT population	12 (100%)	8 (100%)	20 (100%)
Safety population	12 (100%)	8 (100%)	20 (100%)
Discontinued study drug	0	0	0
Adverse event	0	0	0
Discontinued study	0	0	0
Death	0	0	0
Lost to follow-up	0	0	0
Withdrawal by subject	0	0	0
Protocol deviation	0	0	0
Other	0	0	0

Source: Table 8 of the Clinical Study Report.
Abbreviation: mITT, modified intention-to-treat; N, number of subjects; n, number of subjects with at least one event.

6.2.2.4.1. Analysis of DL_{CO}, Spleen Volume, and Liver Volume

ASCEND-Peds supplemented the partial extrapolation of efficacy from the ASCEND trial. although.

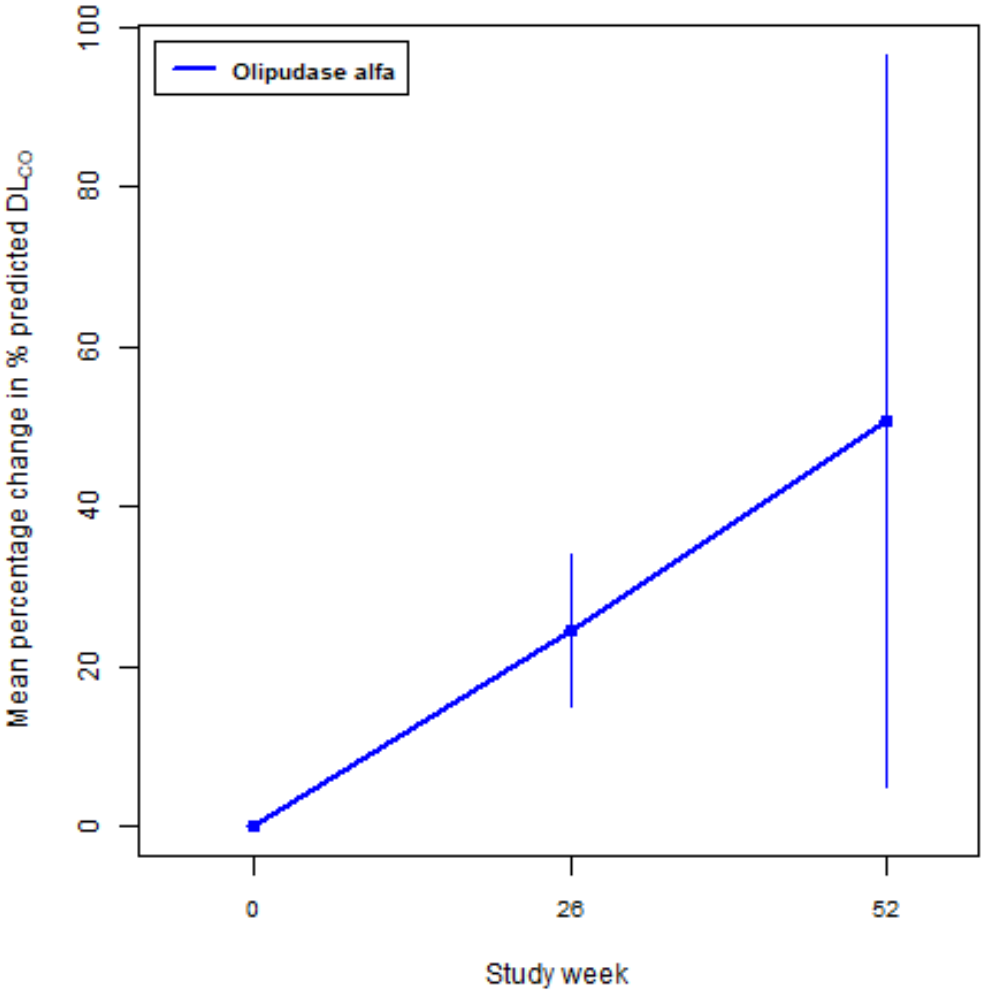
Table 22, Figure 17, and Figure 18 illustrate the trial ASCEND-Peds DL_{CO} results. The average (SD) baseline values were 48.5% (8.1) predicted DL_{CO}., compared to 49.1% (9.7) for the treatment arm of the ASCEND Trial. The average percentage increase at Week 52 was 50.6% (45.7). Only 3 of the 8 pediatric subjects treated with process-C had DLco measurements taken, and none of these subjects were infants. Of note, the percentage increase in DLco was 24.2% (18.6) in the ASCEND trial. As seen in Figure 18, one of these subjects did not have DLco measured at Week 26, and showed little improvement at Week 52, resulting in a flat line. This subject did however show improvements in both liver and spleen volume. For the subjects which had baseline DL_{CO} measurements, their baseline ages ranged from 7.5 to 10.4 years.

Table 22. Percentage Change in % Predicted DL_{CO} in mITT-C Population, ASCEND-Peds

Change in DL_{CO}	Infant (<2)	Child (2 to <12)	Overall
Baseline values			
Number of subjects with value	0	3	3
Mean (SD)		48.51 (8.12)	48.51 (8.12)
Median (min:max)		44.65 (43.04:57.84)	44.65 (43.04:57.84)
Week 52			
Number of subjects with value	0	3	3
Mean (SD)		50.62 (45.72)	50.62 (45.72)
LS mean (95% CI)		53.49 (11.78, 95.2)	53.49 (11.78, 95.2)

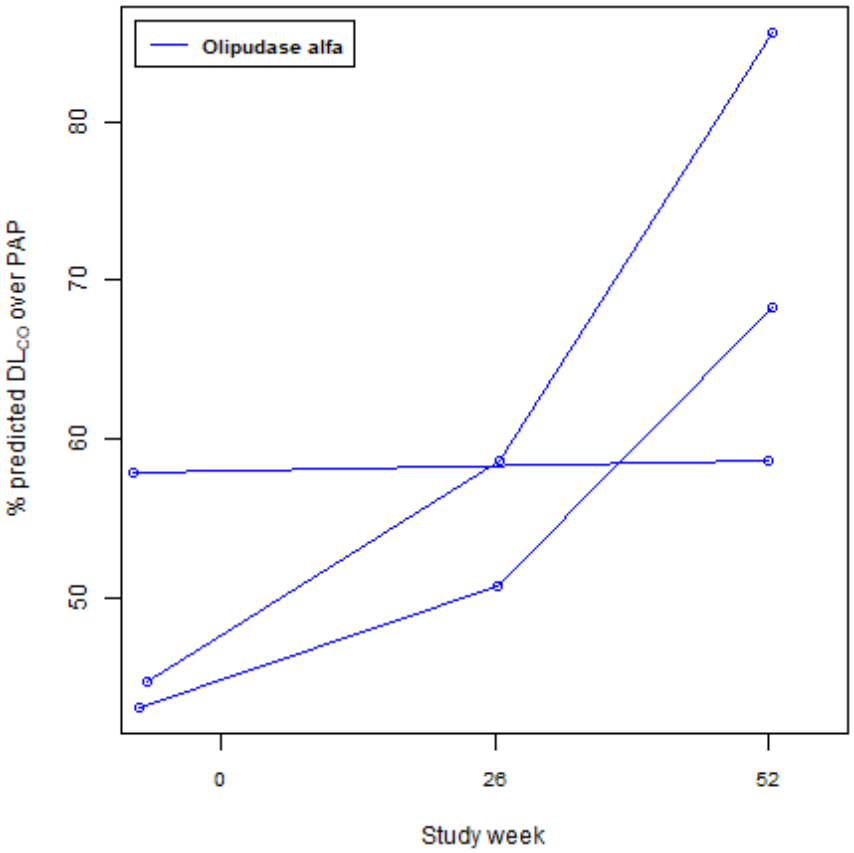
Source: This table was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Abbreviations: CI, confidence interval; DL_{CO}, diffusion capacity for carbon monoxide; max, maximum; min, minimum; mITT-C, modified intent to treat excluding process-B subjects; SD, standard deviation

Figure 17. Means of Percent Change in % Predicted DL_{CO} Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Note: Error bars on the right reflect the observed standard deviations.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period.

Figure 18. Individual Progressions of % Predicted DL_{CO} Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; mITT-C, modified intent to treat excluding process-B subjects; PAP, primary analysis period.

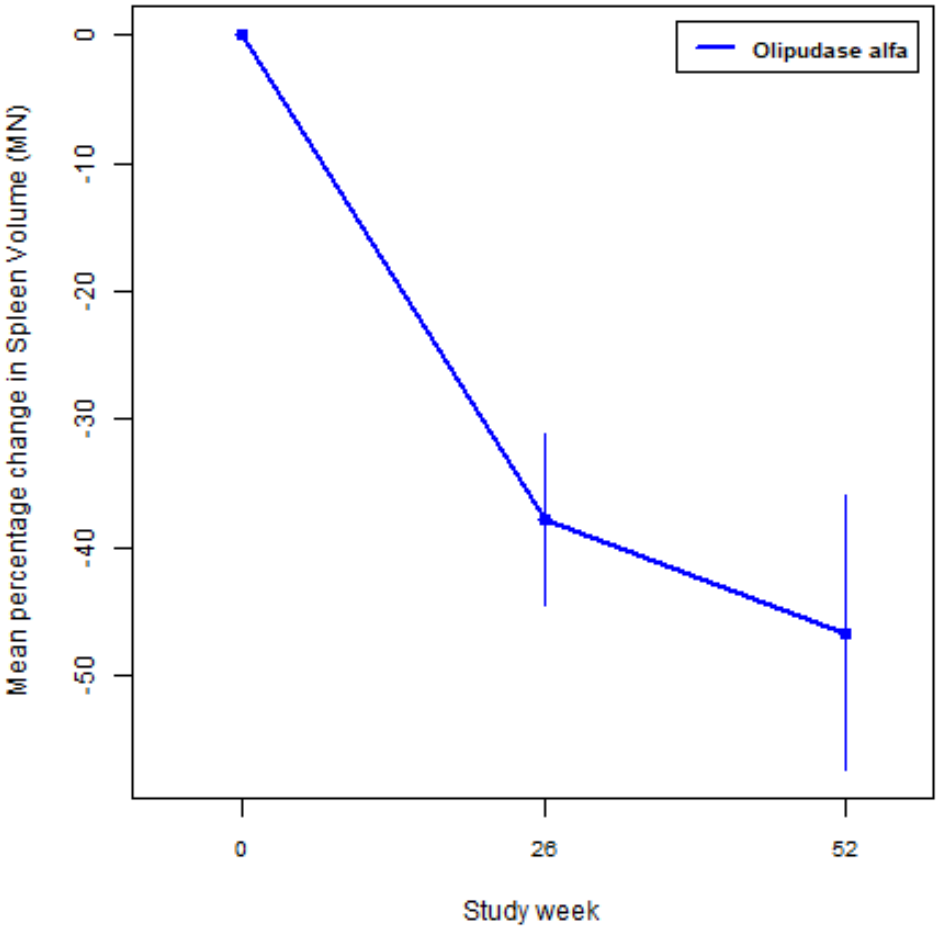
Table 23, Figure 19, and Figure 20 illustrate the ASCEND-Peds spleen volume results. The average (SD) baseline value was 18.3 (5.6) MN, compared to 11.5 (4.8) MN for the treatment arm of the ASCEND Trial. The average (S.D.) percentage decrease was 46.7% (10.7) compared to 38.8% (9.1) in the treatment arm of ASCEND trial.

Table 23. Percentage Change in Spleen Volume (MN) in mITT-C Population, ASCEND-Peds

Change in Spleen Volume	Infant (<2)	Child (2 to <12)	Overall
Baseline values			
Number of subjects with value	1	7	8
Mean (SD)	16.81 (--)	18.5 (6.02)	18.29 (5.61)
Median (min:max)	16.81 (16.81:16.81)	16.79 (11.9:29.29)	16.8 (11.9:29.29)
Week 52			
Number of subjects with value	1	7	8
Mean (SD)	-46.77 (--)	-46.71 (11.54)	-46.72 (10.68)
LS mean (95% CI)	-46.77 (--)	-46.71 (-52.79, -40.64)	-46.74 (-52.08, -41.41)

Source: This table was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Abbreviations: CI, confidence interval; max, maximum; min, minimum; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal; SD, standard deviation.

Figure 19. Means of Percent Change in Spleen Volume (MN) Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Note: Error bars on the right reflect the observed standard deviations.
Abbreviations: mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal

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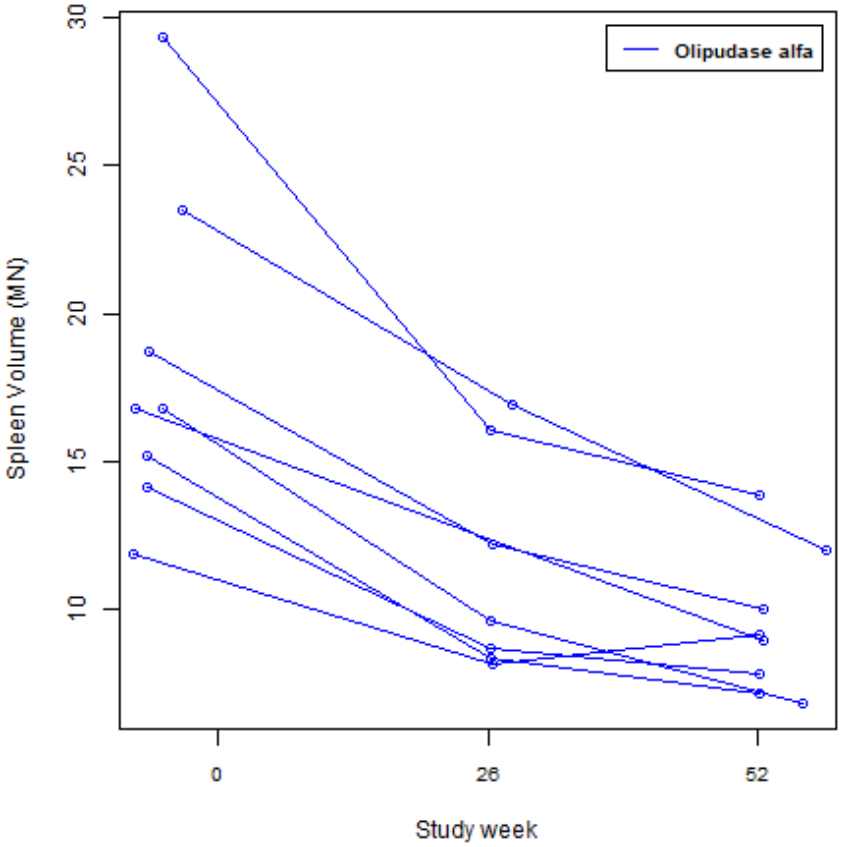
Figure 20. Individual Progressions of Spleen Volume (MN) Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Abbreviations: mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal

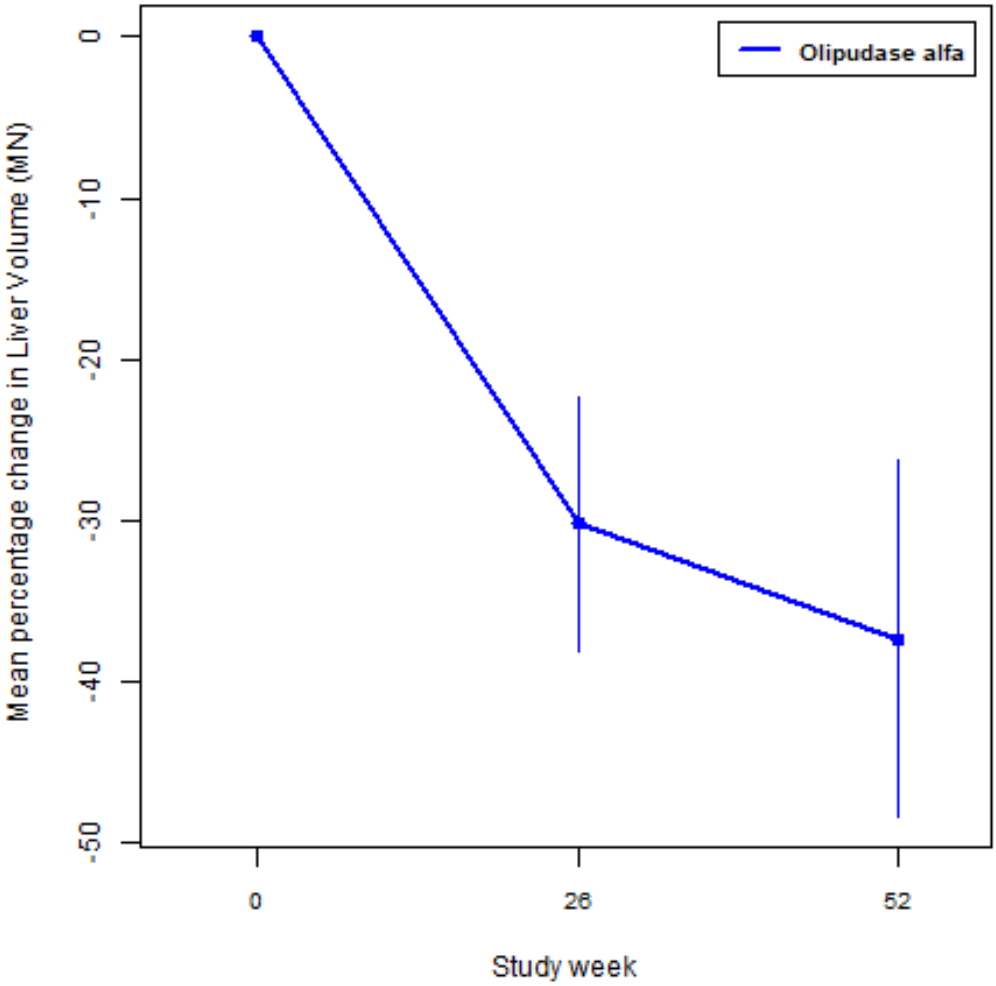
Table 24, Figure 21, and Figure 22 illustrate the ASCEND-Peds liver volume results. The average (SD) baseline value was 2.55 (0.55) MN, compared to 1.4 (0.3) MN for the treatment arm of the ASCEND trial. The average (SD) percentage decrease was 37.3% (11.0) compared to 25.8% (15.8) in the treatment arm of ASCEND trial.

Table 24. Percentage Change in Liver Volume (MN) in mITT-C Population, ASCEND-Peds

Change in Liver Volume	Infant (<2)	Child (2 to <12)	Overall
Baseline values			
Number of subjects with value	1	7	8
Mean (SD)	3.64 (--)	2.39 (0.35)	2.55 (0.55)
Median (min:max)	3.64 (3.64:3.64)	2.46 (1.87:2.92)	2.49 (1.87:3.64)
Week 52			
Number of subjects with value	1	7	8
Mean (SD)	-43.88 (--)	-36.39 (11.56)	-37.33 (11.02)
LS Mean (95% CI)	-43.88 (--)	-36.39 (-42.28, -30.51)	-37.03 (-42.45, -31.6)

Source: This table was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Abbreviations: CI, confidence interval; max, maximum; min, minimum; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal; SD, standard deviation.

Figure 21. Means of Percent Change in Liver Volume (MN) Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Note: Error bars on the right reflect the observed standard deviations.
Abbreviations: mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal.

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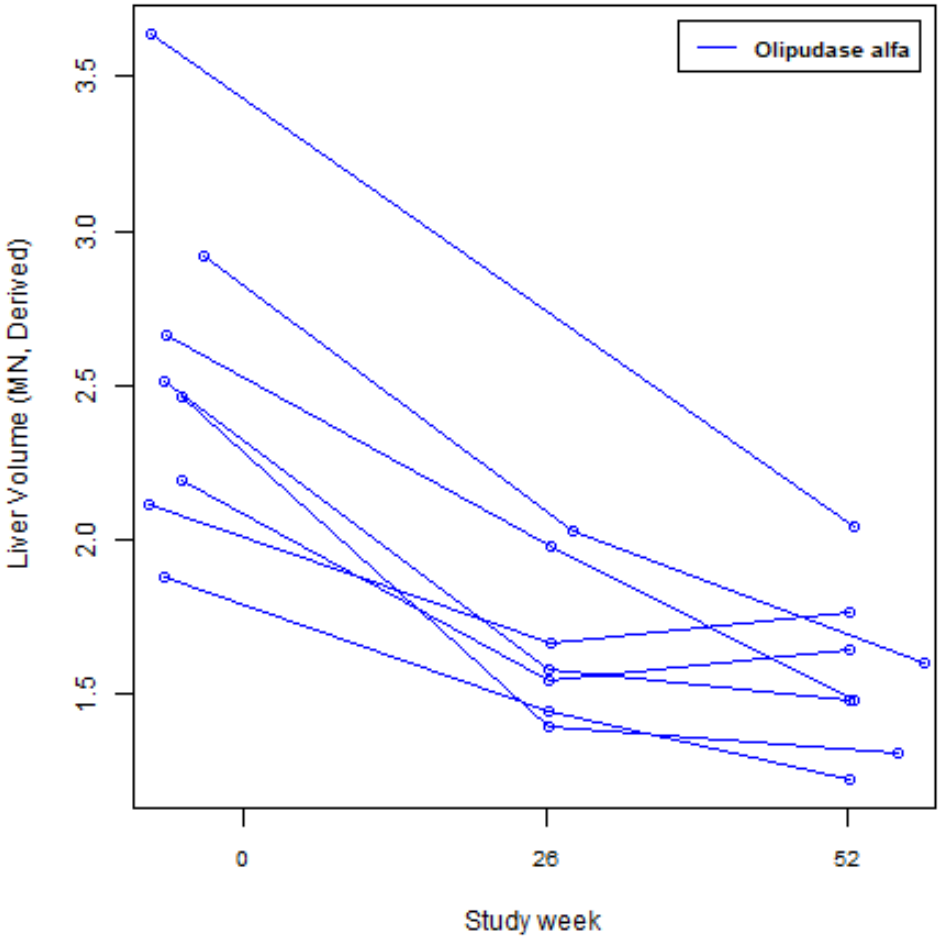
Figure 22. Individual Progressions of Liver Volume (MN) Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Abbreviations: mITT, modified intent to treat; MN, multiples of normal.

6.2.2.4.2. Analysis by Age

Figure 23-Figure 24 give results broken down by age cohort (child: 2 to <12 years, infant: <2 years). Figure 23 illustrates the mean values of percentage increases by age in the first 52 weeks, and Figure 24 illustrates the individual progressions colored by age. While the trial sample size is already quite small before examining subgroups, there are not concerning differences between the age groups, either in baseline values or percentage increases. It should be noted that DL_{CO} values are not available for any subjects below age 7.

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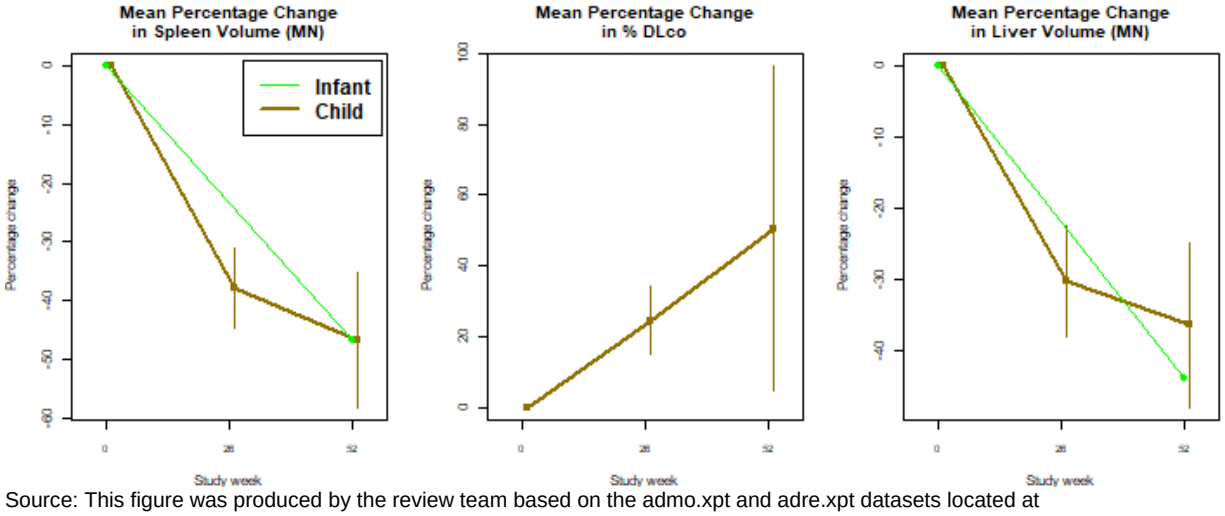
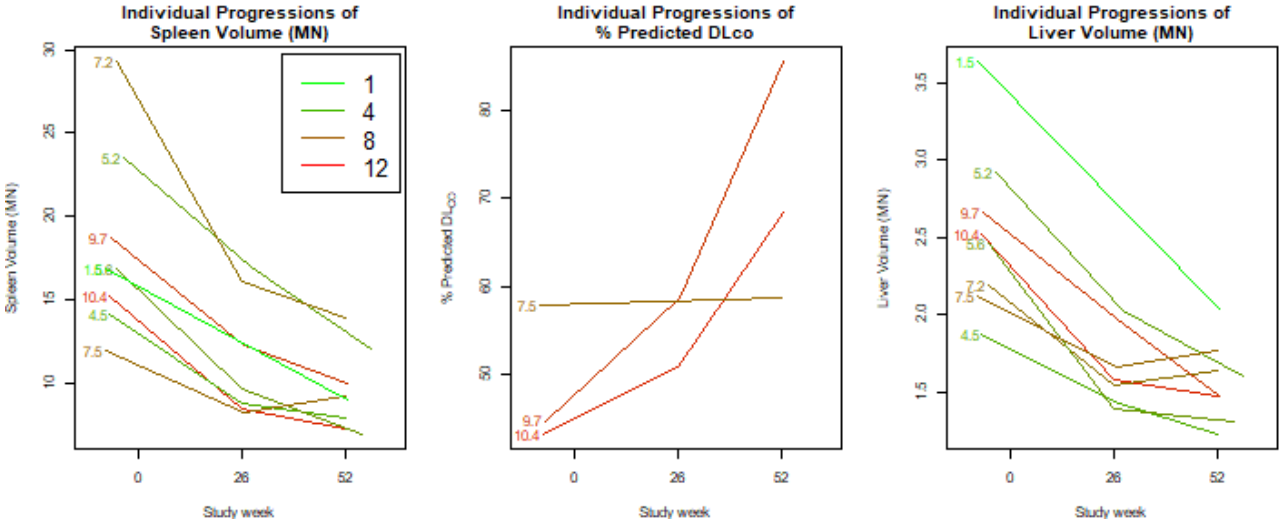
Figure 23. Means of Percent Changes by Age, for Spleen Volume (MN), % Predicted DL_{CO}, and Liver Volume (MN) Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the admo.xpt and adre.xpt datasets located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Note: Error bars on the right reflect the observed standard deviations.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal.

Figure 24. Individual Progressions of Spleen Volume (MN), % Predicted DL_{CO}, and Liver Volume (MN) Among mITT-C Population During First 52 Weeks, ASCEND-Peds



Source: This figure was produced by the review team based on the admo.xpt and adre.xpt datasets located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Note: Numbers to the left of the individual's lines indicate the subject's age at first infusion.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal.

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6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Evidence of Effectiveness in Adults and Pediatric Subjects

Issue

Does the ASCEND trial sufficiently demonstrate effectiveness? In particular, as the placebo-controlled trial DFI12712 (ASCEND) "won" on one of its two primary endpoints (DL_{CO}) as per the pre-defined and agreed statistical testing strategy, is there sufficient evidence of benefit? Since DL_{CO} has not been used in approval for any other treatments, does the improvement in DL_{CO} plus the improvement in other supportive endpoints provide evidence of efficacy? Can partial extrapolation from the ASCEND trial with supportive evidence from ASCEND-Peds support efficacy in the pediatric population?

Background

Trial DFI12712 (ASCEND) contains two primary endpoints, and a pre-defined statistical testing strategy to define study success criteria and to control the Type I error rate. In the original protocol, the two primary endpoints consisted of 1) the percent change in adjusted DL_{CO} in % predicted of normal and 2) the percent change in spleen volume (MN), from baseline to Week 52. In the amended protocol dated December 13, 2016, at the request of FDA, the spleen volume endpoint was amended to include an SRS subject reported outcome (PRO) component. This component is a 7-day average taken over 5 separate daily symptom-severity assessments (scored 1 to 10) corresponding to abdominal pain, abdominal discomfort, early satiety, abdominal body image, and ability to bend down, and collected from an eDiary. (Note: This amendment was only reflected in the United States.) This new combination endpoint would require both significant improvement in spleen volume as well as trend improvement in SRS (required p-value of 0.15 rather than 0.05) for the combination endpoint to be deemed successful. The statistical testing strategy was adjusted to continue to allow for a "win" on either of the two primary endpoints (primary endpoint of DLco and the primary combination endpoint of spleen volume + SRS). Numerous secondary and tertiary endpoints were specified but would only be formally tested sequentially if both the primary endpoints were significant.

The primary objective of trial ASCEND-Peds was to evaluate safety and tolerability and therefore all efficacy endpoints were considered exploratory.

Assessment

Per the pre-defined statistical testing strategy, ASCEND was deemed successful based on its DL_{CO} endpoint, which showed highly significant improvement for olipudase alfa subjects over placebo (p-value<0.0001). Moreover, of the two components of the primary combination endpoint, spleen volume showed highly significant improvement (p-value<0.0001). However, the SRS component of the combination endpoint showed no drug effect.

In ASCEND, the DL_{CO} endpoint showed a difference at Week 52 in olipudase alfa over placebo of 21.0% (95% CI: 13.7, 28.4, p-value<0.0001) in the percentage increase, and a corresponding

absolute difference of 9.51% (95% CI: 6.8, 12.3, p-value<0.0001) (Table 13). These strong trends are illustrated in Figure 4 through Figure 7. Other pulmonary endpoints showed similarly favorable results. Table 17 shows that the five other key pulmonary endpoints examined (% predicted FVC, FVC in mL, high-resolution computed tomography ground glass scores, high-resolution computed tomography interstitial scores, chest x-ray interstitial scores) all showed improvements in olipudase alfa over placebo.

The ASCEND-Peds trial results showed an average percentage increase in percent predicted DL_{CO} of 53.5% (CI: 11.8, 95.2), however, only 3 of the 8 subjects had DL_{CO} measurements taken, and no infants were included in this group (lowest age was 7.5 years).

Regarding DL_{CO} as an endpoint, agreement was made between the Applicant and the Agency to use DL_{CO} as a primary endpoint since an improvement in DL_{CO} may reflect an improvement in lung gas exchange secondary to a reduction in lung SPM. However, there is no established threshold (regulatory or literature-based) for a clinically meaningful DL_{CO} change in response to an intervention. Although a threshold of 15% decline in percent predicted DL_{CO} has been proposed by some professional organizations to represent clinically significant disease progression for some ILDs, it is not certain that this threshold of decline could be used to determine a meaningful treatment response. (Raghu et al. 2011; Khanna et al. 2015; Cottin et al. 2017; Xaubet et al. 2017). In other words, the magnitude of decline in diffusion capacity indicating worsening disease may not be the same as the magnitude of improvement needed to determine a clinically meaningful response to a therapeutic intervention. As such, the threshold for a clinically meaningful DL_{CO} treatment response for ILDs, and by extension the ILD component of ASMD, remains unclear. For these reasons, DL_{CO} has not been used as the primary basis to support any drug approvals.

However, despite the aforementioned limitations in assessing and analyzing DL_{CO}, the demonstration of a highly statistically significant increase on DL_{CO} (as observed in ASCEND) provides, at the very least, strong support that olipudase treatment results in a PD effect. Furthermore, the magnitude of treatment effect seen in percent predicted DL_{CO} in the ASCEND trial was larger than that seen in many of the other pivotal trials for approved ILD therapies (September 2014a; September 2014b; March 2021). This is noteworthy as the evaluation of DL_{CO} for ILD programs have focused on reduction in decline rather than improvement. None of the ILD programs evaluated by the Center for Drug Evaluation and Research (CDER) have demonstrated an improvement in DL_{CO}.

The spleen volume (MN) component of the combination endpoint, as well as other supportive endpoints, also showed significant and positive results for olipudase alfa over placebo.

Figure 9 through Figure 10 and Table 15 illustrate these trends: The spleen volume component showed a difference of 39.2% (CI: 33.7, 44.7, p-value<0.0001) in the percentage decrease at Week 52 in olipudase alfa over placebo, and a corresponding absolute decrease of 4.4 (MN) (CI: 3.7, 5.1, p-value<0.0001). Table 18 illustrates these percentage differences in other key endpoints. Liver volume (MN), hemoglobin, platelets, lipid panel (HDL, LDL, VLDL, triglycerides), liver function tests (AST, ALT, total bilirubin) all show numerical improvements The ASCEND-peds largely mirrors these significant changes in DL_{CO}, spleen volume, and liver volume (Table 22-Table 24).

The SRS component of the combination endpoint is illustrated in Figure 13 through Figure 16 and Table 16, and shows similar improvements in both the treatment and placebo arms, although

the placebo arm shows marginally greater improvement. This outcome may be due to an insensitive PRO. Of note, the SRS has not been validated in the ASMD population as it was derived from an assessment of subject perception of splenomegaly symptoms in myelofibrosis. The divergence in spleen volume and SRS scores and other endpoints in ASCEND may be explained by the very different patient populations of ASMD and myelofibrosis. These include substantial differences in disease characteristics as splenomegaly can have a pediatric onset with slow progression in ASMD whereas splenomegaly in myelofibrosis does not occur until adulthood and has a dominance of constitutional symptoms. (Verstovsek et al. 2012; Pardanani et al. 2015). Myelofibrosis typically has an onset after 50 years of age while the majority of ASMD patients have an onset prior to age 5. For comparison, in the myelofibrosis trials JAKARTA (Pardanani et al. 2015) and COMFORT I (Verstovsek et al. 2012), the median age at baseline was 65 and 66, respectively, while in ASCEND, the median age at baseline was 30 years. Considering these different ages of onset and the median age at baseline for ASCEND, JAKARTA and COMFORT I, it is possible that:

- In comparison to JAKARTA and COMFORT I, patients, ASCEND patients in general have lived with their symptoms for longer periods prior to the baseline assessment of spleen symptoms in each trial, potentially allowing ASCEND patients to adapt.
- In comparison to JAKARTA and COMFORT I, patients, ASCEND patients have experienced their spleen symptoms since a very early age. While JAKARTA and COMFORT I patients experienced decades of life free of spleen symptoms, ASMD patients have not had that privilege and hence the baseline assessment of spleen symptoms might have a different interpretation.
- There are important differences regarding the involvement of other organ systems besides the spleen in ASMD (e.g., lung, liver) versus myelofibrosis (e.g., pronounced constitutional symptoms such as fever, fatigue, night sweat (Garmezy et al. 2021) that may impact the subjective assessment of symptomatology in these two distinct patient populations.

Expansion of the indication for olipudase to include pediatric ASMD patients relies on the partial extrapolation from the ASCEND study, an adequate and well controlled study in adults, given similarity in disease pathology and manifestations in adults and pediatric patients with ASMD. Both patient populations share similar somatic manifestations, including hepatosplenomegaly and interstitial lung disease thataffects individuals of all ages. Although the progression of disease can range from mild to severe with the more severe infantile form leading to death within a few years due to the rapid progression of manifestations versus the mild form allowing for survival up to adulthood, the underlying mechanism, characterized by the accumulation of sphingomyelin and secondary lipids in the different tissues, is the same and is responsible for the observed phenotypes. The anticipated response to therapy between adults and pediatric patients would be expected to be similar as olipudase alfa provides an exogenous source of the underlying enzymatic defect, ASM, which is responsible for catabolizing sphingomyelin (SPM) into ceramide and phosphocholine. Deficiency of ASM leads to the accumulation of SPM and secondary increases in cholesterol and other metabolically related lipids causing the somatic manifestations. One major difference between the pediatric and adult patients are the additional central nervous manifestations in addition to the somatic manifestations that are seen in ASMD type A and type A/B phenotypes, which occur in pediatric patients. However, olipudase alfa is not expected to treat these CNS manifestations as it does not cross the blood brain barrier. Lastly,

exploratory efficacy was assessed in the ASCEND-Peds trial, which evaluated the same endpoints as the ASCEND trial, including DLco, liver and spleen volume.

The ASCEND-Peds had similar positive efficacy results compared to ASCEND. During the first 52 weeks, the treatment arm of ASCEND and ASCEND-Peds showed an average percentage decrease in spleen volume (MN) of 38.8% (CI: 34.6, 42.9) and 46.7% (CI: 41.4, 52.1), respectively. For percentage increase in DL_{CO} the analogous numbers were 21.1% (CI: 13.7, 28.4) and 53.5% (CI: 11.8, 95.2) (The latter CI is particularly wide because only three subjects in ASCEND-Peds had DL_{CO} measurements taken). For percentage decrease in liver volume (MN) the changes were 26.5% (CI: 20.0, 33.0) and 37.0% (CI: 31.6, 42.5). Similar to ASCEND, the subjects in ASCEND-Peds showed improvements in platelet count, the lipid panel (HDL, LDL, VLDL, triglycerides), and the liver function tests (AST, ALT, total bilirubin); although unlike ASCEND there was no improvement in hemoglobin. Moreover, the main efficacy results were largely similar across age groups (Figure 13 and Figure 14). Taken as a whole, this provides substantial evidence of efficacy to allow for the indication to include pediatric subjects.

Conclusion

The review team concluded that the ASCEND trial is an adequate and well controlled trial that demonstrates the efficacy of olipudase alfa. In addition to meeting the pre-defined success criteria for the DL_{CO} endpoint, the ASCEND trial demonstrates improvement in liver volume and LFTs, as well as spleen size. We concluded that these are clinically meaningful because progressive loss of pulmonary function and liver failure are the most common causes of death in patients with ASMD. Furthermore, splenomegaly can lead to worse quality of life (pain, early satiety, nausea, vomiting) alongside the risk of rupture with massive splenomegaly. The positive efficacy results from the ASCEND trial can be partially extrapolated to the pediatric population due to similar pathogenesis and mechanism of action of the olipudase alfa. The results of the ASCEND trial are mirrored in the ASCEND-peds trial.

6.3.2. Confirmatory Evidence

Issue

In addition to the primary evidence of efficacy from the single adequate and well-controlled ASCEND trial, is there appropriate confirmatory evidence to conclude substantial evidence of effectiveness?

Background

Substantial evidence of effectiveness, which is the regulatory requirement for approval, generally consists of evidence from at least two adequate and well-controlled investigations. In certain circumstances, a single adequate and well-controlled investigation demonstrating efficacy together with appropriate confirmatory evidence may be sufficient to generate substantial evidence of effectiveness. Such circumstances are described in the FDA draft guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). For this BLA, the Applicant conducted a single adequate and well-controlled investigation in adult subjects, (ASCEND). Confirmatory evidence is derived from the (1) well-

established etiology of the disease, (2) the mechanism of action of the therapy, and (3) PD biomarker data from olipudase alfa clinical trials in adult and pediatric subjects with ASMD.

Assessment

(1) Etiology of Disease

ASMD is a lysosomal disease caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene that result in deficient activity of the enzyme acid sphingomyelinase (ASM). ASM catalyzes the hydrolysis of SPM to ceramide and phosphocholine. The deficiency in ASM causes an intracellular accumulation of SPM as well as cholesterol and other cell membrane lipids in various tissues including the spleen, liver, and lungs.

(2) Mechanism of Action of Therapy

Olipudase alfa (a recombinant human ASM) provides an exogenous source of ASM. Plasma ceramide and lysosphingomyelin (or lyso-SPM, a deacylated form of SPM) were used as PD biomarkers to assess the pharmacological effect of olipudase alfa in subjects with ASMD.

(3) Pharmacodynamic Biomarker Data

Reductions of plasma ceramide and lyso-SPM were consistently observed in subjects with ASMD treated with olipudase alfa across the clinical trials in the BLA. These PD biomarker data provide strong mechanistic evidence of olipudase alfa and therefore serve as confirmatory evidence of effectiveness in subjects with ASMD with the following considerations:

- Reductions of plasma ceramide and lyso-SPM are relevant to the mechanism of action of olipudase alfa in the setting of well-understood disease pathophysiology of ASMD;
- Reductions in plasma ceramide and lyso-SPM represent distinct measurements of drug effect from the efficacy endpoints measured in the single adequate and well-controlled investigation; and
- Reductions in plasma ceramide and lyso-SPM were observed in an early phase clinical Study DFI13412 that was independent from the single adequate and well-controlled investigation.

The details of the PD biomarker data are summarized below.

Trial DFI 12712 (ASCEND):

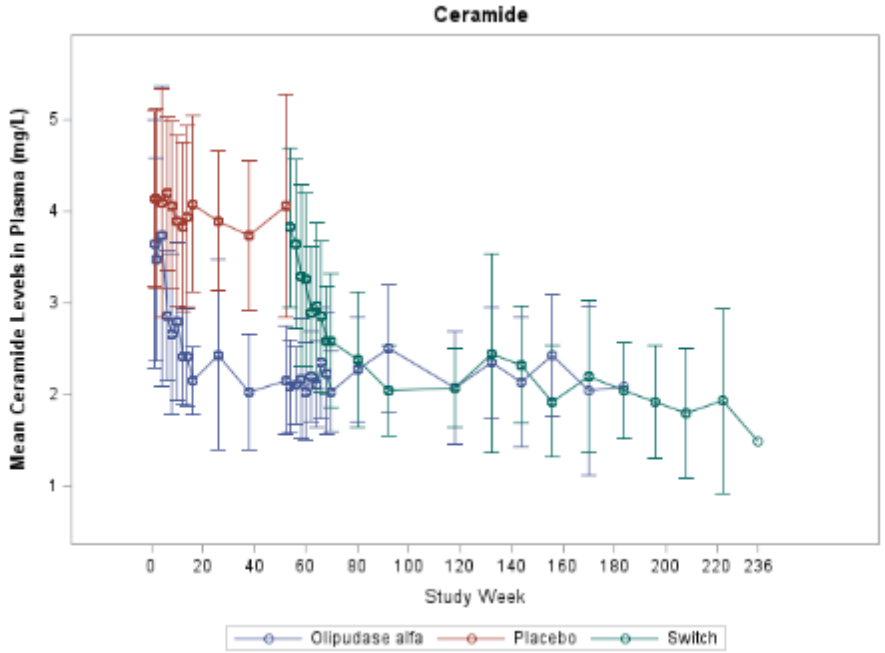
Plasma Ceramide

Figure 25 shows the mean concentration-time profiles of pre-dose plasma ceramide levels over 236 weeks (PAP+ETP) by treatment group. During the PAP period (first 52 weeks), no significant reduction in plasma ceramide levels was observed in the placebo treatment group. In the olipudase alfa treatment group, mean plasma ceramide levels gradually decreased from baseline over time with a mean percentage reduction of 30% from baseline at Week 16 and 35% reduction at Week 52. Similar trend of reduction in mean plasma ceramide levels was observed in subjects who switched from placebo to olipudase alfa treatment in ETP. The reduction in

plasma ceramide levels was well maintained up to 236 weeks in subjects receiving olipudase alfa throughout the ETP.

Of note, ceramide levels increased transiently at the 24-hour and 48-hour post-infusion timepoints following each olipudase alfa dose administration (data not shown in Figure 25), reflecting the immediate PD effect or enzymatic activity of olipudase alfa in hydrolysis of SM to ceramide in target tissues.

Figure 25. Pre-infusion Mean ± SD Plasma Ceramide Levels in Subjects With ASMD in Trial DFI 12712 (ASCEND)

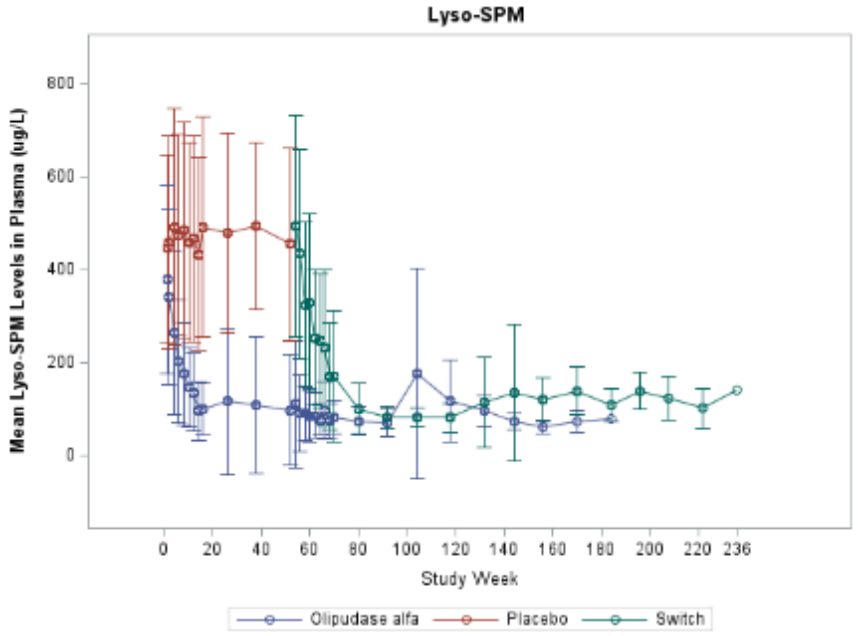


Source: This figure was generated by the review team based on the lb.xpt dataset located at \\cdsesub1\evsprod\BLA761261\0002\m5\datasets\dfi12712\tabulations\sdtm.
Note: Switch: Subjects of placebo arm (red) switched to the olipudase alfa (green) after 52 weeks.
Abbreviations: ASMD, acid sphingomyelinase deficiency; SD, standard deviation.

Plasma Lyso-Sphingomyelin (Lyso-SPM)

Figure 26 shows the mean concentration-time profiles of pre-dose plasma lyso-SPM levels over 236 weeks (PAP+ETP) by treatment groups. During the PAP period, no significant reduction in plasma lyso-SPM levels was observed in the placebo treatment group. In the olipudase alfa treatment group, mean plasma ceramide levels gradually decreased from baseline over time with a mean percentage reduction of 71% from baseline at Week 16 and 78% reduction at Week 52. A similar trend of reduction in mean plasma lyso-SPM levels was observed in subjects who switched from placebo to olipudase alfa treatment in ETP. The reduction in plasma ceramide levels was well maintained up to 236 weeks in subjects receiving olipudase alfa throughout the ETP.

Figure 26. Pre-Infusion Mean ± SD Plasma Lyso-SPM Levels in Subjects With ASMD in Trial DFI 12712 (ASCEND)

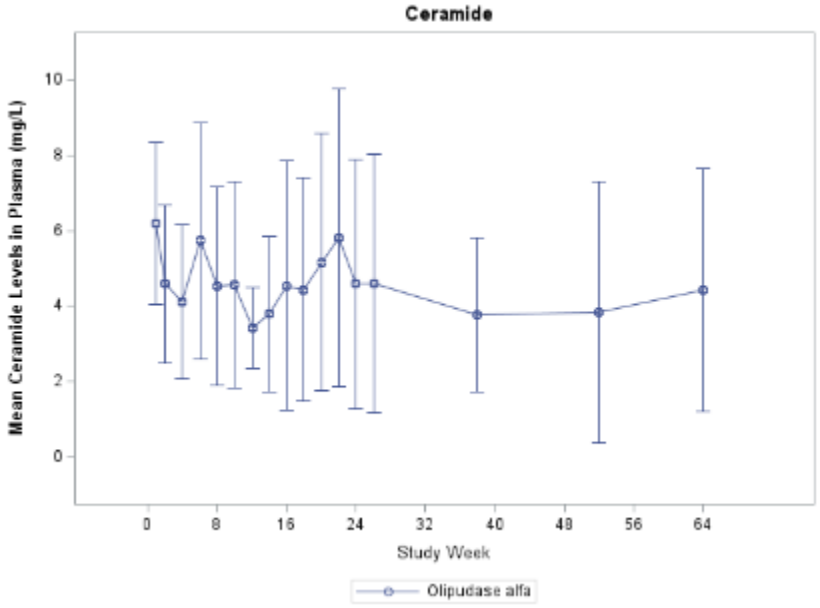


Source: This figure was generated by the review team based on the lb.xpt dataset located at \\cdsesub1\evsprod\BLA761261\0002\m5\datasets\dfi12712\tabulations\sdtm.
Note: Switch: Subjects of placebo arm (red) switched to the olipudase alfa (green) after 52 weeks.
Abbreviations: ASMD, acid sphingomyelinase deficiency; SD, standard deviation.

Trial DFI13803 (ASCEND-Peds)

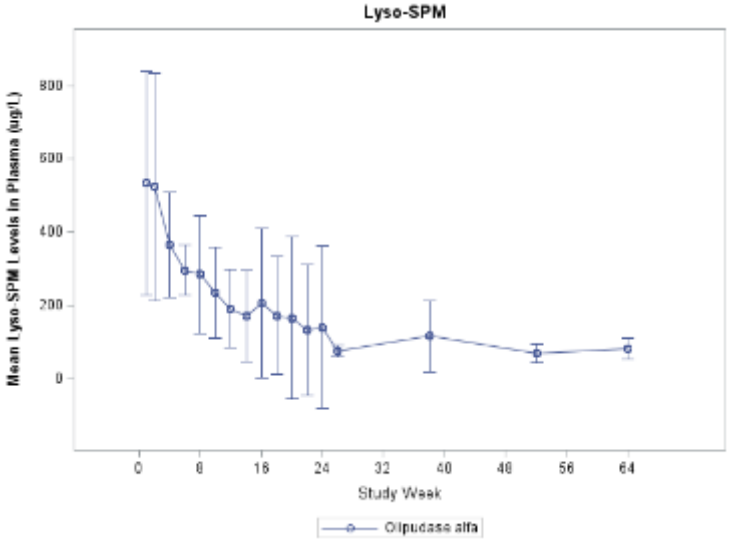
Figure 27 and Figure 28 show the mean concentration-time profiles of plasma ceramide and lyso-SPM levels, respectively, over the 64-week study period in pediatric subjects with ASMD. As this is an open label study without a placebo control, only the data from olipudase alfa treatment group was available. Consistent with the PD effect in adult subjects with ASMD in Trial DFI12712 (ASCEND), reductions in mean plasma ceramide and lyso-SPM levels were observed in pediatric subjects with ASMD. The reduction in plasma ceramide and lyso-SM levels in pediatric subjects was also well maintained in those who continued olipudase alfa treatment in the long term LTS13632 study.

Figure 27. Pre-Infusion Mean ± SD Plasma Ceramide Levels in Subjects With ASMD in Trial DFI13803 (ASCEND-Peds)



Source: This figure was generated by the review team based on the lb.xpt dataset located at \\cdsesub1\evsprod\BLA761261\0002\m5\datasets\dfi13803\tabulations\sdtm.
Abbreviations: ASMD, acid sphingomyelinase deficiency; SD, standard deviation.

Figure 28. Pre-infusion Mean ± SD Plasma Lyso-SPM Levels in Subjects With ASMD in Trial DFI13803 (ASCEND-Peds)



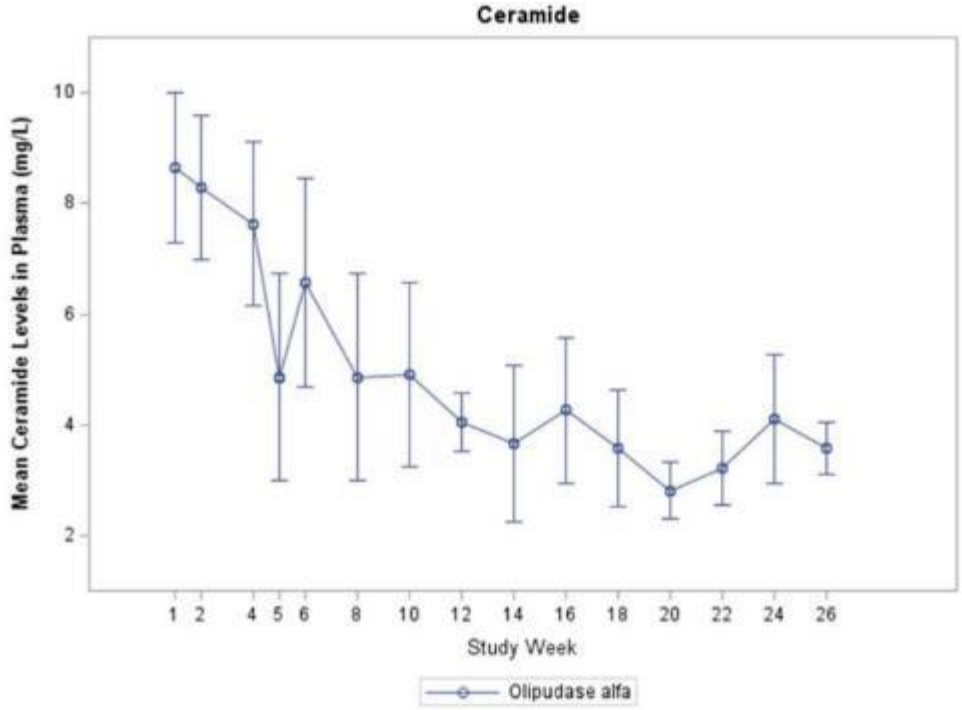
Source: This figure was generated by the review team based on the lb.xpt dataset located at \\cdsesub1\evsprod\BLA761261\0002\m5\datasets\dfi13803\tabulations\sdtm.
Abbreviations: ASMD, acid sphingomyelinase deficiency; SD, standard deviation; SPM, sphingomyelin.

Trial DFI13412

Five adult subjects with ASMD who were first enrolled in Study DFI13412 and continued treatment in the long-term LTS13632 study provided additional PD data for plasma ceramide and lyso-SPM levels following treatment with olipudase alfa. Figure 29 and Figure 30 show the mean concentration-time profiles of plasma ceramide and lyso-SPM levels, respectively, over the

26-week study period in these five subjects. The results were generally consistent with the PD effect observed in adult subjects with ASMD in Trial DFI12712 (ASCEND) and pediatric subjects in Trial DFI1383 (ASCEND-Peds).

Figure 29. Pre-infusion Mean ± SD Plasma Ceramide Levels in Subjects With ASMD in Study DFI13412



Source: This figure was generated by the review team based on the lb.xpt dataset located at \\cdsesub1\evsprod\BLA761261\0002\m5\datasets\lts13632\tabulations\sdtm.
Abbreviations: ASMD, acid sphingomyelinase deficiency; SD, standard deviation.

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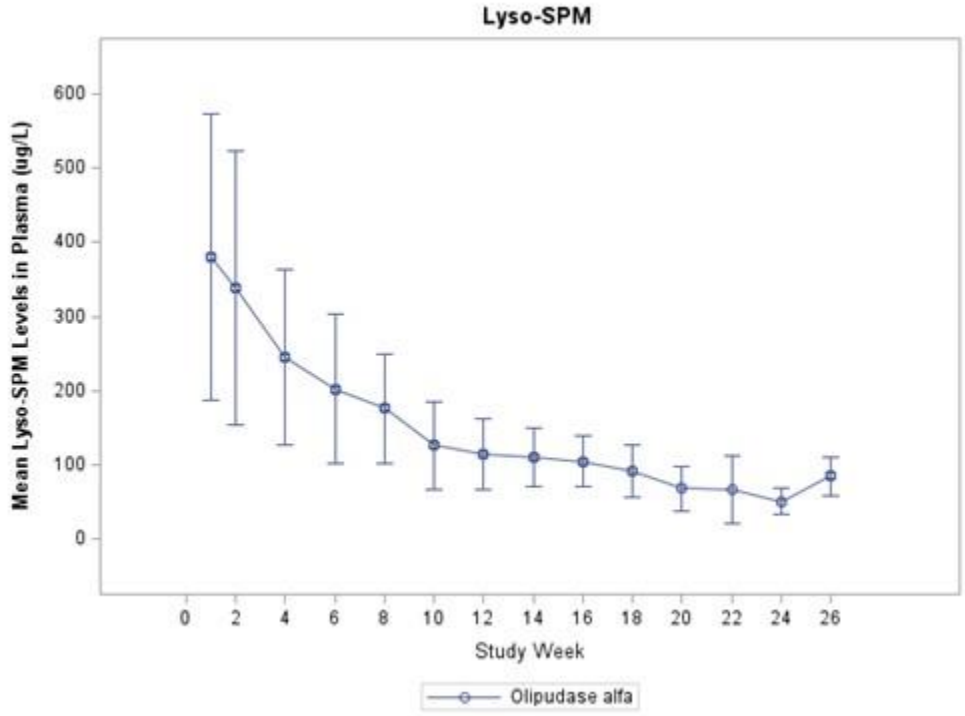
Figure 30. Pre-Infusion Mean ± SD Plasma Lyso-SPM Levels in Subjects With ASMD in Study DFI13412



Source: This figure was generated by the review team based on the lb.xpt dataset located at \\cdsesub1\evsprod\BLA761261\0002\m5\datasets\lts13632\tabulations\sdtm.
Abbreviations: ASMD, acid sphingomyelinase deficiency; SD, standard deviation; SPM, sphingomyelin.

Nonclinical Assessment

The available nonclinical data were reviewed to determine whether the results could serve as confirmatory evidence.

Background and Assessment

No in vitro experiments were conducted in the development program. The Applicant relied extensively on the use of the ASMKO mouse, a widely-used model of ASMD that is considered acceptable by the review team (Horinouchi et al. 1995). Mice homozygous for disruption of the ASM coding region lack ASM activity and accumulate SPM in a manner similar to human ASMD. The mice appear normal at birth. They do not manifest the ASMD phenotype until approximately eight weeks of age, when ataxia and mild tremors become noticeable. By 12 to 16 weeks, they are lethargic, unresponsive to stimuli and cannot feed properly. They develop severe ataxia before 4 months of age, and generally die between 6 to 8 months of age. ASMKO mice differ from the human phenotype, in that they do not develop organomegaly.

ASMKO mice were used to evaluate the efficacy with which treatment with olipudase could clear SPM, primarily from liver, spleen, and kidney. SPM reduction was dose- and duration-dependent when single doses of native ASM or olipudase alfa (1, 3, or 5 mg) were administered to ASMKO mice. A dose of 5 mg/kg reduced SPM levels on days 1 to 7 in liver (maximum -95%, day 7); in spleen (maximum -80%, day 7); and in kidney (maximum -71%, day 7).

Conversely, reductions of SPM levels in lung were of lower magnitude (-43% on day 7). SPM levels began to increase after day 7.

When olipudase alfa was administered to ASMKO mice every other week for 13 weeks (Study 06031), treatment-related trends toward reductions in AST and ALT were reported in males and females, and alkaline phosphatase (ALP) was reduced in treated males; these findings were thought to reflect interruption of pathophysiological disease progression. Vehicle- and diphenhydramine-treated control mice showed histopathological evidence of intracellular SPM accumulation (cytoplasmic vacuolation and foamy macrophages) in liver, kidney, bone marrow (sternum and femur), thymus, lymph node (mandibular and mesenteric), adrenal gland, small intestine, spleen, stomach, trachea, pancreas, cervix, ovary, uterus, and epididymis. Conversely, notations for olipudase-treated mice included observations that these findings were reduced in incidence and severity.

Improved survival was not apparent in this model. This is not surprising: dosing was initiated at 8 to 10 weeks of age. A study of 13 to 17 weeks duration (the longest duration of treatment and recovery) would result in final evaluations that were conducted at ~25 to 27 weeks of age. It is likely that longer dosing durations would be needed to determine whether survival is improved beyond the 6 to 8 month life expectancy in this model. Further, lung function, which deteriorates with SPM accumulation, was not directly assessed in ASMKO animals.

Conclusion

In addition to the one single adequate-well controlled clinical investigation, the well-established etiology of the disease, mechanism of action of the therapy, and the available PD data on reduction of plasma ceramide and lyso-SPM levels provide acceptable confirmatory evidence for the effectiveness of olipudase alfa in subjects with ASMD. The nonclinical data suggest that olipudase treatment attenuates aspects of ASMD pathology, however, they do not rise to the level of confirmatory evidence given the limitations noted above.

6.3.3. Youngest Age Limit for Pediatric Indication

Issue

Is the efficacy and safety information adequate to support an indication in pediatric subjects of <2 years of age?

Background

The clinical development of olipudase alfa included an adequate well controlled trial in adult subjects and an open label single arm study in pediatric subjects. Efficacy, safety, PK, and PD were evaluated in both of these trials. Because the pathophysiology and progression of the disease are sufficiently similar and the response to treatment is also expected to be similar in adult and pediatric subjects, extrapolation of efficacy is appropriate for pediatric patients.

Assessment

Efficacy

Trial DFI13803 (ASCEND-Peds) did not show evidence of differences in efficacy between infants (< 2 years) versus children (2 to <12 years). Figure 15, Figure 18, and Table 22 through Table 24 illustrate that, in general, there were not significant differences in efficacy between the two age cohorts: infant (<2 years) and child (2 to <12 years). Of note, no patients between 12-17 years of age were evaluated. However, as the younger age population and the adult population both showed similar efficacy results, one can extrapolate that efficacy would be expected to be the same in the adolescent population as the disease process in the adolescent population is similar to the adults and pediatric population. For the spleen volume (MN) endpoint, the single infant in the trial showed improvement approximately equal to the overall average: a percentage decrease of 46.8% compared to an average of 46.7% (CI: 41.4, 52.1) overall; and an absolute decrease of 7.9 MN compared to an average of 8.9 MN (CI: 7.9, 9.9) overall. This subject also showed above-average improvement with regard to liver volume (MN): a percentage decrease of 43.9% compared to overall 38.1% (CI: 32.0, 44.1); and an absolute decrease of 1.6 MN compared to overall 1.04 MN (CI: 0.88, 1.20). Of note, DL_{CO} measurements were not taken for any subjects below age 7. Figure 31 illustrates these percentage changes *(top row)* and the absolutes changes *(bottom row)* in Spleen Volume *(left)* and Liver Volume *(right)* across age levels.

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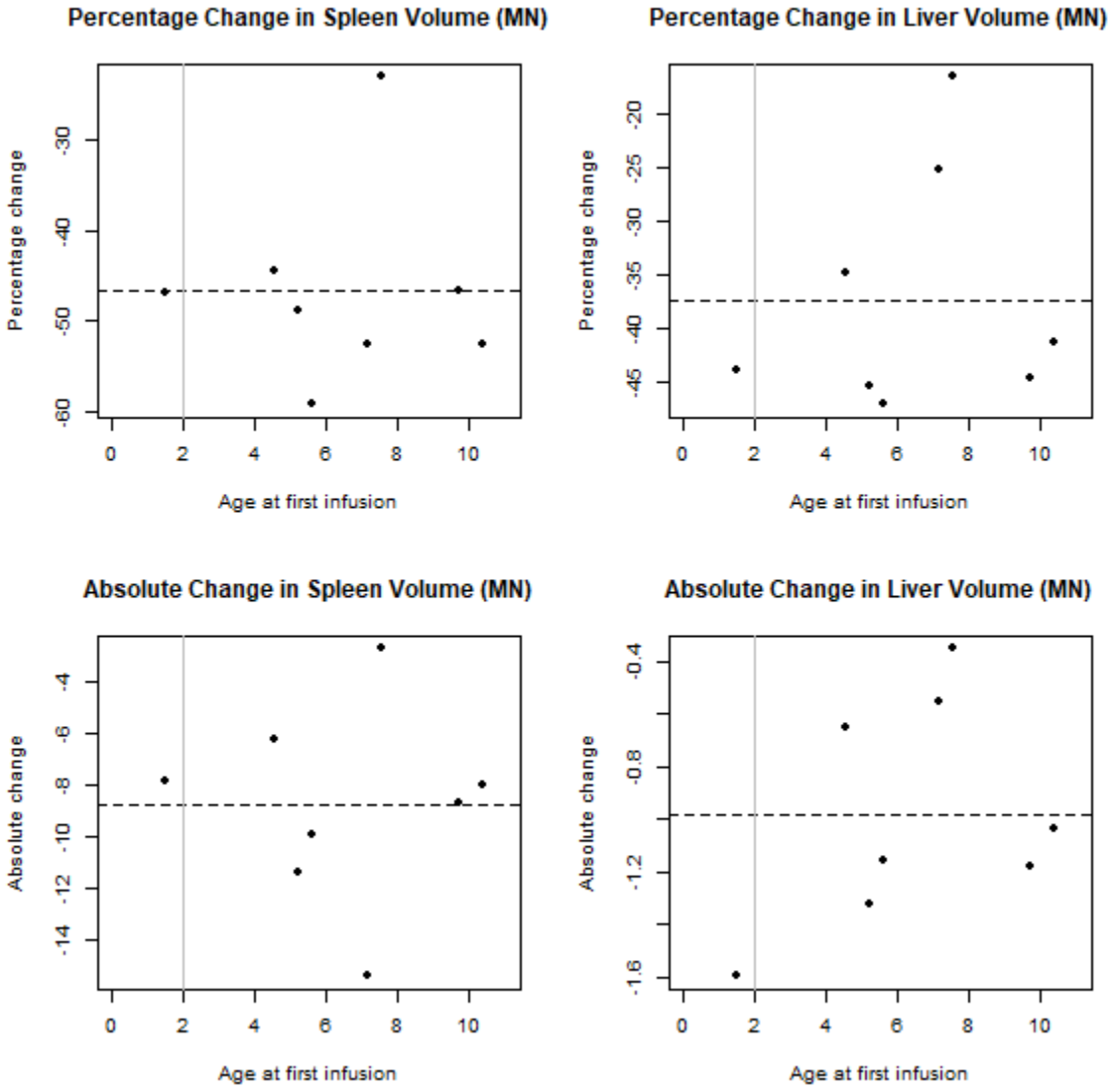
Figure 31. Individual-Level Efficacy Endpoints (Spleen and Liver Volume) by Age at First Infusion in mITT-C Population During First 52 Weeks, DFI13803 (ASCEND-Peds)



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi13803\analysis\adam\datasets.
Note: Gray vertical lines divide the age cohorts (infant/child).
Note: Dotted horizontal lines give mean endpoint value among mITT-C population.
Abbreviations: mITT-C, modified intent to treat excluding process-B subjects; MN, multiples of normal

Information was available for seven subjects <2 years of age (ranging from 7 months to 2 years) and one subject aged 2 years and 27 days in the olipudase alfa Managed Access Program. All subjects were diagnosed with ASMD type B or type A/B and initiated on Process C (b) (4) followed by Process C (b) (4) or initiated on Process C (b) (4) Four of the eight subjects have received treatment for approximately 3 months to 7 months; two of them have reached the maintenance dose of 3 mg/kg. The other four subjects have reached the maintenance dose and treated for 11 months to 2 years. Clinical assessments of the four subjects receiving more than one year of olipudase alfa showed improvements in several clinical parameters. Specifically, liver and spleen volumes, ALT, AST, LDL, triglycerides, and lyso-SPM were decreased; platelet count, HDL,

and body weight were increased. Two subjects had radiological lung abnormalities before treatment; CT returned to normal in one of the subjects and clinical lung examination was normal in both subjects after treatment. One subject was taken off oxygen supplementation.

Safety

In the context of the disease rarity, the ASCEND-Peds trial provided an adequate safety database to evaluate safety in pediatric ASMD patients. However, among the 8 pediatric subjects who participated in ASCEND-Peds, only one subject was <2 years old. The subject was 1.5 years old and experienced an SAE of anaphylactic reaction at Week 12 during the dose escalation period. Anti-olipudase alfa IgG and IgE antibodies tested positive using the blood sample collected at prefusion on the day of anaphylaxis. Anti-olipudase alfa IgG titer was 1600 and was the highest among the titers detected in the pediatric population. Assessment of samples collected after the anaphylaxis event did not reveal an elevation in serum tryptase or circulating immune complex or complement activation.

Olipudase alfa was temporarily suspended between Week 12 and Week 28 and was re-started at Week 28 using a 1:100,000 diluted drug solution and a desensitization procedure that involved 13 administration steps of increasing drug concentrations at increasing infusion rates. Olipudase alfa was subsequently dose escalated to reach the maintenance dose of 3 mg/kg, but multiple APRs occurred during the dose escalation process (see Section 7.6.1.7). Other AEs including ALP increased, urticaria, pyrexia, and vomiting were also reported while the subject was on olipudase alfa treatment.

Two episodes of anaphylactic reactions were also reported in another 16-month-old boy with ASMD type A during the fifth and sixth infusions in the expanded access IND (b) (4) this subject received olipudase alfa Process B. In both instances, the subject developed full body hives and facial swelling with some mild wheezing; premedication with diphenhydramine and prednisolone was administered an hour prior to the infusion in the second event. The infusion was immediately stopped, and the subject was given albuterol nebulizer and IV diphenhydramine with (first event) and without (second event) methylprednisolone. His symptoms resolved within an hour in both events, but oxygen saturation remained in the 88-92% range in the second event and the subject continued treatment with oxygen and nebulization. Olipudase alfa was not restarted after the second episode. The IND was subsequently terminated, and the subject was treated with a fatty acid amide hydrolase inhibitor and died of presumed pneumonia at three years of age. The subject was tested positive for anti-olipudase alfa IgE and IgG antibodies at both study weeks when anaphylaxis occurred.

Of the eight subjects in the Managed Access Program, AEs were reported in four of them. Most of the AEs were consistent with those observed in olipudase alfa clinical trials; these AEs are described below:

> One subject had an emesis after the second infusion, and G-tube feeding was paused. The subject had a fever and was restless the next day but recovered from fever the following day. Another subject experienced two episodes of vomiting and fever 24 hours after the third infusion; laboratory results showed no increases in C-reactive protein (CRP), transaminases, LDH, and bilirubin. The third subject was hospitalized due to vomiting, skin pallor, elevated heart rate, decreased oxygen saturation, physical sluggishness, bradypnea, Glasgow coma scale 8, and reduced response to painful stimuli 24 hours after

the fifth infusion. There were other symptoms and laboratory findings including fever, vomiting, increased CRP, and increased procalcitonin, which were consistent with APR. The subject was treated empirically with antibiotics and antiviral agent and was recovered in about a week without a final diagnosis. The AE was attributed to either an infectious process of unknown etiology or ceramide release. The last subject experienced an SAE of seizures (mild worsening reflux and moderate acute hypoxic epilepsy) which was thought to be related to the progression of the underlying condition.

No AEs were reported for the reminding four subjects.

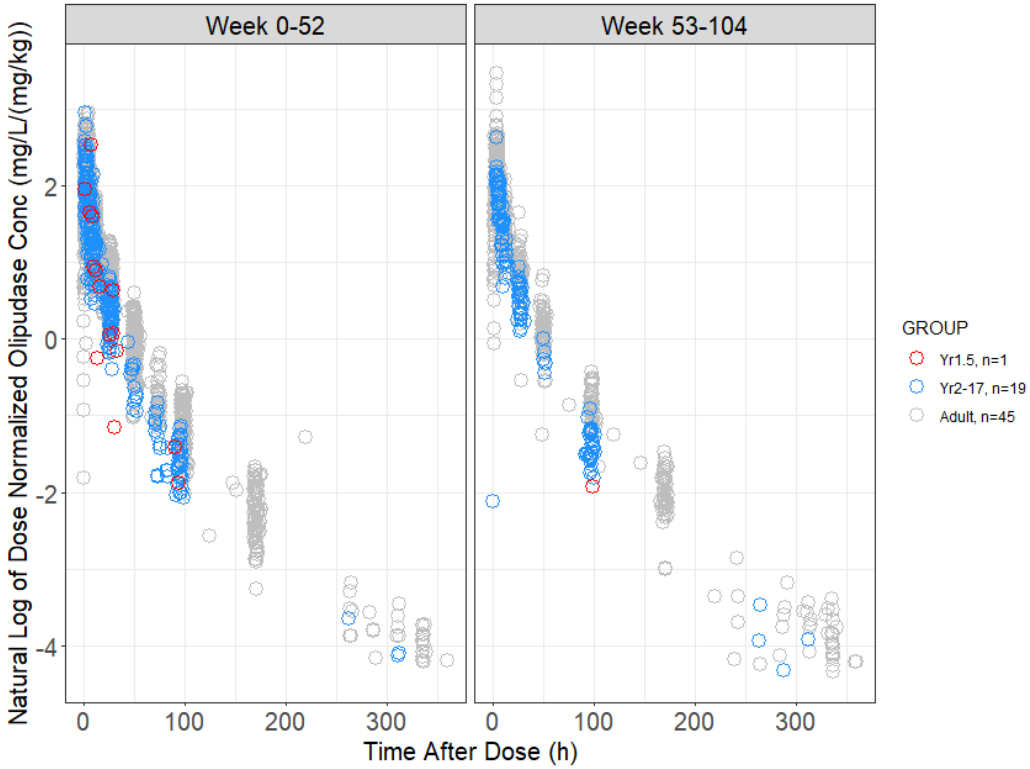
Clinical Pharmacology

Population PK and E-R analyses indicated that younger pediatric subjects (due to lower body weight) had relatively lower olipudase alfa exposure but similar or better PD and efficacy response. The overall PD and efficacy results in pediatric subjects supported partial extrapolation of efficacy from the adults and supported that the proposed body weight-based dosing regimen is acceptable across different age groups.

In the plot of dose normalized olipudase alfa concentration versus time, the lowest drug exposure was observed in the youngest subject group of ages <2 years (n=1), followed by subject group of ages 2 to 17 years (n=19), and adults (n=45) showed the highest drug exposure (Figure 32). Population PK analysis results showed that body weight (which correlates with age) is a covariate of olipudase alfa clearance with a power of 0.75, with the dose normalized clearance estimated to be 8.9, 7.2, 6.4, 5.9, 5.5, 5.2, 5, and 4.8 mL/h/kg for body weight of 10, 20, 30, 40, 50, 60, 70, and 80 kg, respectively. Although younger pediatric subjects are predicted to have lower olipudase alfa exposure than that observed in adults at the currently proposed dose, a recommendation for a higher dose in pediatric subjects (including subjects <2 years of age) is not needed, and the proposed body weight-based dosing regimen is acceptable across different age groups, for the following considerations:

- E-R analysis for efficacy endpoints indicated that pediatric subjects had similar response in increasing DL_{CO} and platelet, and slightly greater response in decreasing spleen volume, compared to adult subjects (Figure 33).
- E-R analysis for PD response in reducing plasma Lyso-SPM showed that bodyweight significantly influenced both I_{max} and IC_{50} of the PK/PD model. A lower IC_{50} and a slightly higher I_{max} were estimated in pediatric subjects with lower bodyweight, which indicates PD response in pediatric subjects were more sensitive to olipudase alfa treatment. See Section 6.1.3 for more details.
- Of note, to achieve its biologic activity and the subsequent therapeutic effect, olipudase alfa needs to be internalized and transported to lysosomes as an exogenous source of ASM. Therefore, plasma olipudase alfa concentration is not considered a key driver for clinical efficacy. This may explain the observed lower plasma concentration but similar or better PD and efficacy responses in younger pediatric subjects with lower body weight.

Figure 32. Dose-Normalized Olipudase Alfa Concentration Over Time by Age Group



Source: FDA reviewer's analysis based on Applicant's population pharmacokinetics dataset "updated.xpt"
Abbreviations: Con, concentration; h, hour; n, total number of subjects.

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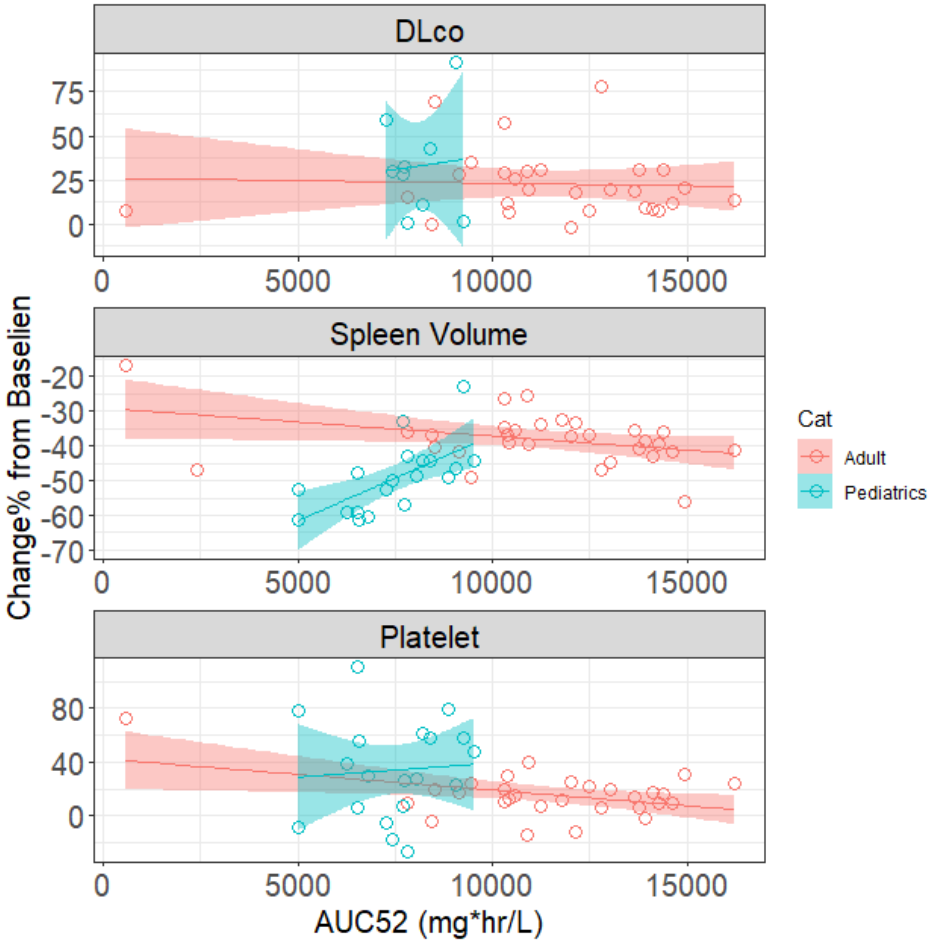
Figure 33. Dose-Normalized Olipudase Alfa Concentration Over Time by Endpoint



Source: FDA reviewer's analysis based on Applicant's E-R datasets "dlco.xpt", "spleen.xpt", "platelet.xpt".
Abbreviations: AUC52, area under the concentration-time curve from first active dose to Week 52; DL_{CO}, diffusion capacity for carbon monoxide

Nonclinical

A juvenile toxicity study was not conducted with olipudase alfa. All nonclinical data come from studies in animals that had reached sexual maturity before dosing initiated.

Conclusion

Treatment experience in children <2 years of age is limited as only one subject less than 2 years of age was enrolled in the pediatric clinical trial. However, seven subjects less than 2 years of age were enrolled in the managed access program with majority of patients able to tolerate the treatment and receiving the maintenance dose. Efficacy showed improvement in the clinical assessments; the interpretability is unclear due to lack of standardization of assessments that occur in expanded access programs. ASMD represents a continuum of disease with disease onset that may occur at a very early age. The key drivers of disease burden in ASMD are expected to be similar across age groups, as in one does not see a disparity of disease in different organ systems at different age groups. Mechanistically, olipudase alfa would be expected to have a similar response to patients regardless of the age group. Therefore, the clinical response of olipudase alfa in subjects <2 years of age would be expected to be similar to those >2 years of

age. However, it is noted that pediatric subjects, specifically, the youngest subjects had very high ADA titers. As safety is limited in patients <2 years of age, the applicant will be required to conduct a 5-year observational study in this population evaluating for safety, especially anaphylaxis. ad

6.3.4. Inclusion of ASMD Type A Patients in Indication

Issue

Clinical data are not available for efficacy and safety evaluations in subjects with ASMD type A due to the exclusion of these subjects in olipudase alfa clinical trials. Is it acceptable to include Type A subjects in the proposed indication?

Background

The Applicant seeks marketing approval of olipudase alfa for (b) (4) treatment of non-CNS manifestations of ASMD in pediatric and adult subjects. This proposed indication will include subjects with ASMD type A, B, and A/B, but efficacy and safety data are limited in subjects with ASMD type A.

Assessment

Although subjects with ASMD type A can be distinguished from subjects with type B and type A/B due to the early infantile onset and neurodegenerative course of the disease, type A subjects also exhibits non-CNS manifestations that are characteristics of subjects with type B and type A/B. Specifically, type A subjects also have hepatosplenomegaly and ILD. Similarly to type B and type A/B, they also have persistently elevated transaminases. Hepatomegaly worsens over time, and eventually the liver becomes massive causing liver failure. ILD results in frequent respiratory infections and respiratory failure leading to death. These potential life-threatening manifestations represent the severe end of a spectrum of peripheral disease caused by the same gene defect in all disease subtypes. Olipudase alfa acts by providing an exogenous source of ASM enzyme to catabolize the accumulated substrate SPM in peripheral organs such as the lung, liver, and spleen, and clinical trial data have demonstrated reduction in SPM levels further leading to improvements in DLco and organ volumes in ASMD type B and A/B receiving olipudase alfa. Due to the mechanism of action of olipudase alfa, as well as same pathophysiology and peripheral organ involvement, similar improvements in lung function and spleen volume are expected in ASMD type A. Safety data are limited as the only patient with Type A who has been treated developed anaphylaxis.

Conclusion

While the neurological manifestation differs among ASMD type A, B, and A/B, disease pathophysiology is the same and similar somatic manifestations are observed in all disease phenotypes. Similar improvements in lung function, spleen volume and liver volume are expected regardless of disease phenotype due to the mechanism of action of olipudase alfa. Therefore, we recommend indicating treatment to include ASMD type A patients. However, we note that only one patient with Type A has been treated with olipudase alfa and consequently developed anaphylaxis. Therefore, the applicant will be required to conduct a postmaketing

observational study in ASMD type A patients to evaluate for safety, especially serious hypersensitivity reactions.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

7.1.1. Overall Safety Concern

Two safety issues of significant concern emerged in the nonclinical olipudase alfa development program:

Cardiovascular collapse was observed upon administration of doses ≥10 mg/kg (0.27-fold theMRHD, as assessed by body surface area (BSA) to ASMKO mice. While doses of ≤5mg/kg were well-tolerated and efficacious in clearing SPM from liver and spleen in ASMD, they were less effective in depleting SPM from the lung. In an effort to increase pulmonary SPM clearance, higher doses of rhASM were administered. Unexpectedly, single doses ≥10 mg/kg to ASMKO – but not wild-type- mice were associated with mortality in 10 to 72 hours, generally preceded by lethargy; this suggested that lethality was associated with sudden release and/or catabolism of high levels of SPM. Initial cytokine profiles revealed marked increases in granulocyte colony-stimulating factor, keratinocyte chemoattractant (KC), and interleukin (IL)-6, beginning 3 to 4 hours after dosing. However, cardiovascular monitoring in conscious, instrumented ASMKO mice uncovered early onset of protracted hypotension and bradycardia (60 to 120 min after dosing). When profiles of ceramide, sphingosine, and sphingosine-1-phosphate were generated, rapid increases in plasma ceramide (t =5 and 30 min after olipudase administration) were reported. Considered together, the proximate cause of death was protracted cardiovascular collapse, associated with abrupt release of large concentrations of SPM catabolites. It was subsequently determined that repeated administration of known tolerated olipudase doses (3 mg/kg) every other day for 3 to 4 doses would “de-bulk” lysosomes of SPM, thereby permitting administration of doses ≥10 mg/kg without apparent toxicity. A dose-escalation protocol was developed for clinical administration of olipudase, to be conducted over the course of 16 weeks. This mitigates the concern for abrupt release of SPM in subjects with ASMD, serving as the “debulking” strategy.

Exencephaly, a rare neural tube malformation, was noted among fetuses of wild-type pregnant mice (although not rabbits) treated with 3, 10, or 30 mg/kg olipudase daily during organogenesis. Data are reproduced below, in Table 25. Historical control data for the testing facility for the previous 7 years reported only 3 affected fetuses (N=4820) in 3/372 litters. Maternal olipudase area under the concentration-time curve (AUC) exposures in mice at the developmental NOAEL (3 mg/kg) are approximately 1/7th those associated with the MRHD.

Table 25 Exencephaly Data, Mouse Embryo-Fetal Development Study

	Olipudase Dose				
Exencephaly	**(Saline/ Control)**	**(DPH/ Control)**	**DPH/ Olipudase (3 mg/kg)**	**DPH/ Olipudase (10 mg/kg)**	**DPH/ Olipudase (30 mg/kg)**
#Fetuses/litters examined	326/24	329/25	168/14	266/21	307/23
Affected fetuses/litters	0/0	0/0	0/0	2/1	3/1
% affected fetuses	0/0	0/0	0/0	0.75%	0.98%
% affected litters	0/0	0/0	0/0	4.8%	4.3%

Discipline concerns for this finding are further discussed in Section 7.7.1 entitled "Key Review Issues Relevant to Evaluation of Risk".

Because neural tube defects occur early in gestation – often before pregnancy is recognized – women treated with olipudase who could become pregnant should use highly-effective contraception.

There were no other nonclinical safety issues of significant concern as assessed in the toxicology studies conducted during the development program. Nonclinical studies supporting marketing include a 13-week study in ASMKO mice, 26-week studies in rats and monkeys, a safety pharmacology study in monkeys, and reproductive and developmental toxicity studies in wild-type mice and rabbits. The NOAELs and associated exposures are listed in Table 26.

Table 26 NOAEL Margins in Olipudase Alfa GLP Toxicity Studies

Toxicity Study	**Study Number**	**Species**	**NOAEL (mg/kg) M/F**	**Safety** Margin **Based on AUC***
13-Week	06031	Mouse (AMSKO)	3	1.49**
26-Week	02027	Rat	30	2.8/1.8
	07007	Monkey	30	3.9
Safety pharmacology	08004	Monkey	30	5.6
EFD	TER0694	Mouse (CD1)	Maternal: 30	1.5
			Developmental: 3	0.13
EFD	TER0698	Rabbit	30	10.5
PPND	DPN0380	Mouse	30[3*]	1.5
FEED	FER0510	Mouse	30[**, 4*]	1.5

Source: Reviewer-generated.
*AUC in human: 602 µg*hr/ml at 3 mg/kg every 14 days.
** C_{max}, derived from Study 10-00262 Pnp
[3*] Data from EFD.
[4*] No TK data in male CD1 mice
Abbreviations: ASMKO, acid sphingomyelinase knockout; AUC, area under the concentration-time curve; EFD, embryo fetal development; FEED, Fertility and Early Embryonic Development ; GLP, good laboratory practices; PPND, pre- and postnatal development.

7.1.2. Safety Pharmacology

The effects of an IV infusion of olipudase alfa (30 mg/kg) on hemodynamic, electrocardiogram (ECG) (PR, QRS, RR, QT, and QTcB [Bazett's]) intervals, and respiratory parameters (rate and tidal volume) were evaluated in conscious, instrumented monkeys. Recordings were initiated 2 hours prior to dosing and continued for 24 hours after olipudase administration. Arterial blood was sampled for pH, partial pressure of carbon dioxide, partial pressure of oxygen, saturated oxygen, and blood bicarbonate. There was no effect of olipudase alfa on any parameter tested. The NOAEL was 30 mg/kg.

7.1.3. Absorption, Distribution, Metabolism, Excretion

Some assessment of PK/TK was conducted in all species tested. AUC and C_{max} did not differ among mouse strains nor genetically modified animals after administration of a single 3 mg/kg dose, although the Vss in ASMKO mice was approximately 2.3-fold that in wild-type mice. Elimination $t_{1/2}$ in mice (whether wild-type or ASMKO) ranged from 2 to 6 hours. Elimination half-life in monkeys was ~7.3 hours. As such, the frequency of administration (every other week) in all repeated dose general toxicity studies exceeded the plasma clearance of olipudase.

7.1.4. General Toxicology

There were no target organs of toxicity identified in wild-type mice, rats, or cynomolgus monkeys. Twenty-six week studies in rats and monkeys were conducted at doses up to 30 mg/kg, administered every other week. Olipudase was generally well-tolerated, with the exception of anticipated hypersensitivity reactions. The NOAEL in each study was 30 mg/kg. Margins at associated AUC values were <3 and 4.1-fold the olipudase MRHD in rats and monkeys, respectively.

Genotoxicity studies for olipudase alfa were not conducted, per International Conference on Harmonisation guidance *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (June 2011) and the guidance for industry *Investigational Enzyme Replacement Therapy Products, Nonclinical Assessment* (October 2019).

According to the ERT guidance (October 2019), "evaluating carcinogenic potential generally is not needed to support a marketing application." Further, there were no histopathology findings in the 26-week toxicity studies consistent with carcinogenic potential (e.g., hypertrophy or hyperplasia); nor were there any neoplastic or pre-neoplastic lesions noted in any species to which olipudase alfa was administered. Finally, lifetime administration to rodents is not feasible, due to hypersensitivity observed in these species. As such, a post-marketing carcinogenicity study is not warranted.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Olipudase alfa is an ERT product; potential risks with this class of agents are hypersensitivity reactions including anaphylaxis and IARs. Immunogenicity may be associated with hypersensitivity reactions and/or IARs as well.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Olipudase alfa is a new molecular entity and has not been approved in the United States or any other foreign markets. There is no postmarketing experience at the time of this review.

7.4. FDA Approach to the Safety Review

Safety assessments were performed using primary data from 30 adults and 8 pediatric subjects participated in olipudase alfa clinical trials receiving Process C (Table 27). Safety data were analyzed separately for adults and pediatric subjects because the safety profile was found to be different between the two populations. For adults, 13 and 18 subjects were randomized to receive olipudase alfa and placebo, respectively, during the pivotal trial period ASCEND PAP; safety comparison was performed between the active treatment group and placebo group during this period. In addition, the overall safety in adults was evaluated by using data from all subjects after they were started on olipudase alfa. Because one placebo subject discontinued during ASCEND ETP, data from 30 adults were used for this overall analysis. For pediatric subjects, safety data from the ASCEND Peds and LTS13632 were pooled because LTS13632 was an extension of the ASCEND Peds. Safety data from different age groups were also pooled, as there was only one subject in the youngest age group (i.e., <2 years old). To further support the safety in subjects <2 years of age, supplemental data from 9 pediatric subjects from a single patient IND and Managed Access Program were evaluated.

Table 27. Number of Subjects Included for the Safety Review

	Primary				Supplemental
	Pooled Adult (N =30)		Pooled Pediatric (N = 8)		Pediatric (N = 9)
Data Source	≥18 years OA	≥18 years PLB	2 to 11 years OA	<2 years OA	<2 years OA
Clinical Trial	13	18	7	1	
Single Patient IND					1
Managed Access Program					8*

*One of the subjects was 2 years and 27 days old
Note: Subjects who ever received Process B were excluded.
Abbreviations: OA, olipudase alfa, PLB, placebo

The overall approach to compare safety data between placebo group and active treatment group, between adult and pediatric subjects, and among different manufacturing processes is outlined in Section 3.2. To summarize the safety results, the number (percentage, %) of subjects who experienced adverse events (AEs) between different groups was compared, and EAIR was used for comparisons in instances where treatment duration was not the same among subjects. This review also evaluates potential immune-related risks associated with olipudase alfa, specifically APR, CRS, dose limiting toxicities (DLTs) (including DLT 1, DLT2, and DLT 3) based on a composite of clinical symptoms (reported as AEs) and laboratory values. The definitions for APR, CRS, and DLTs are described in Section 17.1.

7.5. Adequacy of Clinical Safety Database

The pooled safety database is adequate for a sufficient safety assessment of olipudase alfa for the indication of non-CNS manifestations of ASMD in pediatric and adult subjects. A total of 38 subjects with ASMD type B or A/B were evaluated, with a median (range) of olipudase alfa exposure of 3.0 (1.4 – 4.7) years in adult subjects and 2.7 (2.5 – 3.1) years in pediatric subjects. This represents a safety database consisting of 2.2 to 3.3% of ASMD subjects in the United

States receiving at least 1.4 years of olipudase alfa treatment. No subjects with ASMD type A participated in olipudase alfa clinical trials.

Table 28 shows the baseline demographics and clinical characteristics of adult subjects in the safety population. Table 29 summarizes the olipudase alfa exposure in this subject population. There were more females than males in the overall adult population, 72.2% females participated in the placebo group of DFI12712 (ASCEND) PAP. Three quarters of the subjects were <45 years of age, and most of adult subjects were White. Among 30 adult subjects participated in olipudase alfa clinical trials and received Process C, 7 (23.3%) subjects received <2 years of treatment, 23 (76.7%) subjects received >2 years to <4 years of olipudase alfa.

Subject demographics were balance between the active treatment group and the placebo group in DFI12712 (ASCEND) PAP, except that 72.2% of the subjects were females in the placebo group compared to 38.5% female subjects in the active treatment group. This imbalance is unlikely to have any impacts on the safety assessment, as sex is not known to have any prognostic values and effects on olipudase alfa PK and PD (see Section 8.1).

Table 28. Baseline Demographic and Clinical Characteristics, Safety Population, Trials DFI12712 (ASCEND), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

Characteristic	DFI12712 (Adult) PAP OA N=13	DFI12712 (Adult) PAP PLB N=18	DFI12712 (Adult) PAP+ETP OA/OA N=13	DFI12712 (Adult) PAP+ETP PLB/OA N=17	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30
Sex, n (%)					
Female	5 (38.5)	13 (72.2)	5 (38.5)	13 (76.5)	18 (60.0)
Male	8 (61.5)	5 (27.8)	8 (61.5)	4 (23.5)	12 (40.0)
Age, years					
Mean (SD)	34.4 (11.9)	32.7 (17)	34.4 (11.9)	33.4 (17.2)	33.8 (14.9)
Median (min, max)	33 (20, 58)	23.5 (18, 65)	33 (20, 58)	24 (18, 65)	29 (18, 65)
Age group, years, n (%)					
≥18 to <45 years	10 (76.9)	13 (72.2)	10 (76.9)	12 (70.6)	22 (73.3)
≥45 to <65 years	3 (23.1)	4 (22.2)	3 (23.1)	4 (23.5)	7 (23.3)
≥65 years	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Race, n (%)					
Asian	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Other	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
White	11 (84.6)	16 (88.9)	11 (84.6)	15 (88.2)	26 (86.7)
Ethnicity, n (%)					
Hispanic or Latino	4 (30.8)	6 (33.3)	4 (30.8)	6 (35.3)	10 (33.3)
Not Hispanic or Latino	8 (61.5)	12 (66.7)	8 (61.5)	11 (64.7)	19 (63.3)
Not Reported	1 (7.7)	0	1 (7.7)	0	1 (3.3)

Source: adsl.xpt; Software: R.
Note: Adult subjects who ever received Process B were excluded from analysis.
Abbreviations: ETP, extended treatment; ISS, integrated summary of safety; N, number of patients in treatment group; n, number of subjects with given characteristic; OA, olipudase alfa; PAP, primary analysis period; PLB, placebo; SD, standard deviation.

Table 29. Duration of Exposure, Safety Population, Trials DFI12712 (ASCEND), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

Parameter	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Duration of treatment, weeks					
Mean (SD)	54.2 (0.7)	52.6 (7.1)	150.3 (26.1)	118.3 (42.1)	132.1 (39.0)
Median (Q1, Q3)	54 (54, 54.1)	54 (54, 54.1)	152.1 (140.1, 163)	116.7 (95.1, 182.0)	131.9 (106.9, 162.0)
Min, Max	53.9, 56.4	24.1, 56	86.3, 194	20.1, 191.9	20.1, 194.0
Total exposure (person years)	14	18	37	38.5	76.0
Patients treated, by duration, n (%)					
<52 weeks	0	1 (5.6)	0	1 (5.9)	1 (3.3)
≥52 to <104 weeks	13 (100)	17 (94.4)	1 (7.7)	5 (29.4)	6 (20.0)
≥104 to <208 weeks	0	0	12 (92.3)	11 (64.7)	23 (76.7)
≥208 to <312 weeks	0	0	0	0	0
≥312 weeks	0	0	0	0	0

Source: adex.xpt and adsl.xpt; Software: R.
Note: Adult subjects who ever received Process B were excluded.
Note: Duration is up to the data cutoff dates.
Note: Exposure while on placebo was excluded in the DFI12712 (Adult) PAP+ETP PLB/OA study arm.
Abbreviations: ETP, extended treatment; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OA, olipudase alfa; PAP, primary analysis period; PLB, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation

Of the 8 pediatric subjects enrolled in the olipudase alfa clinical program and received Process C, 7 subjects were between 2 to 12 years old, and one subject was 1.5 years old (Table 30). No adolescents aged 12 to 17 years of age were evaluated as they received Process B. Approximately 40% of the pediatric subjects were males. All subjects were White and treated for 2.5 to 3.1 years of olipudase alfa (Table 31).

Table 30. Baseline Demographic and Clinical Characteristics by Age Group, Safety Population, Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS), Pediatric Subjects Who Received Only Process C

Characteristic	Child OA LTS13632/DFI13803 N=7	Infant/early child OA LTS13632/DFI13803 N=1	Pooled Pediatric OA LTS13632/DFI13803 N=8
Sex, n (%)			
Female	4 (57.1)	0	4 (50.0)
Male	3 (42.9)	1 (100)	4 (50.0)
Age, years			
Mean (SD)	6.7 (2.2)	1 (NA)	6 (2.9)
Median (min, max)	7 (4, 10)	1 (1, 1)	6 (1, 10)
Age group, years, n (%)			
<2 years	0	1 (100)	1 (12.5)
≥2 to <12 years	7 (100)	0	7 (87.5)
Race, n (%)			
White	7 (100)	1 (100)	8 (100)
Ethnicity, n (%)			
Not Hispanic or Latino	7 (100)	1 (100)	8 (100)

Source: adsl.xpt; Software: R.
Note: Pediatric subjects who ever received Process B were excluded.
Abbreviations: ISS, integrated summary of safety; N, number of patients in treatment group; n, number of patients with given characteristic; OA, olipudase alfa; SD, standard deviation.

Table 31. Duration of Exposure, Safety Population, Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS), Pediatric Subjects Who Received Only Process C

Parameter	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Duration of treatment, weeks			
Mean (SD)	140.5 (11.5)	148.9 (NA)	(11.1)
Median (Q1, Q3)	133.9 (132.4, 146)	148.9 (148.9, 148.9)	(133.1, 147.5)
Min, Max	130.9, 162	148.9, 148.9	130.9, 162
Total exposure (person years)	19	3	22
Subjects treated, by duration, n (%)			
<52 weeks	0	0	0
≥52 to <104 weeks	0	0	0
≥104 to <208 weeks	7 (100)	1 (100)	8 (100)
≥208 to <312 weeks	0	0	0
≥312 weeks	0	0	0

Source: adex.xpt and adsl.xpt; Software: R.
Note: Pediatric subjects who ever received Process B were excluded.
Note: Duration is up to the data cutoff dates.
Abbreviations: ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OA, olipudase alfa; Q1, first quartile; Q3, third quartile; SD, standard deviation.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, Integrated Safety Set Including Subjects Who Received Only Process C

7.6.1.1. Overall Adverse Events Summary, Integrated Safety Set Including Subjects Who Received Only Process C

7.6.1.1.1. Adult Population

Table 32 summarizes the overall occurrences of AEs in all adult subjects participated in clinical trials. There were no deaths. SAEs occurred in 10/30 (33.3%) of adult subjects; all of these SAEs were non-fatal and not life-threatening. Twelve (40%) subjects experienced AEs that led to dose modification of olipudase alfa; no subjects discontinued treatment due to the occurrence of AEs. Mild to moderate AEs were reported as the maximum severity AEs in 80% of adult subjects.

During ASCEND PAP, SAEs occurred more often in the placebo group than the active treatment group (22% vs. 15%); more active treatment subjects had AEs leading to dose interruption (23% vs. 17%). Severe AEs were reported as the maximum severity AEs in a higher proportion of subjects in the placebo than in the active treatment group (33% vs. 8%). Vice versa, mild to moderate AEs were reported more often as the maximum severity AEs in the active treatment group (92% versus 67%) (Table 32).

Table 32. Overview of Adverse Events, Safety Population, Trials DFI12712 (ASCEND), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

Event Category	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
SAE	2 (15.4)	4 (22.2)	4 (30.8)	6 (35.3)	10 (33.3)
SAEs with fatal outcome	0	0	0	0	0
Life-threatening SAEs	0	2 (11.1)	0	0	0
AE leading to permanent discontinuation of study drug	0	0	0	0	0
AE leading to dose modification of study drug	3 (23.1)	3 (16.7)	6 (46.2)	6 (35.3)	12 (40.0)
AE leading to interruption of study drug	3 (23.1)	3 (16.7)	6 (46.2)	5 (29.4)	11 (36.7)
AE leading to reduction of study drug	0	0	0	2 (11.8)	2 (6.7)
AE leading to dose delay of study drug	0	0	0	0	0
Other	0	0	0	0	0
AE	13 (100)	18 (100)	100)	17 (100)	30 (100)
Severe	1 (7.7)	6 (33.3)	2 (15.4)	4 (23.5)	6 (20.0)
Moderate	7 (53.8)	10 (55.6)	8 (61.5)	8 (47.1)	16 (53.3)
Mild	5 (38.5)	2 (11.1)	3 (23.1)	5 (29.4)	8 (26.7)

Source: adae.xpt; Software: R
Note: Adult subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Note: Duration is up to the data cutoff dates.
Note: Severity as assessed by the investigator.
Note: Life-threatening SAEs were determined using the AESLIFE variable in the ADAE dataset, which included two subjects (012712-032-001-003 and 012712-392-001-001).
Abbreviations: AE, adverse event; ETP, extended treatment; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with at least one event; OA, olipudase alfa; PAP, primary analysis period; PLB, placebo; SAE, serious adverse event

7.6.1.1.2. Pediatric Population

Table 33 summarizes the overall occurrences of AEs in pediatric subjects. There were no deaths, and SAE occurred in 50% of the pediatric subjects. No AEs led to the permanent discontinuation of study treatment. Severe AEs occurred in 37.5% pediatric subjects.

Compared to adults, SAEs, AEs leading to dose modification, and severe AEs as the maximum severity AEs were observed in a higher percentage of pediatric subjects. On the other hand, mild to moderate AEs were reported as the maximum severity AEs in a smaller percentage of pediatric subjects.

Table 33. Overview of Adverse Events, Safety Population, Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS), Pediatric Subjects Who Received Only Process C

Event Category	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
SAE	3 (42.9)	1 (100)	4 (50.0)
SAEs with fatal outcome	0	0	0
Life-threatening SAEs	0	0	0
AE leading to permanent discontinuation of study drug	0	0	0
AE leading to dose modification of study drug	4 (57.1)	1 (100)	5 (62.5)
AE leading to interruption of study drug	3 (42.9)	1 (100)	4 (50.0)
AE leading to reduction of study drug	2 (28.6)	0	2 (25.0)
AE leading to dose delay of study drug	0	0	0
Other	0	0	0
AE	7 (100)	1 (100)	8 (100)
Severe	2 (28.6)	1 (100)	3 (37.5)
Moderate	5 (71.4)	0	5 (62.5)
Mild	0	0	0

Source: adae.xpt; Software: R.
Note: Pediatric subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Note: Duration is up to the data cutoff dates.
Note: Severity as assessed by the investigator.
Abbreviations: AE, adverse event; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with at least one event; OA, olipudase alfa; SAE, serious adverse event.

7.6.1.2. Deaths, Integrated Safety Set, Subjects Who Received Only Process C

No deaths were reported up to the data cutoff dates in both adult and pediatric populations.

7.6.1.3. Serious Adverse Events, Integrated Safety Set, Subjects Who Received Only Process C

7.6.1.3.1. Adult Population

A total of 24 treatment emergent SAEs were observed in 10/30 (33.3%) adult subjects with ASMD receiving Process C (Table 34), and all SAEs resolved in these subjects. Of these SAEs, one was unlikely related and 22 were not related to olipudase alfa treatment. One SAE of superficial phlebitis was deemed related to the study protocol procedure.

Four SAEs (cellulitis, gastritis viral, lower limb fracture, and hepatic hemorrhage) occurred in one subject each in the active treatment group, whereas one patient experienced hepatic hemorrhage in the placebo group during the ASCEND PAP. These SAEs were deemed not related to the study treatment. One SAE of extrasystole in one subject during the ASCEND ETP is considered unrelated to treatment as it occurred prior to receiving treatment.

The review team agrees with the Applicant's assessment of attribution of study treatment to treatment emergent SAEs and provides below the description of the SAE that was possibly related to the study procedure.

Subject 012712- (b) (6) was an 18-year-old female who experienced an SAE of superficial phlebitis (left wrist) of severe intensity on Day 436 (Week 62) during ASCEND ETP. The subject was treated with caffeine/papaver somniferum latex/paracetamol tablet and received IV fondaparinux for two weeks. The phlebitis resolved 28 days later, and the event was considered related to the protocol procedure.

During the 120-day safety update, two treatment emergent SAEs were reported in two adult subjects. One subject reported a moderate unrelated event of pneumonia. Another subject reported a severe event of syncope that was considered unrelated to the study treatment. The latter study participant had experienced syncope several times in the past before enrolling in the study.

Table 34. Serious Adverse Events by Preferred Term, Safety Population, Trials DFI12712 (ASEND), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Any serious AE	2 (15.4)	4 (22.2)	4 (30.8)	6 (35.3)	10 (33.3)
Loss of consciousness	0	0	0	2 (11.8)	2 (6.7)
Cellulitis	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Cholecystitis acute	0	0	1 (7.7)	0	1 (3.3)
COVID-19	0	0	1 (7.7)	0	1 (3.3)
Extrasystoles	0	0	0	1 (5.9)	1 (3.3)
Gastritis viral	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Hepatic hemorrhage	1 (7.7)	1 (5.6)	1 (7.7)	0	1 (3.3)
Hepatocellular carcinoma	0	0	0	1 (5.9)	1 (3.3)
Inguinal hernia	0	0	0	1 (5.9)	1 (3.3)
Lower limb fracture	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Non-cardiac chest pain	0	0	0	1 (5.9)	1 (3.3)
Phlebitis superficial	0	0	0	1 (5.9)	1 (3.3)
Pneumothorax	0	0	0	1 (5.9)	1 (3.3)
Urinary tract infection	0	0	0	1 (5.9)	1 (3.3)
Anemia	0	1 (5.6)	0	0	0

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Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Appendicitis	0	1 (5.6)	0	0	0
Epistaxis	0	1 (5.6)	0	0	0
Liver abscess	0	1 (5.6)	0	0	0
Peritonitis	0	1 (5.6)	0	0	0
Pleural effusion	0	1 (5.6)	0	0	0
Shock hemorrhagic	0	1 (5.6)	0	0	0
Syncope	0	1 (5.6)	0	0	0

Source: adae.xpt; Software: R.
Note: Adult subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period, except for the AEs occurred in the placebo group during DFI12712 PAP.
Note: Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Note: Duration is up to the data cutoff dates.
Abbreviations: AE, adverse event; ETP, extended treatment; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of patients with adverse event; OA, olipudase alfa; PAP, primary analysis period; PLB, placebo; SOC, system organ class.

7.6.1.3.2. Pediatric Population

In the pediatric population, 11 treatment emergent SAEs occurred in 4 (50%) patients (Table 35). Three of the SAEs in two subjects (25%) were considered related, 1 was unlikely related, and 6 were not related to olipudase alfa treatment. One SAE of localized edema was considered related to the protocol procedure. No additional SAEs were reported in pediatric patients in the 120-day Safety Update.

Table 35. Serious Adverse Events by Preferred Term, Safety Population, Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS), Pediatric Subjects Who Received Only Process C

Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Any serious AE	3 (42.9)	1 (100)	4 (50.0)
Gastroenteritis	1 (14.3)	1 (100)	2 (25.0)
Anaphylactic reaction	0	1 (100)	1 (12.5)
Femur fracture	1 (14.3)	0	1 (12.5)
Localized oedema	1 (14.3)	0	1 (12.5)
Pneumonia mycoplasmal	1 (14.3)	0	1 (12.5)
Poor venous access	1 (14.3)	0	1 (12.5)

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Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Rash	1 (14.3)	0	1 (12.5)
Respiratory failure	1 (14.3)	0	1 (12.5)
Talipes	1 (14.3)	0	1 (12.5)
Urticaria	1 (14.3)	0	1 (12.5)

Source: adae.xpt; Software: R
Note: Pediatric subjects who ever received Process B were excluded.
Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is up to the data cutoff dates.
Abbreviations: AE, adverse event; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of subjects with adverse event; OA, olipudase alfa; SOC, system organ class

The review team agrees with the Applicant's assessment of the attribution of study treatment to the SAEs in pediatric patients. Included below is the description of the three drug-related SAEs occurring in two patients.

Subject 013803- (b) (6) a 5-year-old male, experienced two separate SAEs of moderate intensity in ASCEND Peds; both events were considered related to the study treatment. The subject experienced an SAE of urticaria on the torso, neck, and both ears during olipudase alfa infusion on Day 211 (Week 30). The infusion was stopped, and IV dimetindene maleate and IV prednisolone were administered. The event resolved on the same day. He missed the next two doses at Week 32 and Week 34 because of other unrelated AEs (nasopharyngitis, otitis media, and rhinitis). Olipudase alfa was restarted on Week 36, when pre-treatment with oral cetirizine and IV prednisolone were initiated prior to each subsequent drug infusion. On Day 281 (Week 40), the patient had an SAE of rash on the trunk, upper legs, and right ear leading to hospitalization. The infusion was temporarily interrupted, and he was administered IV dimetindene maleate and IV prednisolone. On the same day, the patient recovered from rash; the infusion was restarted and completed. The subject continues to receive olipudase alfa. The subject was tested positive for anti-olipudase alfa IgG but not IgE antibodies.

Subject 013803- (b) (6) was a 1.5-year-old boy who experienced a drug-related SAE of anaphylactic reaction of severe intensity approximately 30 minutes into olipudase alfa infusion of 0.6 mg/kg at Week 12 (Day 83). The subject had hives on the abdominal area, swelling of the ear and lips, erythema of the ears, coughing and mild rhonchi with no wheezing. The infusion was stopped, and epinephrine, methylprednisolone, and diphenhydramine were administered. The event resolved an hour later. Assessment of antidrug antibodies was conducted using a sample collected pre-infusion on Day 83. Anti-olipudase alfa IgG was tested positive with a titer of 1600; anti-olipudase alfa IgE antibodies were also positive at 1.30 IU/mL (normal reference range <0.35 IU/mL). Additional immunological testing was performed at about 2.5 hours after the anaphylactic reaction. Serum tryptase was 6.7 μg/L (normal reference range ≤12.5 μg/L), circulating immune complex was at 0.8 μg eq/mL, and complement activation was negative. Olipudase alfa treatment was temporary suspended from Week 14 to Week 26 and was restarted at 0.3 mg/kg at Week 28 with a desensitization procedure (after consultation by an immunologist expert and an evaluation by the Safety Data Monitoring Committee). The desensitization procedure included 13 steps. The first 12 steps lasted 30 minutes each and included six

concentrations from 1 ng/mL to 100 ng/mL, each being infused at a rate of 0.1 mL/min and then 0.3 mL/min. The last step administered a concentration of 0.1 mg/mL at a rate of 0.6 mL/min for the remainder of the infusion. Olipudase alfa solution was diluted 1:100,000, and a coating solution was added to the infusion bags to prevent drug adherence to the IV tubing that could occur due to the low concentration. Olipudase alfa dose was re-escalated to reach the maintenance dose of 3 mg/kg, and the subject continues to receive olipudase alfa.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Integrated Safety Set, Subjects Who Received Only Process C

None of the adult and pediatric subjects permanently discontinued treatment due to the occurrence of AEs. Three adult subjects discontinued study treatment during ASCEND ETP for reasons other than AEs. Two of the three subjects were in the olipudase alfa/olipudase alfa group; one withdrew consent and the other one discontinued based on subject's decision. One subject in the placebo/olipudase alfa group discontinued for reasons related to the COVID-19 pandemic.

7.6.1.5. Treatment-Emergent Adverse Events, Integrated Safety Set, Subjects Who Received Only Process C

7.6.1.5.1. Adult Population

Table 36 summarizes the treatment emergent adverse events (TEAEs) of olipudase alfa by preferred term (PT) occurring in ≥6.7% (i.e., ≥2 subjects) of all adults in clinical trials. Adverse drug reactions (ADRs), as defined by a higher frequency in the active treatment group than the placebo group during PAP and assessed to be related or possibly related to olipudase alfa were headache, cough, diarrhea, hypotension, ocular hyperemia, erythema, pharyngitis, dyspnea, urticaria, papule, myalgia, and throat irritation. While nausea, arthralgia, abdominal pain, abdominal pain upper, pyrexia, and vomiting occurred more frequently in the placebo group than in the active treatment group, they were also considered as ADRs because of their high occurrence during the ETP and the attribution of the treatment to these AEs cannot be ruled out. Two other ADRs that occurred in only one adult each and not listed in Table 36 include asthenia and C-reactive protein abnormal.

The TEAEs observed in adults by FDA MedDRA Query (narrow) occurring in ≥6.7% adult subjects are listed in (Table 207 in Section 17.2).

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Table 36. Treatment-Emergent Adverse Events Occurring at a Frequency of ≥6.7% in All Adults , Safety Population, Trials DFI12712 (ASCEND), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Any TEAEs	13 (100)	18 (100)	13 (100)	17 (1000	30 (100)
Headache	7 (53.8)	8 (44.4)	7 (53.8)	9 (52.9)	16 (53.3)
Nasopharyngitis	6 (46.2)	6 (33.3)	6 (46.2)	4 (23.5)	10 (33.3)
URTI	5 (38.5)	4 (22.2)	6 (46.2)	4 (23.5)	10 (33.3)
Nausea	1 (7.7)	8 (44.4)	2 (15.4)	7 (41.2)	9 (30.0)
Abdominal pain	1 (7.7)	3 (16.7)	2 (15.4)	5 (29.4)	7 (23.3)
Arthralgia	2 (15.4)	3 (16.7)	3 (23.1)	4 (23.5)	7 (23.3)
Cough	4 (30.8)	2 (11.1)	4 (30.8)	3 (17.6)	7 (23.3)
Pruritus	0	3 (16.7)	0	7 (41.2)	7 (23.3)
Abdominal pain upper	1 (7.7)	3 (16.7)	2 (15.4)	4 (23.5)	6 (20.0)
Pyrexia	2 (15.4)	4 (22.2)	2 (15.4)	4 (23.5)	6 (20.0)
Back pain	0	4 (22.2)	1 (7.7)	4 (23.5)	5 (16.7)
Diarrhea	2 (15.4)	2 (11.1)	2 (15.4)	3 (17.6)	5 (16.7)
Gastroenteritis	1 (7.7)	2 (11.1)	2 (15.4)	3 (17.6)	5 (16.7)
Myalgia	1 (7.7)	0	2 (15.4)	3 (17.6)	5 (16.7)
Procedural pain	1 (7.7)	2 (11.1)	2 (15.4)	3 (17.6)	5 (16.7)
Urticaria	1 (7.7)	0	2 (15.4)	3 (17.6)	5 (16.7)
Vomiting	1 (7.7)	7 (38.9)	1 (7.7)	4 (23.5)	5 (16.7)
Fatigue	0	3 (16.7)	2 (15.4)	2 (11.8)	4 (13.3)
Nasal congestion	0	1 (5.6)	2 (15.4)	2 (11.8)	4 (13.3)
ALT increased	0	0	0	3 (17.6)	3 (10.0)
AST increased	0	0	0	3 (17.6)	3 (10.0)
Cellulitis	1 (7.7)	0	1 (7.7)	2 (11.8)	3 (10.0)
Conjunctivitis	1 (7.7)	0	1 (7.7)	2 (11.8)	3 (10.0)
COVID-19	0	0	2 (15.4)	1 (5.9)	3 (10.0)
Dental caries	0	0	1 (7.7)	2 (11.8)	3 (10.0)
Dizziness	0	2 (11.1)	1 (7.7)	2 (11.8)	3 (10.0)
Dyspepsia	2 (15.4)	0	2 (15.4)	1 (5.9)	3 (10.0)
Dyspnea	1 (7.7)	0	2 (15.4)	1 (5.9)	3 (10.0)
Epistaxis	1 (7.7)	1 (5.6)	2 (15.4)	1 (5.9)	3 (10.0)
Influenza	1 (7.7)	1 (5.6)	2 (15.4)	1 (5.9)	3 (10.0)
Iron deficiency	0	0	1 (7.7)	2 (11.8)	3 (10.0)
Musculoskeletal chest pain	3 (23.1)	3 (16.7)	3 (23.1)	0	3 (10.0)
Neck pain	0	1 (5.6)	0	3 (17.6)	3 (10.0)
Oropharyngeal pain	1 (7.7)	1 (5.6)	1 (7.7)	2 (11.8)	3 (10.0)
Weight increased	0	0	0	3 (17.6)	3 (10.0)
Abdominal discomfort	0	0	1 (7.7)	1 (5.9)	2 (6.7)
Anxiety	0	3 (16.7)	0	2 (11.8)	2 (6.7)
Breast pain	0	0	1 (7.7)	1 (5.9)	2 (6.7)
Constipation	1 (7.7)	0	1 (7.7)	1 (5.9)	2 (6.7)
Contusion	0	2 (11.1)	1 (7.7)	1 (5.9)	2 (6.7)
Dysmenorrhea	0	2 (11.1)	1 (7.7)	1 (5.9)	2 (6.7)
Dysuria	0	1 (5.6)	0	2 (11.8)	2 (6.7)

Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Eczema	1 (7.7)	0	2 (15.4)	0	2 (6.7)
Erythema	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Fall	0	3 (16.7)	1 (7.7)	1 (5.9)	2 (6.7)
Fungal infection	1 (7.7)	0	1 (7.7)	1 (5.9)	2 (6.7)
Hypertension	0	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Hypoesthesia	0	1 (5.6)	0	2 (11.8)	2 (6.7)
Hypotension	2 (15.4)	2 (11.1)	2 (15.4)	0	2 (6.7)
Insomnia	1 (7.7)	3 (16.7)	1 (7.7)	1 (5.9)	2 (6.7)
Joint swelling	0	2 (11.1)	1 (7.7)	1 (5.9)	2 (6.7)
Loss of consciousness	0	0	0	2 (11.8)	2 (6.7)
Muscle spasms	0	1 (5.6)	0	2 (11.8)	2 (6.7)
Ocular hyperemia	2 (15.4)	1 (5.6)	2 (15.4)	0	2 (6.7)
Otitis media	1 (7.7)	0	2 (15.4)	0	2 (6.7)
Pain in extremity	1 (7.7)	4 (22.2)	1 (7.7)	1 (5.9)	2 (6.7)
Papule	1 (7.7)	0	2 (15.4)	0	2 (6.7)
Pharyngitis	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Presyncope	1 (7.7)	0	2 (15.4)	0	2 (6.7)

Source: adae.xpt; Software: R.
Note: Adult subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Note: Duration is up to the data cutoff dates.
Note: Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of patients with adverse event; OA, olipudase alfa; URTI, upper respiratory tract infection.

7.6.1.5.2. Pediatric Population

In the pediatric population, TEAEs occurred by PT and by FDA MedDRA Query are presented in Table 37 and Table 208 (see Section 17.2), respectively. TEAEs observed in ≥12.5% subjects (i.e., ≥1 subject) and are deemed related or possibly related to olipudase alfa included pyrexia, cough, diarrhea, rhinitis, vomiting, abdominal pain (abdominal pain and abdominal pain upper), headache, urticaria, nausea, rash (rash and erythema), arthralgia, pruritus, fatigue (fatigue and asthenia), pharyngitis, C-reactive protein increased, hypotension, anaphylactic reaction, hypersensitivity, infusion site swelling, tachycardia, and pharyngeal swelling.

Table 37. Subjects With Adverse Events Occurring at ≥0% Frequency, Safety Population, Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS), Pediatric Subjects Who Received Only Process C

Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Any AE	7 (100)	1 (100)	8 (100)
Pyrexia	7 (100)	1 (100)	8 (100)
Nasopharyngitis	6 (85.7)	1 (100)	7 (87.5)
Cough	5 (71.4)	1 (100)	6 (75.0)
Diarrhea	5 (71.4)	1 (100)	6 (75.0)

Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Rhinitis	6 (85.7)	0	6 (75.0)
Abdominal pain	4 (57.1)	0	4 (50.0)
Gastroenteritis	3 (42.9)	1 (100)	4 (50.0)
Headache	4 (57.1)	0	4 (50.0)
Upper respiratory tract infection	3 (42.9)	1 (100)	4 (50.0)
Urticaria	3 (42.9)	1 (100)	4 (50.0)
Vomiting	3 (42.9)	1 (100)	4 (50.0)
Arthralgia	2 (28.6)	1 (100)	3 (37.5)
Contusion	2 (28.6)	1 (100)	3 (37.5)
Eczema	2 (28.6)	1 (100)	3 (37.5)
Nausea	3 (42.9)	0	3 (37.5)
Oropharyngeal pain	3 (42.9)	0	3 (37.5)
Abdominal pain upper	1 (14.3)	1 (100)	2 (25.0)
Activated partial thromboplastin time prolonged	2 (28.6)	0	2 (25.0)
Arthropod bite	1 (14.3)	1 (100)	2 (25.0)
Blood alkaline phosphatase increased	1 (14.3)	1 (100)	2 (25.0)
Bronchitis	2 (28.6)	0	2 (25.0)
Conjunctivitis	2 (28.6)	0	2 (25.0)
Epistaxis	2 (28.6)	0	2 (25.0)
Erythema	2 (28.6)	0	2 (25.0)
Influenza	2 (28.6)	0	2 (25.0)
Nasal congestion	1 (14.3)	1 (100)	2 (25.0)
Oral herpes	2 (28.6)	0	2 (25.0)
Otitis media	1 (14.3)	1 (100)	2 (25.0)
Pain in extremity	2 (28.6)	0	2 (25.0)
Pharyngitis	2 (28.6)	0	2 (25.0)
Pruritus	2 (28.6)	0	2 (25.0)
Rash	1 (14.3)	1 (100)	2 (25.0)
Rhinorrhea	1 (14.3)	1 (100)	2 (25.0)
Skin laceration	2 (28.6)	0	2 (25.0)
Tonsillar hypertrophy	2 (28.6)	0	2 (25.0)
Anaphylactic reaction	0	1 (100)	1 (12.5)
Asthenia	1 (14.3)	0	1 (12.5)
Back pain	1 (14.3)	0	1 (12.5)
Blood bilirubin increased	1 (14.3)	0	1 (12.5)
C-reactive protein increased	1 (14.3)	0	1 (12.5)
Cerumen impaction	0	1 (100)	1 (12.5)
Chest pain	1 (14.3)	0	1 (12.5)
Complication associated with device	0	1 (100)	1 (12.5)
Constipation	0	1 (100)	1 (12.5)
Cystitis	1 (14.3)	0	1 (12.5)
Dental fistula	1 (14.3)	0	1 (12.5)
Dermal cyst	1 (14.3)	0	1 (12.5)
Dermatitis contact	1 (14.3)	0	1 (12.5)
Dermatitis diaper	0	1 (100)	1 (12.5)
Device occlusion	1 (14.3)	0	1 (12.5)
Dizziness	1 (14.3)	0	1 (12.5)
Dry skin	1 (14.3)	0	1 (12.5)
Ear discomfort	0	1 (100)	1 (12.5)
Ear infection	0	1 (100)	1 (12.5)

Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Ear inflammation	0	1 (100)	1 (12.5)
Ear pain	1 (14.3)	0	1 (12.5)
Encopresis	1 (14.3)	0	1 (12.5)
Enteritis	1 (14.3)	0	1 (12.5)
Enterobiasis	1 (14.3)	0	1 (12.5)
Epstein-Barr virus infection	0	1 (100)	1 (12.5)
Fall	1 (14.3)	0	1 (12.5)
Fatigue	0	1 (100)	1 (12.5)
Femur fracture	1 (14.3)	0	1 (12.5)
Flank pain	1 (14.3)	0	1 (12.5)
Foot deformity	1 (14.3)	0	1 (12.5)
Hand-foot-and-mouth disease	1 (14.3)	0	1 (12.5)
Head injury	1 (14.3)	0	1 (12.5)
Herpes virus infection	1 (14.3)	0	1 (12.5)
Hypercalcemia	1 (14.3)	0	1 (12.5)
Hyperkeratosis	0	1 (100)	1 (12.5)
Hypotension	1 (14.3)	0	1 (12.5)
Infusion site swelling	1 (14.3)	0	1 (12.5)
International normalized ratio increased	1 (14.3)	0	1 (12.5)
Iron deficiency	1 (14.3)	0	1 (12.5)
Ligament sprain	1 (14.3)	0	1 (12.5)
Localized edema	1 (14.3)	0	1 (12.5)
Middle ear effusion	0	1 (100)	1 (12.5)
Miliaria	1 (14.3)	0	1 (12.5)
Mouth cyst	1 (14.3)	0	1 (12.5)
Muscle oedema	1 (14.3)	0	1 (12.5)
Neck pain	1 (14.3)	0	1 (12.5)
Oral mucosal blistering	1 (14.3)	0	1 (12.5)
Otitis externa	1 (14.3)	0	1 (12.5)
Otitis media acute	0	1 (100)	1 (12.5)
Papule	1 (14.3)	0	1 (12.5)
Peripheral swelling	1 (14.3)	0	1 (12.5)
Petechiae	0	1 (100)	1 (12.5)
Pharyngeal swelling	0	1 (100)	1 (12.5)
Pharyngotonsillitis	1 (14.3)	0	1 (12.5)
Pneumonia mycoplasmal	1 (14.3)	0	1 (12.5)
Poor venous access	1 (14.3)	0	1 (12.5)
Post-traumatic pain	1 (14.3)	0	1 (12.5)
Procedural pain	1 (14.3)	0	1 (12.5)
Respiratory failure	1 (14.3)	0	1 (12.5)
Respiratory tract infection	1 (14.3)	0	1 (12.5)
Right ventricular systolic pressure increased	1 (14.3)	0	1 (12.5)
Scratch	0	1 (100)	1 (12.5)
Sensory disturbance	1 (14.3)	0	1 (12.5)
Sinusitis	0	1 (100)	1 (12.5)
Skin abrasion	1 (14.3)	0	1 (12.5)
Skin exfoliation	1 (14.3)	0	1 (12.5)
Skin irritation	0	1 (100)	1 (12.5)
Skin mass	1 (14.3)	0	1 (12.5)

Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Stomatitis	1 (14.3)	0	1 (12.5)
Sunburn	1 (14.3)	0	1 (12.5)
Tachycardia	1 (14.3)	0	1 (12.5)
Talipes	1 (14.3)	0	1 (12.5)
Thrombocytopenia	1 (14.3)	0	1 (12.5)
Tonsillitis	1 (14.3)	0	1 (12.5)
Urinary incontinence	1 (14.3)	0	1 (12.5)
Vaccination site pain	1 (14.3)	0	1 (12.5)
Varicella	1 (14.3)	0	1 (12.5)
Viral infection	1 (14.3)	0	1 (12.5)
Vitamin D deficiency	1 (14.3)	0	1 (12.5)

Source: adae.xpt; Software: R
Note: Pediatric subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Note: Duration is up to the data cutoff dates.
Note: Coded as MedDRA preferred terms.
Note: Ear inflammation replaces: Ear infection
Note: Fall replaces: Skin abrasion
Note: Muscle oedema replaces: Localized oedema
Abbreviations: AE, adverse event; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OA, olipudase alfa.

7.6.1.6. Adverse Events of Special Interest, Hypersensitivity, Integrated Safety Set, Subjects Who Received Only Process C

7.6.1.6.1.1. Adult Population

TEAEs of hypersensitivity were assessed using the Hypersensitivity SMQ (the Applicant's analysis; see Response to FDA IR dated April 29, 2022 Appendix 1 Table 11; SDN 36) as well as the FDA MedDRA Query for Hypersensitivity (Broad) (Table 38). Results from the two queries were compared, and further evaluation was performed by reviewing patient narratives to confirm the relatedness of the TEAEs to olipudase alfa. Refer to the Applicant's response to FDA IRs dated July 5, 2022 (SDN 48) and July 13, 2022 (SDN 50).

Ten (33.3%) adult subjects were determined to have related or possibly related hypersensitivity AEs, which included urticaria, pruritus, erythema, rash, rash erythematous, eczema, angioedema, and erythema nodosum. Of note, the erythema and eczema hypersensitivity reactions included above occurred in a subject as identified by the Hypersensitivity SMQ but not by the FDA MedDRA Query. On the other hand, the rash pruritic identified by FDA MedDRA Query in Table 38 occurred in one subject but was considered not drug related. All drug related hypersensitivity reactions were assessed to be mild or moderate and resolved. Dose interruption occurred in two of the ten subjects as a result of hypersensitivity reactions.

Table 38. Subjects With Adverse Events in FDA Medical Query (Broad) for Hypersensitivity, by Preferred Term, Safety Population, Trials DFI12712 (ASCEND), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

Group Query Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Hypersensitivity FMQ Broad (GQ)	1 (7.7)	5 (27.8)	2 (15.4)	9 (52.9)	12 (40.0)
Pruritus	0	3 (16.7)	0	8 (47.1)	8 (26.7)
Urticaria	1 (7.7)	0	2 (15.4)	3 (17.6)	5 (16.7)
Angioedema	0	0	0	1 (5.9)	1 (3.3)
Erythema nodosum	0	0	0	1 (5.9)	1 (3.3)
Rash	0	2 (11.1)	0	1 (5.9)	1 (3.3)
Rash erythematous	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Rash pruritic	0	0	0	1 (5.9)	1 (3.3)
Infusion site urticaria	0	1 (5.6)	0	0	0
Rash morbilliform	0	1 (5.6)	0	0	0

Source: adae.xpt; Software: R
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa period.
Note: Duration is up to the data cutoff dates
Note: Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; ETP, extended treatment; FMQ, FDA medical query; GQ, group query; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OA, olipudase alfa; PAP, primary analysis period; PLB, placebo.

7.6.1.6.1.2. Pediatric Population

Table 39 summarizes pediatric subjects with AEs in the FDA MedDRA Query (Broad) for Hypersensitivity. Four (50%) subjects were assessed to have drug related hypersensitivity that included urticaria, pruritis, rash, erythema, and localized edema. This percentage of pediatric subjects with drug related hypersensitivity was slightly higher than that in adults (33%). A severe anaphylactic reaction was reported in a male patient <2 years old; information about the anaphylactic reaction can be found in Section 7.6.1.3.2. This subject also experienced a mild pharyngeal swelling later in the trial over 72 hours after the previous infusion; the AE was not considered drug related. Another subject had skin peeling on feet secondary to walking on hot asphalt that was coded as skin exfoliation. The event was assessed as not related to the study treatment and resolved after nine days. This other subject also experienced drug related erythema and localized edema that were identified by the Applicant's hypersensitivity SMQ and not by the FDA MedDRA Query. With the exception of the anaphylactic reaction, all hypersensitivity reactions were of mild or moderate intensity and resolved with dose interruption or temporarily treatment discontinuation.

Table 39. Subjects With Adverse Events in FDA Medical Query (Broad) for Hypersensitivity, by Preferred Term, Safety Population, Trial Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS),, Pediatric Subjects Who Received Only Process C

Group Query Preferred Term	Child OA LTS13632/DFI13803 N=7 n (%)	Infant/early child OA LTS13632/DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/DFI13803 N=8 n (%)
Hypersensitivity FMQ Broad (GQ)	3 (42.9)	1 (100)	4 (50.0)
Urticaria	3 (42.9)	1 (100)	4 (50.0)
Pruritus	2 (28.6)	0	2 (25.0)
Rash	1 (14.3)	1 (100)	2 (25.0)
Anaphylactic reaction	0	1 (100)	1 (12.5)
Pharyngeal swelling	0	1 (100)	1 (12.5)
Skin exfoliation	1 (14.3)	0	1 (12.5)

Source: adae.xpt; Software: R.
Note: Pediatric subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa period.
Note: Duration is up to the data cutoff dates.
Note: Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; FMQ, FDA medical query; GQ, group query; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OA, olipudase alfa

7.6.1.7. Adverse Events of Special Interest, Protocol-Defined Infusion-Associated Reactions, Integrated Safety Set, Subjects Who Received Only Process C

7.6.1.7.1. Adult Population

Protocol-defined IARs (i.e., any TEAEs occurred within 24 hours after the start of infusion and were considered related or possibly related to the study treatment by the investigator) (n=108) were reported in 15 (50%) of the adult subjects. All IARs were mild or moderate and did not result in permanent discontinuation of study treatment. IARs that occurred in at least two adults include headache, pruritis, urticaria, vomiting, erythema, nausea, and pyrexia (Table 40).

Table 40. Patients With Protocol-Defined Infusion-Associated Reactions (IARs) Occurring at ≥0% Frequency, Safety Population, Trials DFI12712 (ASCNED), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Any AE	5 (38.5)	5 (27.8)	6 (46.2)	9 (52.9)	15 (50.0)
Headache	3 (23.1)	2 (11.1)	3 (23.1)	1 (5.9)	4 (13.3)
Pruritus	0	1 (5.6)	0	3 (17.6)	3 (10.0)
Urticaria	1 (7.7)	0	1 (7.7)	2 (11.8)	3 (10.0)
Vomiting	1 (7.7)	1 (5.6)	1 (7.7)	2 (11.8)	3 (10.0)
Erythema	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Nausea	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Pyrexia	1 (7.7)	0	1 (7.7)	1 (5.9)	2 (6.7)
Abdominal pain	0	0	0	1 (5.9)	1 (3.3)

Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Alanine aminotransferase increased	0	0	0	1 (5.9)	1 (3.3)
Angioedema	0	0	0	1 (5.9)	1 (3.3)
Aspartate aminotransferase increased	0	0	0	1 (5.9)	1 (3.3)
C-reactive protein increased	0	0	0	1 (5.9)	1 (3.3)
Chills	0	0	0	1 (5.9)	1 (3.3)
Cough	0	0	0	1 (5.9)	1 (3.3)
Dizziness	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Dyspnea	0	0	0	1 (5.9)	1 (3.3)
Eczema	0	0	1 (7.7)	0	1 (3.3)
Hot flush	0	0	0	1 (5.9)	1 (3.3)
Hypotension	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Illness	0	0	1(7.7)	0	1 (3.3)
Joint swelling	0	0	0	1 (5.9)	1 (3.3)
Myalgia	0	0	0	1 (5.9)	1 (3.3)
Rash erythematous	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Skin lesion	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Throat irritation	0	0	0	1 (5.9)	1 (3.3)

Source: adae.xpt; Software: R.
Note: Adult subject who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Note: Duration is up to the data cutoff dates.
Note: Coded as MedDRA preferred terms.
Note: Protocol-defined infusion-associated reactions were determined using the AEIAR variable in the ADAE dataset.
Abbreviations: AE, adverse event; ETP, extended treatment period; IAR, infusion-associated reaction; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of subjects with adverse event; OA, olipudase alfa; PAP, primary analysis period; PLB, placebo

7.6.1.7.2. Pediatric Population

The occurrence of IARs was higher in pediatric than in adult subjects; 61 IARs were reported in 6 (75.0%) pediatric subjects. All IARs were mild or moderate and did not result in permanent discontinuation of study treatment. IARs reported in at least one pediatric subject are listed in Table 41) below.

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Table 41. Patients With Protocol-Defined Infusion-Associated Reactions (IARs) Occurring at ≥0% Frequency, Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS), , Pediatric Patients Who Received Only Process C

Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Any AE	5 (71.4)	1 (100)	6 (75.0)
Urticaria	3 (42.9)	1 (100)	4 (50.0)
Erythema	2 (28.6)	0	2 (25.0)
Headache	2 (28.6)	0	2 (25.0)
Nausea	2 (28.6)	0	2 (25.0)
Pyrexia	1 (14.3)	1 (100)	2 (25.0)
Vomiting	1 (14.3)	1 (100)	2 (25.0)
Abdominal pain	1 (14.3)	0	1 (12.5)
Anaphylactic reaction	0	1 (100)	1 (12.5)
Blood alkaline phosphatase increased	1 (14.3)	0	1 (12.5)
Blood bilirubin increased	1 (14.3)	0	1 (12.5)
C-reactive protein increased	1 (14.3)	0	1 (12.5)
Muscle oedema	1 (14.3)	0	1 (12.5)
Rash	1 (14.3)	0	1 (12.5)
Skin mass	1 (14.3)	0	1 (12.5)

Source: adae.xpt; Software: R
Note: Pediatric subjects who ever received Process B were excluded.
Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa period.
Duration is up to the data cutoff dates.
Muscle edema replaces: Localized edema
Protocol-defined infusion-associated reactions were determined using the AEIAR variable in the ADAE dataset.
Abbreviations: AE, adverse event; IAR, infusion-associated reaction; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of patients with adverse event; OA, olipudase alfa

7.6.1.8. Adverse Events of Special Interest, Acute Phase Reaction, Integrated Safety Set, Subjects Who Received Only Process C

Results from a first-in-human Phase 1, single-dose, dose escalation trial SPHINGO00605 provided the basis for the assessments of APRs, CRS, and DLTs in the current application. Clinical data from SPHINGO00605 were not included in the pooled safety analysis because it was a single-dose study. SPHINGO00605 was terminated early after 11 subjects had been dosed due to a subject experienced hyperbilirubinemia and constitutional symptoms (nausea, vomiting, pyrexia, fatigue, and/or pain) after a single dose of 1 mg/kg. The 0.6 mg/kg was identified as the maximum tolerated starting dose based on the pattern of occurrence of AEs.

According to the Clinical Study Report of SPINGO00605 (submitted under IND 012757), single doses of olipudase alfa administered included 0.03 mg/kg (n=3), 0.1 mg/kg (n=3), 0.3 mg/kg (n=2), 0.6 mg/kg (n=2), and 1 mg/mg (n=1). Doses up to 0.1 mg/kg were well tolerated, whereas AEs related to olipudase alfa occurred in cohorts given doses of 0.3 mg/kg or higher. The most commonly reported TEAEs were increased blood bilirubin and acute phase reactants (including but not limited to high-sensitivity CRP, IL-6, IL-8, calcitonin, and ferritin), the majority of which were judged as being related to olipudase alfa treatment. Most of the related AEs occurred within

the 48 hours after infusion and resolved by 28 days after infusion without sequelae. No deaths or related SAEs were reported; there was one unrelated SAE of post-liver biopsy pain. Cardiovascular instability or adrenal hormone dysfunction were not observed.

Based on the above findings, samples for laboratory testing were collected daily for 48 or 72 hours after study drug administration in ASCEND and ASCEND Peds. The Applicant evaluated APR and CRS using a composite of clinical symptoms and laboratory values from these samples (see Section 17 for the definitions of APR and CRS). Upon treatment, the rapid metabolism of accumulated SPM into ceramide and other pro-inflammatory breakdown products may induce APR especially during the dose escalation phase (i.e., the first 14 or16 weeks after initiation of olipudase alfa). Similar to APR, CRS is attributed to the release of excessive amounts of cytokines shortly after administration of certain therapeutic products.

Ten events of APRs were identified in one adult (3.3%) and pediatric subject (12.5%) each (Table 42); both subjects were identified by an investigator. Most of the APRs occurred at 48 hours post infusion during the dose escalation period, except that multiple APRs occurred after the dose re-escalation period in a pediatric patient (13803-(b) (6)) who had anaphylaxis reaction. The most commonly clinical symptoms associated with APRs were pyrexia and vomiting. CRP elevations were observed for all APRs, with levels ranging from 4xULN to 58xULN. Serum iron decreased to approximately 0.4x lower limit of normal. Elevated calcitonin and ferritin were observed.

Depending upon the clinical circumstances, the investigator treated APRs like other IARs by repeating or reducing olipudase dose at the subsequent infusion. All APRs resolved over time, and both patients reached the maintenance dose of 3 mg/kg. Because APR mostly occurred during dose escalation and re-escalation, it is important to recognize and monitor clinical symptoms associated with APR within 72 hours post infusion during dose escalation or re-escalation after missed doses or dose interruption. Patients should be managed by repeating or reducing olipudase alfa dose and monitored for symptom resolution. Laboratory evaluation of acute phase reactants may be performed to confirm the diagnosis but is not necessary.

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Table 42. Listing of Subjects With Acute Phase Reaction (APR), ISS, Subjects Who Received Only Process C

Patient ID (A/I)	Product	Dose at Event, Maintenance Dose (mg/kg)	Study Week, Hours Post Infusion	Symptoms in PT	xULN				xLLN
					CRP	Calcitonin	IL-6	Ferritin	Iron
012712 (b) (6) (A)	C (b) (4)	0.6, 3	6, 24	Pyrexia	4.3	0.94	0.24	1.4	0.5
012712 (A)	C	0.6, 3	6, 48	Neck pain	4.5	0.81	0.44	1.5	0.42
013803 (A)	C	0.3, 3	4, 48	Vomiting	4.9	2.8	-	0.17	-
013803 (A)	C	0.6, 3	8, 48	Pyrexia, vomiting	14.4	2.8	-	2.26	-
013803 (A)	C	0.6, 3	10, 48	Pyrexia, vomiting	7.9	3.0	-	0.17	-
013803 (A)	C	0.3, 3	30, 48	Pyrexia	9.8	2.9	-	0.21	0.38
013803 (A)	C	0.6, 3	32, 48	Pyrexia, vomiting	58.2	1.7	-	1.4	-
013803 (A)	C	0.6, 3	34, 48	Diarrhea, pyrexia	6.0	1.8	-	0.14	-
013803 (A)	C	1, 3	38, 48	Pyrexia, vomiting	12.4	2.5	-	0.19	-
013803 (A)	C	1, 3	42, 48	Diarrhea	4.7	2.1	-	0.12	-

Source: ISS Section 3.1.5.2 and Appendix 4.33.1, DFI13803 CSR Section 11.3.4.1 and Section 15.3.3 Patient Narratives, adex.xpt
Abbreviations: A, Algorithm-identified APR ISS, integrated safety set.
Note: Subjects who ever received Process B were excluded.

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7.6.1.9. Adverse Events of Special Interest, Cytokine Release Syndrome, Integrated Safety Set

No subjects were identified to have CRS in clinical trials.

7.6.1.10. Adverse Events of Special Interest, Liver Transaminases, Total Bilirubin, and Alkaline Phosphatase, Integrated Safety Set, Subjects Who Received Only Process C

7.6.1.10.1. Dose Limiting Toxicities, Integrated Safety Set, Subjects Who Received Only Process C

The Applicant evaluated elevations in liver transaminases, total bilirubin, and alkaline phosphatase (ALP) using predefined quantifiable DLTs (see Section 17.1 and footnotes of Table 43 and Table 44 for definition of DLTs). These pre-specified criteria for DLT take into consideration the baseline level of the laboratory tests, some of which may be elevated in patients with ASMD. Across the three clinical trials ASCEND, ASCEND Peds, and LTS13632, a total of 10 patients (7 adult subjects and 3 pediatric subjects) experienced AEs that met the DLT criteria.

Overall, results from the evaluation of DLTs suggest that DLTs could occur as a result of the disease. The attribution of olipudase alfa to the elevations of liver function tests cannot be ruled out, however. Most of the DLTs occurred during the initial dose escalation period and at 48 hours post infusion

See Section 7.6.1.10.3 for more information about assessment and monitoring of liver transaminases.

7.6.1.10.1.1. Adult Population

Seven (23.3%) adult subjects receiving Process C experienced at least one DLT in ASCEND trial. Among these subjects, one subject was randomized to receive olipudase alfa and six subjects were randomized to receive placebo during PAP. (Table 43).

The single subject who was randomized to the active treatment group had a DLT during ETP before drug infusion during re-escalation of olipudase alfa dose after missing doses. This subject also had a creatine kinase (CPK) >3xULN at the same study visit (see Section 7.6.1.11.2).

Of the six subjects who were randomized to receive placebo, four subjects had at least one DLT and two subjects did not experience a DLT during PAP. This finding shows that DLT could occur as a result of ASMD while on placebo. After switching to olipudase alfa during the ETP, one of six subjects experienced a DLT prior to olipudase alfa infusion. Four other subjects experienced at least one DLT after switching to olipudase alfa infusion. All of these DLTs occurred during the dose escalation period; most of them occurred 48 hours after infusion

Table 43. Listing of Dose-Limiting Toxicities (DLTs), Adult Population, Integrated Safety Set, Adult Subjects Who Received Only Process C

	Placebo Arm						Active Treatment Arm					
	PAP			ETP			PAP			ETP		
Adult Population	DLT	Study Week	Hours Post Infusion	DLT	Study/ Treat-ment Week	Hours Post Infusion	DLT	Study Week	Hours post infusion	DLT	Study/ Treat-ment Week	Hours Post Infusion
012712 (b) (6)	DLT2	52	Pre-infusion		-			-			-	
012712	DLT2	52	Pre-infusion	DLT2	56/0	Pre-infusion		-			-	
012712	DLT2	4	24	DLT1/DLT3	56/4	24		-			-	
012712	DLT2	6	24	DLT3	5/4	48		-			-	
012712	DLT2	16	Pre-infusion		-			-			-	
012712		-		DTL1/DLT3	62/10	48		-			-	
012712		-		DLT3	66/14	48		-			-	
012712		-			-			-		DLT1/DLT3	122/ 122	Pre-infusion
012712		-		DLT1/DLT3	68/16	48		-			-	
012712	DLT2	14	Pre-infusion	DLT2	68/16	48		-			-	
012712	DLT2	26	Pre-infusion		-			-			-	
012712	DLT2	52	24		-			-			-	

Source: Table 2 and patient listing dfi12712-ae-dlt-l-x.pdf in the Applicant's response to FDA IR dated March 23, 2022 for Questions 3, 4, and 5 (SDN 27), and Appendix 1.3.2 of the Applicant's response to FDA IR dated April 13, 2022 (SDN 32)
Note: Adult subjects who ever received Process B were excluded.
Note: DLT1: Any increase in AST, ALT, total bilirubin, or AP >3x baseline and > ULN.
Note: DLT2: Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT >2x ULN.
Note: DLT3: Any increase in ALT or AST >3x ULN combined with an increase in ALT or AST >2x baseline.
Abbreviations: DLT, dose-limiting toxicities; ETP, extension treatment period; PAP, primary analysis period; OA, olipudase alfa; NA, not available.

7.6.1.10.1.2. Pediatric Population

The proportion of subjects receiving Process C experiencing DLTs was higher in pediatric subjects than in the adult subjects. Three of 8 (37.5%) pediatric subjects experienced at least one DLT during olipudase alfa treatment. One subject had two DLT2 prior to olipudase alfa infusion (Table 44). Two other subjects had a DLT during the dose escalation period 48 hours after drug infusion. One of these subjects was 013803-(b) (6) who temporarily stopped olipudase alfa treatment from Week 8 to Week 28 due to an SAE of anaphylactic reaction. The subject also experienced DLTs during the this off-treatment period and before re-initiation of olipudase alfa infusion on Week 28.

Table 44. Listing of Dose-Limiting Toxicities (DLTs), Pediatric Population, Integrated Safety Set, Pediatric Subjects Who Received Only Process C

	DFI13803 (ASCEND-Peds)		
Pediatric Population	**DLT**	**Week**	**Hours Post Infusion**
013803-(b) (6)	DLT2	12	Pre-infusion
013803	DLT2	13	Pre-infusion
013803	DLT2	14	48
013803	DLT3	14	Pre-infusion
013803	DLT3	22	Pre-infusion
013803	DLT3	28	Pre-infusion
013803	DLT2	28	48

Source: Tables 2 and patient listing iss2021-ae-dlt-l-x.pdf in the Applicant's response to FDA IR dated March 23, 2022 for Questions 3, 4, and 5 (SDN 27), and Appendix 1.3.2 of the Applicant's response to FDA IR dated April 13, 2022 (SDN 32).
Note: Pediatric subject who ever received Process B were excluded.
Note: DLT1: Any increase in AST, ALT, total bilirubin, or AP >3x baseline (before olipudase alfa therapy) and > ULN.
Note: DLT2: Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT >2x ULN.
Note: DLT3: Any increase in ALT or AST >3x ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy).
Abbreviations: DLT, dose-limiting toxicities; ETP, extension treatment period; PAP, primary analysis period.

7.6.1.10.2. Evaluation of Drug-Induced Serious Hepatotoxicity , Integrated Safety Set, Subjects Who Received Only Process C

The Agency performed an evaluation of drug-induced serious hepatoxicity for all subjects. Four potential cholestasis and seven cases in the Temples' corollary were identified.

Four adult subjects had elevated total bilirubin >2x ULN with maximum ALT/AST <3x ULN suggesting cholestasis. Three of the four subjects met these criteria while on olipudase alfa treatment during ASCEND PAP; the remaining subject (012712-(b) (6)) met these criteria while on placebo during ASCEND PAP and on active treatment during ASCEND ETP. Three of the four subjects (012712-(b) (6) 012712-(b) (6) and 012712-(b) (6)) had a history of Gilbert syndrome, which likely contributed to the elevations of total bilirubin levels. The remaining subject (012712-(b) (6)) was heterozygous for *UGT1A1*28*. The maximum total bilirubin in this subject was 2.17xULN while on olipudase alfa treatment; the laboratory values decreased to near normal value over time.

Of the seven subjects (six adults, one pediatric) identified in the Temples's corollary, one adult subject had a few isolated elevations in total bilirubin level and one elevation in ALT/AST levels. The rest of the laboratory values were within normal range. The other six subjects had maximum total bilirubin below or slightly higher than ULN. Refer to Section 7.6.1.10.3 for more information about the assessment and monitoring of liver transaminases.

7.6.1.10.3. Individual Liver Function Tests, Integrated Safety Set, Subjects Who Received Only Process C

In addition to the evaluation of laboratory abnormalities based on the Applicant's pre-defined DLT criteria, the impact of olipudase alfa on ALT, AST, total bilirubin, and ALP was assessed individually.

Overall, the mean ALT level pre-infusion decreased from a mean of approximately 40 IU/L to 22 IU/L over 52 weeks in adult subjects treated with olipudase alfa in ASCEND PAP, compared to no changes in the placebo group. Likewise, the mean AST level pre-infusion declined from a mean value of approximately 45 IU/L to 22 IU/L over 52 weeks during ASCEND PAP in adult subjects receiving olipudase alfa; the mean AST level pre-infusion did not change over time in adult subjects in the placebo group. In pediatric subjects, the mean ALT level pre-infusion declined from 48 IU/L at baseline to approximately 20 IU/L at Week 52. The mean AST pre-infusion level decreased from approximately 80 IU/L, which was higher than the mean value in adult subjects, to approximately 36 IU/L at Week 52.

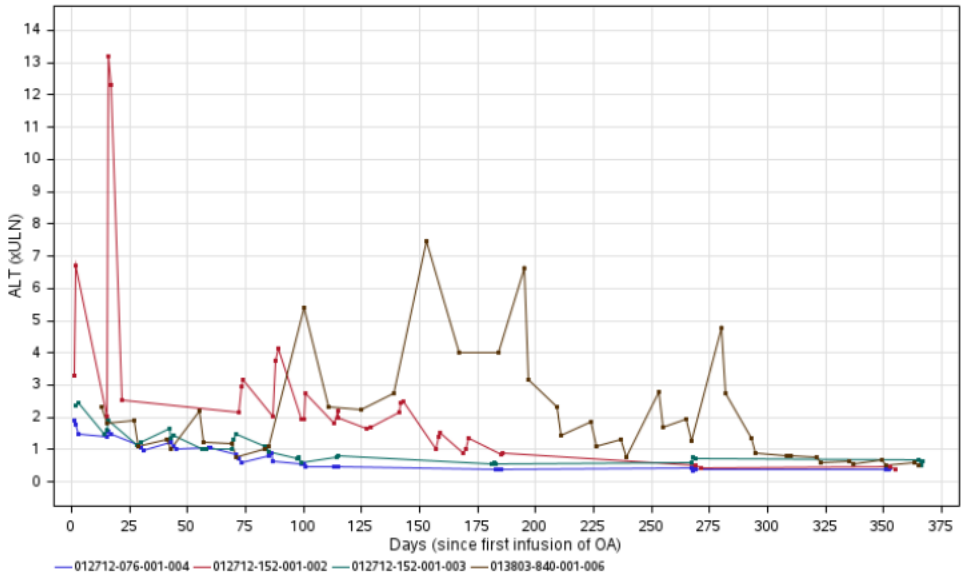
Individual time profiles of ALT and AST over time show transient increases in liver transaminases within 72 hours after drug infusion, which occurred mostly during the dose escalation period, and enzyme levels generally returned to or near pre-infusion level by the time of the next infusion (Figure 34). Elevated transaminase levels ranging from >3xUNL to >13xULN were observed in 4 (13.3%) adults (including the three subjects who experienced DLT1 and DLT3 in Table 43) and 1 (12.5%) pediatric subject (the subject who experienced DLT3 in Table 45) during the dose escalation periods, ALT and AST values were good predictors of post infusion values; transaminase elevations were most noticeable among patients whose baseline ALT/AST was >2 ULN during dose escalation (Figure 34). As such, it is important to assess and monitor ALT and AST levels and manage patients during olipudase alfa treatment as follows.

- Assess ALT and AST levels at baseline prior to olipudase alfa treatment for all patients.
- During dose escalation and re-escalation after missed doses or dose interruption:
  - Assess ALT and AST levels within 72 hours pre-infusion.
  - Obtain additional ALT and AST levels within 72 hours post-infusion in patients whose ALT or AST >2xUNL at baseline or pre-infusion. Assessing these post-infusion transaminase levels may help making treatment decisions once the pre-infusion transaminase values prior to the next dose administration have been determined (see item c. below). It allows clinicians to evaluate the trend and determine a potential relationship to the infusion.
  - If the pre-infusion ALT or AST levels prior to the next dose administration are elevated above baseline and >2xULN, olipudase alfa dose can be adjusted (prior dose repeated or reduced) or treatment can be temporarily withheld until the liver transaminases return to the patient's baseline levels.

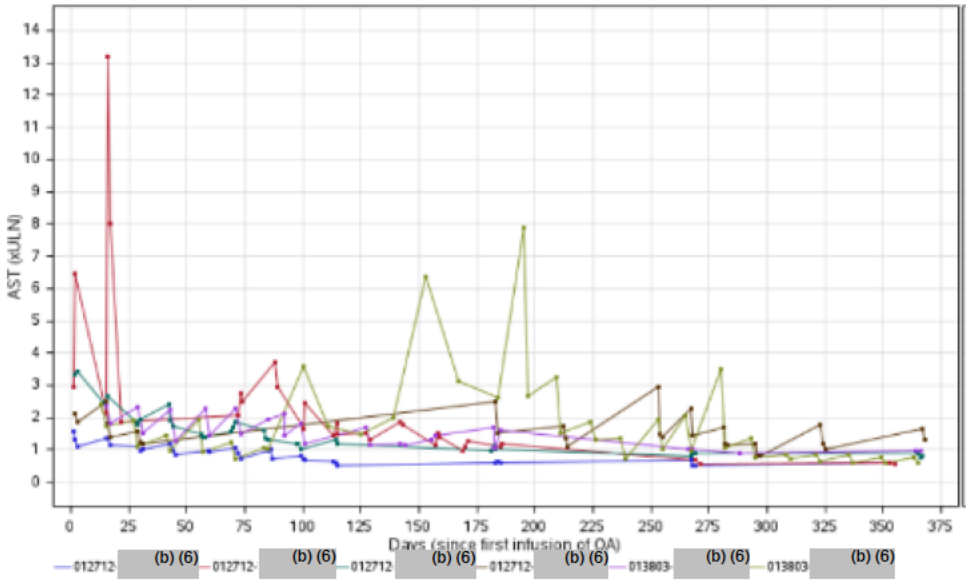
Assessment of graphic profiles of total bilirubin and ALP did not reveal significant elevations after olipudase alfa infusion in individual subjects.

Figure 34. Liver Transaminases over Time in Subjects Whose Baseline (A) ALT >2xULN and (B) AST >2xULN by Week 52

(A)



(B)



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Source: Appendix 1 Tables 1 and 2 of the Applicant's response to FDA IR dated June 7, 2022 (SDN 42).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
Note: Subjects who ever received Process B were excluded.

7.6.1.11. Laboratory Findings, Integrated Safety Set, Subjects Received Only Process C

This section reviews routine safety assessments, including clinical laboratory tests other than the liver function tests (i.e., renal function tests and other clinical chemistry tests) as described in Section 7.6.1.10 above, hematology parameters, electrocardiogram, and vital signs obtained from all subjects participated in the clinical trials.

No clear trends were observed for all clinical laboratory assessments. The mean values for renal function tests, other clinical chemistry tests, and hematology parameters were mostly within normal ranges. Three isolated elevations of CK were observed in three subjects that are unlikely related to the study treatment. Hypoglycemic episodes <70 mg/dL were observed in a small fraction of all glucose measurements performed and were not associated with clinical signs and symptoms. Hemoglobin decrease in two subjects were likely due to an error and the subject's underlying condition. No significant QTcF outliers and trends in vital signs were observed.

7.6.1.11.1. Kidney Function Tests, Integrated Safety Set, Subjects Received Only Process C

Mean serum creatinine values in adults at baseline and at Year 3 were 0.71 and 0.78 mg/d, respectively. Serum creatinine increased ≥1.5x baseline in 10.3% (3/29) of the adults. However, even with the elevation, creatinine values were still within the normal range.

In pediatric subjects, the mean creatinine value increased from 0.34 mg/dL at baseline to 0.46 mg/dL at Year 2.5. Serum creatinine increased ≥2x baseline from 0.25 mg/dL to 0.5 mg/dL in one pediatric subject. Even with the elevation, the creatinine level was still within the normal limit.

7.6.1.11.2. Other Clinical Chemistry Tests: Creatine Kinase, Integrated Safety Set, Subjects Who Received Only Process C

Creatine kinase (CK) levels were generally obtained every two weeks in ASCEND and every 12 weeks in LTS13632; CK measurements were not included in ASCEND Peds but were performed in the extension trial LTS13632. In general, CK increases from baseline were observed at Week 26 and continued through the last timepoint in adult subjects.

Increase of CK values >3x and >9xULN were observed in two adult patients and >75xULN in one pediatric subject with associated myalgias. All levels were collected at pre-infusion, and all elevations were attributed to strenuous/extreme exercise. No corrective treatment was given, and all elevations improved at the next scheduled laboratory assessment. These isolated CK elevations are unlikely related to olipudase alfa.

7.6.1.11.3. Other Clinical Chemistry Tests: Glucose, Integrated Safety Set, Subjects Who Received Only Process C

Pre-infusion glucose values were monitored as part of the regularly scheduled laboratory assessments during clinical trials. Twenty-two hypoglycemia with pre-infusion glucose levels dropped below <70 mg/dL were observed in 9/30 (30%) adults and in 1/8 (12.5%) pediatric subject. However, this number represents 2% of total glucose assessments (n=1083) in all subjects. These observations of hypoglycemia were not associated with any clinical signs and symptoms, returned to normal value, and were unlikely of clinical significance.

7.6.1.11.4. Other Clinical Chemistry Tests: Lipids, Integrated Safety Set, Subjects Who Received Only Process C

Patients with ASMD have dyslipidemia due the disease. Lipids were considered efficacy parameters in the clinical trials, and levels of HDL, LDL, VLDL, and triglycerides improved from baseline after olipudase alfa treatment. See Section 6.2.1.4.4 for more information.

7.6.1.11.5. Hematology Parameters, Integrated Safety Set, Subjects Who Received Only Process C

Patients with ASMD can also have low platelet counts, and hemoglobin and platelet counts were considered efficacy parameters in the clinical trials. After olipudase alfa treatment, hemoglobin and platelet count slightly increased over time from baseline (see Section 6.2.1.4.4).

In both adult and pediatric subjects, mean values of neutrophils and lymphocytes fluctuated within normal limits with minimal changes. Mean values of prothrombin time were within the normal ranges and did not significantly change over time. Mean activated partial thromboplastin times decreased over time but were within the normal limits.

Hemoglobin (Hgb) decline >5 g/dL from baseline was observed in two adult subjects during olipudase alfa treatment. One subject had Hgb level dropped from 12.7 g/dL to 8.4 g/dL approximately 27 hours after infusion, but Hgb level increased to 13.1 g/dL two weeks later. The site investigator attributed the hemoglobin change to a dilution effect. There were no reports of any corresponding bleeding or hemorrhage that could explain this sudden drop in hemoglobin values; there was no further investigation or treatment for the decreased hemoglobin values.

Another subject had a Hgb level decreased from 9.2 g/dL to 7.3 g/dL approximately 27 hours after drug infusion. Hgb went back up to 9.8 g/dL two weeks later. Hgb in this subject had been trending downwards from a baseline value of 12.4 g/dL since study enrollment, and an AE of anemia was reported three months into placebo treatment. The decrease in Hgb was likely attributed to the subject's condition as well as additional blood collection during the clinical trial.

7.6.1.11.6. Electrocardiogram Assessment, Integrated Safety Set

The Applicant provided assessments of safety ECGs collected in five clinical trials including the single dose study, SPHINGO00605, and the four multiple dose trials. No significant QTcF outliers were seen. A few PR outliers were observed. The increases were not dose related and were observed at isolated timepoints within each subject. The increases in the PR interval do not appear to be mediated by direct effect on cardiac ion channels. There were no drug related changes in the PR, QRS, and QTcB in monkeys at 50-fold anticipated clinical exposure in humans. Please see QT-IRT review dated March 16, 2022 for more information.

7.6.1.11.7. Vital Signs, Integrated Safety Set, Subjects Who Received Only Process C

Vital signs did not change significantly over time in both the adults and the pediatric subjects.

In adults, the mean systolic blood pressure was 118 and 119 mmHg at baseline and at Year 3, respectively. The mean diastolic blood pressure was 70 mmHg at both timepoints. The mean heart rate was 75 at baseline and was 68 at Year 3, and the mean respiratory rate was 19 at both timepoints. There were a few outliers of heart rate and respiratory rate.

In pediatric subjects, the mean systolic and diastolic blood pressures were 105 and 68 mmHg, respectively, at baseline and were 110 and 70 mmHg, respectively, at Year 2.5. The mean heart rate decreased from a value of 102 at baseline to 80 at Year 2.5. The mean respiratory rates were 24 and 14 at baseline and at Year 2.5, respectively.

7.6.2. Safety Findings and Concerns, Treatment Period, Integrated Safety Set, Subjects Who Received Only Process C

7.6.2.1. Overall Adverse Event Summary, During and After Dose Escalation, Integrated Safety Set, Subjects Who Received Only Process C

During the first 14 to 16 weeks of treatment, olipudase alfa was escalated from a low dose to reach a maintenance dose of 3 mg/kg every two weeks. EAIR for most of the TEAEs were higher during the initial dose escalation period than the dose maintenance period in both the adult (Table 45) and pediatric subjects (Table 46). In addition, DLTs occurred mostly during the dose escalation period (see Section 7.6.1.10.1). These findings are consistent with the debulking of SPM during initial dose escalation resulting in increases in ceramide concentrations and subsequently to elevations in acute phase reactants, liver transaminases, and total bilirubin.

Table 45. Treatment-Emergent Adverse Events (TEAEs) Occurring in >25% of Subjects by Initial Dose Escalation Period, Integrated Safety Set, Adult Subjects Who Received Only Process C

	During Initial Dose Escalation (N=30)		After Initial Dose Escalation (N=30)	
TEAE	**N (%)**	**EAIR (PY)**	**N (%)**	**EAIR (PY)**
Subjects with >=1 event	28 (93.3)	1229.21 (2.3)	29 (96.7)	447.12 (6.5)
Headache	12 (40.0)	165 (7.3)	14 (46.7)	37.7 (37.1)
Nasopharyngitis	6 (20.0)	66.1 (9.1)	8 (26.7)	16.8 (47.7)
Upper respiratory tract infection	2 (6.7)	20.6 (9.7)	8 (26.7)	15.3 (52.1)

Source: Table 1 of the Applicant's response to FDA IR dated May 17, 2022 (SDN 40).
Note: Adult subjects who ever received Process B were excluded.
Note: For patients with event, the patient year is calculated as time from first olipudase alfa infusion of the defined period to the time of first event in the defined period; for patients without event in the defined periods, it is calculated as the total duration of olipudase alfa exposure in the defined period. EAIR =100 x n/PY.
Note: Initial dose escalation period is the first time when patient reached the 3mg/kg; or if a patient never reached 3mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.
Note: MedDRA version 23.1 has been used for coding the adverse events.
Note: PT sorted by decreasing frequency according to during initial dose escalation period, and then after initial dose escalation period (if two PTs with same incidence).
Abbreviations: EAIR, exposure adjusted incidence rate; Events, number of event in the category; N, Number of patients treated within each group; n (%), number and % of patients with at least one event in the category; PY, Patient Year

Table 46. Treatment-Emergent Adverse Events (TEAEs) Occurring in >25% of Subjects by Initial Dose Escalation Period, Integrated Safety Set, Pediatric Subjects Who Received Only Process C

	During Initial Dose Escalation (n=8)		After Initial Dose Escalation (n=8)	
TEAE	N (%)	EAIR (PY)	N (%)	EAIR (PY)
Subjects with >=1 event	8 (100)	1385 (0.6)	8 (100)	1922 (0.4)
Pyrexia	5 (62.5)	249 (2.0)	7 (87.5)	126 (5.6)
Cough	5 (62.5)	217 (2.3)	6 (75.0)	81.3 (7.4)
Diarrhea	5 (62.5)	312 (1.6)	5 (62.5)	41.0 (12.2)
Nasopharyngitis	3 (37.5)	109 (2.8)	7 (87.5)	139 (5.0)
Rhinitis	3 (37.5)	101 (3.0)	5 (62.5)	56.0 (8.9)
Headache	3 (37.5)	99.3 (3.0)	4 (50.0)	39.1 (10.2)
Vomiting	3 (37.5)	145 (2.1)	3 (37.5)	24.2 (12.4)
Nausea	3 (37.5)	105 (2.8)	1 (12.5)	6.08 (16.5)
Abdominal pain	2 (25.0)	72.8 (2.7)	4 (50.0)	40.7 (9.8)
Contusion	2 (25.0)	77.1 (2.6)	3 (37.5)	22.4 (13.4)
Arthralgia	1 (12.5)	29.6 (3.4)	3 (37.5)	20.1 (14.9)
Oropharyngeal pain	1 (12.5)	30.3 (3.3)	3 (37.5)	23.4 (12.8)
Urticaria	1 (12.5)	37.4 (2.7)	3 (37.5)	24.2 (12.4)

Source: Table 2 of the Applicant's response to FDA IR dated May 17, 2022 (SDN 40).
Note: Pediatric subjects who ever received Process B were excluded.
Note: For patients with event, the patient year is calculated as time from first olipudase alfa infusion of the defined period to the time of first event in the defined period; for patients without event in the defined periods, it is calculated as the total duration of olipudase alfa exposure in the defined period. EAIR =100 x n/PY.
Note: Initial dose escalation period is the first time when patient reached the 3mg/kg; or if a patient never reached 3mg/kg, then the cut would be the first time the patient maintains the maximum tolerated dose consecutively for 6 visits.
Note: MedDRA version 23.1 has been used for coding the adverse events.
Note: PT sorted by decreasing frequency according to during initial dose escalation period, and then after initial dose escalation period (if two PTs with same incidence).
Abbreviations: EAIR, exposure adjusted incidence rate; Events, number of events in category; N, Number of patients treated within each group; n (%), number and % of patients with at least one event in the category, PY, patient year.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Exencephaly Seen in Mouse Embryo-Fetal Studies

Issue

A rare malformation, exencephaly, was identified in a mouse study of embryo-fetal development.

Background

Pregnant women were excluded from clinical trials with olipudase. As such, there are no clinical data available on the risks of olipudase alfa on maternal or fetal health during pregnancy.

Assessment

In a study of embryo-fetal development (EFD) in pregnant mice, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from GDs 6 through 15. There was no maternal toxicity that was not attributed to hypersensitivity, which always resulted in maternal mortality. Exencephaly was observed in five fetuses of two pregnant mice treated with 10 and 30 mg/kg. The maternal No Observed Adverse Effect Level (NOAEL) is 30 mg/kg; the $AUC_{0\text{-}24}$ at this dose is ~1.6 the exposure associated with the MRHD. The developmental NOAEL is 3 mg/kg; the $AUC_{0\text{-}24}$ at this dose is approximately $1/7^{th}$ the exposure associated with the MRHD. The Lowest Observed Adverse Effect Level (LOAEL) is 10 mg/kg; the $AUC_{0\text{-}24}$ at this dose is approximately 1/2 the exposure associated with the MRHD.

This malformation was not seen when olipudase (3, 10, or 30 mg/kg) was administered to rabbits daily from GD 6 to GD 19. Maternal and developmental NOAELs were 30 mg/kg and associated with exposures that are ~10.9-fold those at the MRHD.

The Division's concerns for the finding of exencephaly in mice arise from four lines of evidence:

- Historical control data for this finding relative to its incidence in the mouse study (TER0694). Five fetuses were noted in the present study, representing 1 litter each in the 2 highest dose groups. Historical control data were furnished for the period from June 2009-May 2014 (the present study was initiated in late 2016). During that 5-year period, 13 definitive studies were conducted, in which 4820 fetuses were examined from 372 litters; 3 fetuses (0.06%) from 3 litters (0.81%) were reported with exencephaly.

  Notably, the litter incidence for the mid- and high-dose groups does not exceed that of the historical control (~5%, reflective of prevailing study designs that use 20-25 pregnant animals per dose group when 1 litter is affected). That said, it is possible to construe this information in a different light. Briefly, 3/13 studies in the database reported a single occurrence of exencephaly, which suggests that 1 affected fetus/1 litter might be expected by chance in every 4^{th} study. This is contrasted with the present data, whereby 5 fetuses/2 litters – one litter each in the two highest dose groups – are reported in a single study.

Importantly, there were no affected fetuses in 2 contemporaneous control groups, representing 655 fetuses in 49 litters.

- Articles in the published literature suggest biological plausibility. Brief exposures to ceramide or fingolimod (an S1P receptor modulator) in early organogenesis evoked exencephaly in chicks and mice, respectively (Gelineau-van Waes et al. 2012; Ross et al. 2019). These papers likewise suggest that there is an early, critical developmental window for susceptibility to improper neural tube closure.
  Reviewer Comment: while dosing of pregnant mice occurred throughout organogenesis, safety margin calculation was conducted from the conservative assumption that a single exposure during this developmental window can evoke exencephaly.
- Concentrations of ceramide that evoked neural tube defects in chicks are clinically-relevant in early olipudase alfa treatment. The ceramide spike in ASMD patients' plasma after administration of 2 doses of olipudase (maximum 17 µg/mL) is only half the concentration of C-2 ceramide (34 µg/mL) that evokes exencephaly in embryonic chicks after brief (24h) incubation.
- S1P receptor modulators are selective developmental toxicants. Although sphingosine 1 phosphate (S1P) is a metabolite of sphingomyelin, all marketed S1P receptor modulators are associated with profound nonclinical developmental toxicity. In all cases, the LOAEL for at least 1 nonclinical species is <10-fold.

  From *ICH Harmonized Guideline, Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals, S5(R3)*, Note 2:

  > An analysis of 22 known human or presumed human teratogens showed that if MEFL [malformations or embryo lethality] was observed, exposure at the lowest observed adverse effect level (LOAEL) in at least one species was <6-fold the exposure at the MRHD (February 2020) The analysis also showed that for human teratogens that were detected in animal species, the exposure at the NOAEL in at least one species was <4-fold the exposure at the MRHD.

Considered together, these 4 lines of evidence strongly suggest that the finding of exencephaly in mice is genuine and plausibly related to the metabolites of sphingomyelin and therefore associated with treatment with olipudase alfa. Since this was not observed in rabbits (NOAEL 11-fold MRHD), the mouse is clearly the more sensitive species.

Conclusion

Dose initiation or escalation, at any time during pregnancy or planning for pregnancy, is not recommended as it may lead to elevated metabolite levels that may increase the risk of exencephaly and potentially, also fetal malformations or embryo-fetal mortality seen in nonclinical studies with the drug class of S1P receptor modulators. Levels of S1P during maintenance phase are unknown. Additionally, there is a risk of serious hypersensitivity reactions with dose initiation/escalation that could adversely impact the health of the pregnancy. The decision to continue or discontinue Xenpozyme in the maintenance phase in pregnancy should consider the mother's need for Xenpozyme, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal ASMD disease.

7.7.2. Elevated Levels of Host Cell Proteins Seen in Process C (b) (4) and Process C (b) (4)

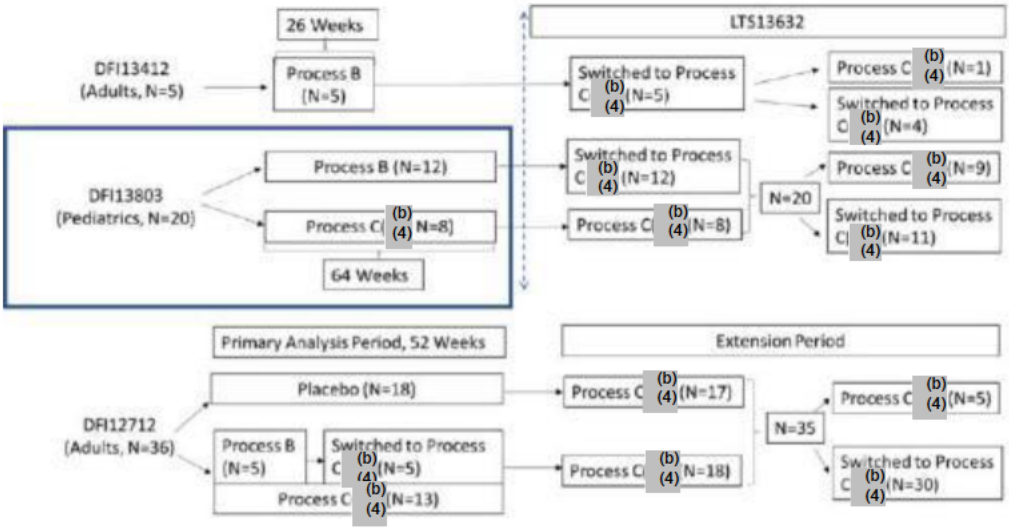
Issue

Elevated host cell protein (HCP) levels are noted with Process C (b) (4) and Process C (b) (4) compared to process B.

Background

The pivotal clinical trials have included material from all processes. As process B is noted to have a lower amount of HCP than process C (b) (4) and Process C (b) (4) a comparative analysis was conducted between Process B and Process C assessing any notable differences in safety, and immunogenicity and whether the elevated HCP levels could account for such differences. The table below provides a summary of the different processes used to treat the patients in the adult pivotal trial and the pediatric trial.

Figure 35. Summary of Subjects Treated in Trials DFI13412, DFI13803 (ASCEND-Peds), LTS13632, and DFI12712 (ASCEND) by Manufacturing Process: Process B, C (b) (4) C (b) (4)



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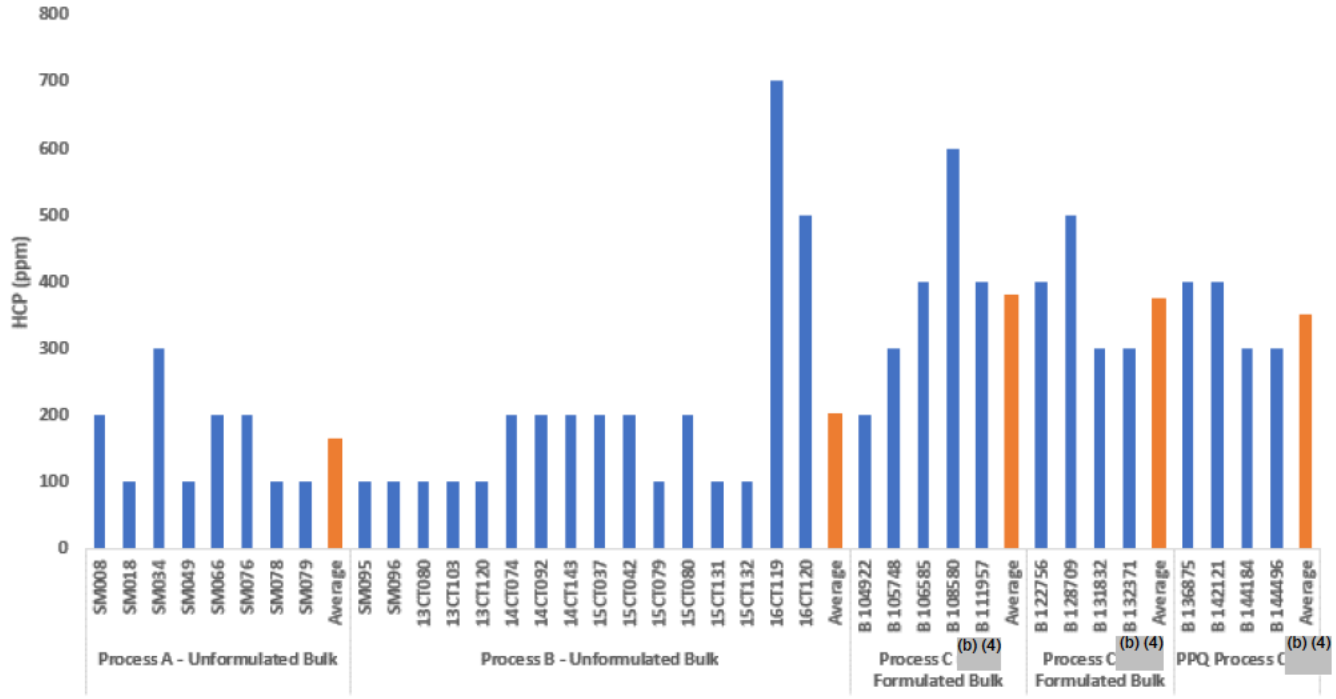
Source: ISS Figures 1 and 2
Abbreviations: N, total number of subjects

Assessment

CMC perspective

The Process C (b) (4) and Process C (b) (4) batches are not comparable to Process A and Process B batches in terms of HCP level (Figure 36).

Figure 36. HCP Level in Olipudase Alfa Drug Substance



Source: Generated by the Assessment Team.
Note: Orange bars represent averages within each process.
Abbreviations: HCP, host cell proteins; ppm, parts per million; PPQ, process performance qualification

The usual expectation for a Chinese hamster ovary (CHO) cell-based process is a clearance below 100 ppm. From a CMC perspective, if the clinical review does not identify safety or efficacy signals linked to the higher HCP levels, the higher HCP levels may not be indicative of safety or quality concerns and should not preclude approval from a CMC perspective.

The Applicant has provided a mass spectrometry-based analysis of the HCP. The top 15 hits include: Clusterin, Nidogen-1 (G3HWE4), Galectin-3-binding protein, Phospholipid transfer protein, Cathepsin D, Follistatin-related protein 1, Nidogen-1 (G3I3U5), serum albumin, complement C3, laminin subunit beta-1, glutathione S-transferase containing protein, elongation factor 2, Actin, pyruvate kinase isozymes M1/M2-like isoform 1, and transketolase).

Safety

Between Process B and Process C (b) (4)

The comparison of safety data between Process B and Process C (b) (4) is performed using information submitted from the initial BLA submission. Overall, Process B appears to be associated with more AEs compared to Process C (b) (4) possibly attributed to a higher specific activity (i.e., potency) of Process B compared to Process C (b) (4) (see Section 9).

During olipudase alfa clinical development program, 22 subjects (10 adult and 12 pediatric) initiated treatment with Process B and later switched to Process C (b) (4) the other 38 subjects initiated treatment with Process C (b) (4) (Table 47). At the time of the data cutoff date of 120-Day Safety Update, 58 of the 60 subjects who received Process C (b) (4) had switched to Process C (b) (4)

Table 47. Subject Disposition by Manufacturing Process, Integrated Safety Set

	Safety		Immunogenicity		Platelet Count		Spleen Volume
Number of Patients Treated With Process C (b) (4))	Exposure on C (b) (4) ≥3 Months	Exposure on C (b) (4) ≥6 Months	Last Assessment ≥3 Months Since C (b) (4)	Last Assessment ≥6 Months Since C (b) (4)	Last Assessment ≥3 Months Since C (b) (4)	Last Assessment ≥6 Months Since C (b) (4)	Last Assessment ≥6 months Since C (b) (4)
DFI12712 ETP/Adult	33	30	32	28	32	29	28
LTS13632/Adult	5	4	5	4	5	1	0
LTS13632/Pediatric	20	19	20	18	20	13	11
Total	58	53	57	50	57	43	39

Source: 120-Day Safety Update Table 13.

EAIR for TEAEs (Table 48), protocol defined IARs, and hypersensitivity IARs (Table 49) were higher while on Process B than on Process C (b) (4) On the other hand, EAIR for treatment emergent SAEs and TEAEs leading to treatment interruption were higher while on Process C (b) (4) than on Process B (Table 48). However, the number of treatment emergent SAEs that were considered related to the study treatment was small; only one adult subject had a drug-related SAE and two pediatric subjects each receiving Process B and Process C (b) (4) had at least one drug-related SAE. The reason for a higher EAIR for TEAEs leading to drug interruption with Process C (b) (4) is not clear. There was only one anaphylactic reaction in a pediatric subject who was on Process C (b) (4)

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Table 48. Overview of TEAEs While on Process B Versus Process C(b) (4)

	While on Process B (Initial exposure on Process B)		While on Process C(b) (4) (Initial exposure on Process C(b) (4))		While on Process B or C(b) (4) (Initial exposure on Process B)	
Adverse Event	**n/N (%)**	**EAIR (PY)**	**n/N (%)**	**EAIR (PY)**	**n/N (%)**	**EAIR (PY)**
TEAEs						
Overall	22/22 (100)	2551 (0.9)	38/38 (100)	1144 (3.3)	22/22 (100)	2551 (0.9)
Adult	10/10 (100)	3581 (0.3)	30/30 (100)	1094 (2.7)	10/10 (100)	3581 (0.3)
Pediatric	12/12 (100)	2058 (0.6)	8/8 (100)	1385 (0.6)	12/12 (100)	2058 (0.6)
Any treatment-emergent SAEs						
Overall	5/22 (22.7)	11.6 (43.0)	13/38 (34.2)	18.4 (70.6)	8/22 (36.4)	8.70 (92.0)
Adult	2/10 (20.0)	9.12 (21.9)	9/30 (30.0)	15.6 (57.7)	2310 (30.0)	6.12 (49.0)
Pediatric	3/12 (25.0)	14.2 (21.1)	4/8 (50.0)	31.1 (12.9)	5/12 (41.7)	11.6 (13.0)
TEAEs leading to treatment interruption						
Overall	1/22 (4.5)	2.19 (45.7)	14/38 (36.8)	19.6 (71.3)	1/22 (4.5)	0.87 (115)
Adult	0/10 (0)	0 (23.0)	10/30 (33.3)	17.2 (58.2)	0/10 (0)	0 (59.8)
Pediatric	1/12 (8.3)	4.40 (22.7)	4/8 (50.0)	30.3 (13.2)	1/12 (8.3)	1.82 (55.0)

Source: ISS Table 18.
Note: For patients with event, the patient year is calculated as time from first olipudase alfa infusion on this process to the time of first event on this process; for patients without event, it is calculated as the total duration of olipudase alfa exposure. EAIR =100 x n/PY.
Note: 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.
Note: 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.
Abbreviations: 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; TEAE, treatment-emergent adverse event.

Table 49. Overview of IARs While on Process B Versus Process C(b) (4)

IAR	While on Process B (Initial exposure on Process B) n/N (%)	While on Process B (Initial exposure on Process B) EAIR (PY)	While on Process C(b) (4) (Initial exposure on Process C(b) (4)) n/N (%)	While on Process C(b) (4) (Initial exposure on Process C(b) (4)) EAIR (PY)	While on Process B or C(b) (4) (Initial exposure on Process B) n/N (%)	While on Process B or C(b) (4) (Initial exposure on Process B) EAIR (PY)
Protocol-defined IARs						
Overall	14/22 (63.6)	73.9 (19.0)	21/38 (55.3)	44.6 (47.1)	14/22 (63.6)	30.7 (45.6)
Adult	7/10 (70.0)	126 (5.6)	15/30 (50.0)	38.0 (39.5)	7/10 (70.0)	42.4 (16.5)
Pediatric	7/12 (58.3)	52.3 (13.4)	6/8 75.0)	79.1 (7.6)	7/12 (58.3)	24.1 (29.1)
Hypersensitivity IARs						
Overall	7/22 (31.8)	19.8 (35.4)	9/38 (23.7)	11.8 (76.1)	7/22 (31.8)	8.16 (85.8)
Adult	2/10 (20.0)	11.2 (17.8)	5/30 (16.7)	7.95 (62.9)	2/10 (20.0)	4.23 (47.3)
Pediatric	5/12 (41.7)	28.5 (17.5)	4/8 (50.0)	30.3 (13.2)	5/12 (41.7)	13.0 (38.4)
Anaphylaxis IARs						
Overall	0/22 (0)	0 (46.4)	1/38 (2.6)	1.05 (95.1)	0/22 (0)	0 (118)
Adult	0/10 (0)	0 (23.0)	0/30 (0)	0 (76.0)	0/10 (0)	0 (59.8)
Pediatric	0/12 (0)	0 (23.4)	1/8 (12.5)	5.23 (19.1)	0/12 (0)	0 (58.6)

Source: ISS Table 20.
Note: For patients with an event, the patient year is calculated as time from first olipudase alfa infusion on this process to the time of first event on this process; for patients without an event, it is calculated as the total duration of olipudase alfa exposure during the specified analysis period.
Note: Protocol-defined IARs are adverse events that occur during the infusion or within up to 24 hours after the start of the infusion and are considered related or possibly related to study treatment as judged by the investigator or the Sponsor.
Note: An event occurring >=24 h after the start of an infusion may be judged an IAR at the discretion of the investigator or Sponsor.
Note: Hypersensitivity-related infusion-associated reactions (IARs) are protocol-defined IARs that are further identified by Hypersensitivity SMQ 20000214 (broad and narrow).
Note: Anaphylaxis reaction infusion-associated reactions (IARs) are protocol-defined IARs that are further identified based on the algorithmic approach defined in Introductory Guide for SMQs. Specifically, all Anaphylactic reaction SMQ 20000021 search PT terms were included.
Note: 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.
Note: 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.
Abbreviations: N, Number of patients treated; n (%), number and % of patients with at least one event; Events, number of events; EAIR, exposure adjusted incidence rate (100 x n/PY); PY, Patient Year; IAR, infusion-associated reaction.

Acute phase reactions (APRs) and cytokine release syndrome (CRS) were observed in olipudase alfa clinical trials (see Sections 7.6.1.8 and 7.6.1.9 for more information). A higher occurrence of APRs seems be associated with the use of Process B DP (Table 50); they occurred in 2 of 10 (20%) adult subjects who initially received Process B, compared to 1 of 31 (3.2%) adult subjects who were started on Process C (b) (4) Similarly, APRs occurred in 4 of 12 (33.3%) pediatric subjects receiving Process B, compared to 1 of 8 (12.5%) of pediatric subjects receiving Process C (b) (4) in DFI13803 (ASCEND-Peds).

The two APRs observed in the two adult subjects while on Process B were also considered as CRSs. No CRSs occurred with the use of Process C.

Table 50. Overview of APR and CRS While on Process B Versus Process C (b) (4)

	Adult		Pediatric	
Condition	Process B (n=10)	Process C (b) (4) (n=30)	Process B (n=12)	Process C (b) (4) (n=8)
APR	2 (20%)	1 (3.3%)	4 (33.3%)	1 (12.5%)
CRS	2 (20%)	0	0	0

Reviewer's analysis (Also refer to Table 42 and **Error! Reference source not found.**).
Abbreviations: APR, acute phase reaction; CRS, cytokine release syndrome; n, number of subjects in category.

A direct safety comparison between Process B and Process C (b) (4) was conducted using clinical data from the pediatric trial DFI13803 (ASCEND-Peds), in which 12 and 8 subjects received B and Process C (b) (4) respectively, throughout the entire 64-week study period. Overall, most of commonly occurred AEs were reported in a higher percentage of subjects receiving Process B treatment compared to subjects receiving Process C (b) (4) treatment (Table 51).

Table 51. Overview of Adverse Events Occurred in At Least Two Subjects in Either Group by Process, Safety Population, DFI13803 (ASCEND-Peds)

Preferred Term	DFI13803 Olipudase Alfa Process B N=12 n (%)	DFI13803 Olipudase Alfa Process C (b) (4) N=8 n (%)
Any AE	12 (100)	8 (100)
Cough	8 (66.7)	6 (75.0)
Pyrexia	8 (66.7)	7 (87.5)
Vomiting	8 (66.7)	4 (50.0)
Diarrhea	5 (41.7)	6 (75.0)
Fall	5 (41.7)	1 (12.5)
Headache	5 (41.7)	3 (37.5)
Nasopharyngitis	5 (41.7)	6 (75.0)
Nausea	5 (41.7)	3 (37.5)
Oropharyngeal pain	5 (41.7)	3 (37.5)
Upper respiratory tract infection	5 (41.7)	3 (37.5)
Abdominal pain upper	4 (33.3)	1 (12.5)
Contusion	4 (33.3)	2 (25.0)
Ear pain	4 (33.3)	1 (12.5)
Gastroenteritis	4 (33.3)	4 (50.0)
Macule	4 (33.3)	0
Nasal congestion	4 (33.3)	2 (25.0)
Rash	4 (33.3)	2 (25.0)
Alanine aminotransferase increased	3 (25.0)	0
C-reactive protein increased	3 (25.0)	1 (12.5)
Dermatitis contact	3 (25.0)	1 (12.5)
Pain in extremity	3 (25.0)	1 (12.5)

Preferred Term	DFI13803 Olipudase Alfa Process B N=12 n (%)	DFI13803 Olipudase Alfa Process C(b) (4) N=8 n (%)
Papule	3 (25.0)	0
Rhinorrhea	3 (25.0)	1 (12.5)
Scratch	3 (25.0)	1 (12.5)
Serum ferritin increased	3 (25.0)	0
Abdominal pain	2 (16.7)	4 (50.0)
Aspartate aminotransferase increased	2 (16.7)	0
Blood bilirubin increased	2 (16.7)	1 (12.5)
Blood iron decreased	2 (16.7)	0
Decreased appetite	2 (16.7)	0
Dizziness	2 (16.7)	1 (12.5)
Epistaxis	2 (16.7)	2 (25.0)
Feces soft	2 (16.7)	0
Non-cardiac chest pain	2 (16.7)	0
Pruritus	2 (16.7)	2 (25.0)
Rhinitis	2 (16.7)	5 (62.5)
Skin abrasion	2 (16.7)	0
Skin exfoliation	2 (16.7)	1 (12.5)
Arthralgia	1 (8.3)	2 (25.0)
Arthropod bite	1 (8.3)	2 (25.0)
Blood alkaline phosphatase increased	1 (8.3)	2 (25.0)
Conjunctivitis	1 (8.3)	2 (25.0)
Eczema	1 (8.3)	2 (25.0)
Pharyngitis	1 (8.3)	2 (25.0)
Urticaria	1 (8.3)	3 (37.5)
Activated partial thromboplastin time prolonged	0	2 (25.0)
Otitis media	0	2 (25.0)
Tonsillar hypertrophy	0	2 (25.0)

Source: DFI13803 adae.xpt; Software: R.
Note: Treatment-emergent adverse events defined as all AEs that started during the on-treatment period, i.e., after the first infusion start till the end of study. If due to incomplete date/time, this determination could not be made unambiguously, the AE is assumed to be treatment emergent.
Note: Duration is 64 weeks.
Note: DFI13803 olipudase alfa Process B study arm was determined by any subject without a missing PRBSDT (First Process B Infusion Date) value and DFI13803 olipudase alfa Process C(b) (4)study arm was determined by any subject without a missing PRC48SDT (First Process C (b) (4)Infusion Date) value in the adsl.xpt dataset.
Note: MedDRA version 22.0 has been used for coding the adverse events.
Abbreviations: AE, adverse event; MedDRA, medical dictionary for regulatory activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Between C(b) (4) and Process C(b) (4)

The comparison of safety data between Process C(b) (4) and Process C(b) (4)) is performed using information submitted from the 120-Day Safety Update. Process C(b) (4) (i.e., the proposed commercial product) seems to have a better safety profile compared with Process C(b) (4)

Fifty-eight subjects (38 adult, 20 pediatric) had safety data with an exposure ≥3 months on Process C(b) (4) 53 subjects (34 adult, 19 pediatric) had safety data with an exposure ≥6 months on Process C(b) (4). With the exception of TEAEs leading to treatment interruption, EAIR for TEAEs, treatment emergent SAEs, protocol defined IARs, and hypersensitivity IARs were higher while on Process C(b) (4) than on Process C(b) (4) (Table 52 and Table 53).

Table 52. Overview of TEAEs While on Process C(b) (4) Versus Process C(b) (4)

	While on Process C(b) (4) (Initial exposure on Process B or C(b) (4))		While on Process C(b) (4) (Patients switched to Process C(b) (4))	
Adverse Events	**n/N (%)**	**EAIR (PY)**	**n/N (%)**	**EAIR (PY)**
TEAEs				
Overall	60/60 (100)	611 (9.8)	52/59 (88.1)	285 (18.2)
Adult	40/40 (100)	690 (5.8)	36/39 (92.3)	300 (12.0)
Pediatric	20/20 (100)	497 (4.0)	16/20 (80.0)	257 (6.2)
Any treatment-emergent SAEs				
Overall	16/60 (26.7)	13.6 (118)	5/59 (8.5)	8.71 (57.4)
Adult	10/40 (25.0)	13.2 (75.9)	5/39 (12.8)	11.6 (43.1)
Pediatric	6/20 (30.0)	14.3 (41.9)	0/20 (0)	0 (14.3)
TEAEs leading to treatment interruption				
Overall	16/60 (26.7)	13.0 (123)	11/59 (18.6)	21.5 (51.1)
Adult	11/40 (27.5)	13.9 (78.9)	10/39 (25.6)	27.2 (36.8)
Pediatric	5/20 (25.0)	11.2 (44.5)	1/20 (5.0)	7.02 (14.3)

Source: 120-Day Safety Update Table 18
Note: 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.
Note: 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.
Note: 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.
Note: MedDRA version 24.0 has been used for coding the adverse events. Including cumulative data as of 15OCT2021.
Abbreviations: 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 (100 x n/PY); PY, Patient Year; TEAE, treatment-emergent adverse event

Table 53. Overview of IARs While on Process C(b) (4) Versus Process C(b) (4)

	While on Process C(b) (4) (Initial exposure on Process B or C(b) (4))		While on Process C(b) (4) (Patients switched to Process C(b) (4))	
IAR	n/N (%)	EAIR (PY)	n/N (%)	EAIR (PY)
Protocol-defined IARs				
Overall	27/60 (45.0)	30.0 (90.0)	6/59 (10.2)	10.5 (57.1)
Adult	18/40 (45.0)	33.5 (53.8)	4/39 (10.3)	9.17 (43.6)
Pediatric	9/20 (45.0)	24.8 (36.3)	2/20 (10.0)	14.9 (13.5)
Hypersensitivity IARs				
Overall	11/60 (18.3)	9.01 (122)	3/59 (5.1)	5.12 (58.6)
Adult	5/40 (12.5)	6.33 (79.0)	2/39 (5.1)	4.51 (44.3)
Pediatric	6/20 (30.0)	13.9 (43.0)	1/20 (5.0)	6.99 (14.3)

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IAR	While on Process C (b) (4) (Initial exposure on Process B or C (b) (4)) n/N (%)	While on Process C (b) (4) (Initial exposure on Process B or C (b) (4)) EAIR (PY)	While on Process C (b) (4) (Patients switched to Process C (b) (4)) n/N (%)	While on Process C (b) (4) (Patients switched to Process C (b) (4)) EAIR (PY)
Anaphylaxis IARs				
Overall	1/60 (1.7)	0.71 (141)	0/59 (0)	0 (59.8)
Adult	0/40 (0)	0 (88.8)	0/39 (0)	0 (45.5)
Pediatric	0/20 (5.0)	1.91 (52.4)	0/20 (0)	0 (14.3)

Source: 120-Day Safety Update Table 19
Note: For patients with event, the patient year is calculated as time from first olipudase alfa infusion to the time of first event during the specified analysis period; for patients without an event, it is calculated as the total duration of olipudase alfa exposure during the specified analysis period
Note: Protocol-defined IARs are adverse events that occur during the infusion or within up to 24 hours after the start of the infusion and are considered related or poss bly related to study treatment as judged by the investigator or the Applicant.
Note: Hypersensitivity related infusion-associated reactions (IARs) are protocol-defined IARs that are further identified by Hypersensitivity SMQ 20000214 (broad and narrow).
Note: Anaphylaxis reaction infusion-associated reactions (IARs) are protocol-defined IARs that are further identified based on the algorithmic approach defined in Introductory Guide for SMQs. Specifically, all Anaphylactic reaction SMQ 20000021 search PT terms were included.
Note: 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.
Note: 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.
Note: MedDRA version 24.0 has been used for coding the adverse events. Including cumulative data as of 15OCT2021.
Abbreviations: N, Number of patients treated; n (%), number and % of patients with at least one event; Events, number of events; EAIR, exposure adjusted incidence rate (100 x n/PY); PY, Patient Year; IAR, infusion-associated reaction.

Immunogenicity

The ADA incidence by manufacturing process (process B vs process C (b) (4)) in adult and pediatric subjects are summarized in Table 54 and Table 55, respectively. The ADA titer values in subjects who developed ADA are shown in 37. The immunogenicity data from ASCEND-PED study was used for the ADA titer analysis because the study design allowed a direct head-to-head comparison between Process B and Process C (b) (4) with similar treatment schedule and exposure of olipudase alfa. The immunogenicity results showed the following:

- The incidences for treatment-emergent ADA were similar between adult subjects only receiving process B product (40%) and adult subjects only receiving process C (b) (4) product (30%). However, there was a trend of higher ADA incidence in pediatric subjects only receiving process C (b) (4) product (75%) compared to pediatric subjects only receiving process B product (50%).
- In pediatric subjects, Process C (b) (4) product showed overall higher ADA titer values compared to Process B
- More pediatric subjects receiving Process C (b) (4) developed ADA at earlier sampling timepoints, which indicated higher ADA incidence at earlier timepoints in subjects receiving Process C (b) (4) compared to Process B.
- The only pediatric subject (13803- (b) (6)) who is the youngest patient in the trial and developed anaphylaxis initiated and maintained treatment with Process C (b) (4) This subject also developed the highest ADA titer among all pediatric subjects regardless process material received. Of note, anaphylaxis and other hypersensitivity reactions were found to be associated with high ADA titers based on clinical experiences with ERTs.

Table 54. Summary of ADA for Adult Subjects: Process B Versus C(b) (4)

ADA Incidence	While on Process B (Initial exposure on Process B)	While on Process C(b) (4) (Initial exposure on Process B)*	While on Process C(b) (4) (Initial exposure on Process C(b) (4))
Number of evaluable subjects, n	10	10	30
ADA positive at baseline, n (%)	1 (10%)	4 (40%)	3 (10.0%)
Always ADA negative, n (%)	5 (50%)	3 (30%)	18 (60.0%)
Treatment-induced ADAs, n (%)	4 (40%)	3 (30%)	9 (30.0%)
Treatment-boosted ADAs, n (%)	0	0	0
Treatment-emergent ADA, n (%)	4 (40%)	3 (30%)	9 (30%)

Source: ISI report Table 19.
*The baseline is the last ADA sample prior to Process C(b) (4) A subject whose ADA status is positive anytime post-baseline and is negative or missing at baseline is considered to have treatment-induced ADA. A subject whose ADA status is positive at baseline (pre-existing ADA) and the ADA titer level anytime post baseline is significantly higher than that at baseline is considered to have treatment-boosted ADA.
Abbreviations: ADA, anti-drug antibody; n, number of subjects in category.

Table 55. Summary of ADA for Pediatric Subjects: Process B Versus C(b) (4)

ADA Incidence	While on Process B (Initial exposure on Process B)	While on Process C(b) (4) (Initial exposure on Process B)	While on Process C(b) (4) (Initial exposure on Process C (b) (4)	
Number of evaluable subjects, n	12	12	8	
ADA positive at baseline, n (%)	1 (8%)	5 (42%)	1 (13%)	
Always ADA negative, n (%)	5 (42%)	5 (42%)		2 (25%)
Treatment-induced ADA, n (%)	6 (50%)	2 (17%)	5 (63%)	
Treatment-boosted ADA, n (%)	0	2 (17%)	1 (13%)	
Treatment-emergent ADA,	6 (50%)	4 (33%)		6 (75%)

Source: ISI report Table 21.
Abbreviations: ADA, anti-drug antibody; n, number of subjects in category.

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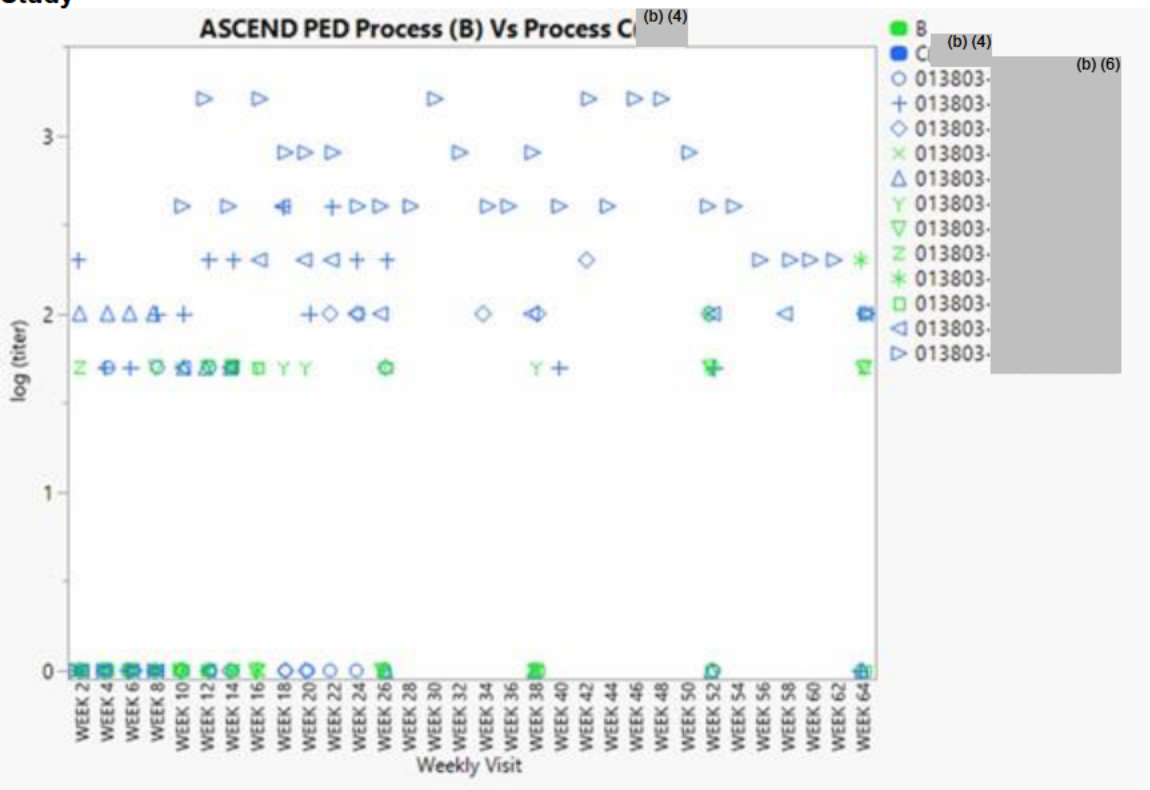
Figure 37. Summary of ADA Titer Values by Process B and Process C (b) (4) From ASCEND-PED Study



Source: Reviewer's generated plot based on the ADIS.xpt dataset.
Abbreviations: ADA, anti-drug antibody

Conclusion

The HCP is found to be much more elevated in Process C (b) (4) and C (b) (4) than in Process B. OBP has requested that the specification for HCP be tightened based on the clinical experience and the Applicant has agreed to tighten the specification for future lots to 700 ppm. As process C (b) (4) is the to-be-marketed process and is noted to have a greater elevation of HCPs compared to Process B, comparative analysis between process B and process C material treated patients were done on safety, and immunogenicity. Specifically, the pediatric trial (DFI13803 ASCEND-Peds) was used to assess differences between processes as the study design allowed a direct head-to-head comparison between Process B and Process C (b) (4) due to similar treatment schedule and exposure of olipudase alfa. Although pediatric subjects receiving Process C (b) (4) had overall higher ADA titer values compared to Process B, it is unclear the clinical relevance as safety appeared to show no difference. It is also unclear whether there is a clinical effect of the elevated HCP levels. However, the team has recommended that the HCP levels should be lower than 700ppm for future lots which has been agreed to by the Applicant.

7.7.3. Boxed Warning for Hypersensitivity Reactions including Anaphylaxis

Issue

There is a risk of hypersensitivity reactions including anaphylaxis during treatment with olipudase alfa. ERTs, as a class, include a boxed warning in the labeling due to the known class effect of hypersensitivity reactions occurring with ERTs. However, the Applicant did not include a boxed warning in their proposed labeling.

Background

Among patients that received olipudase alfa, treatment related hypersensitivity AEs were reported in 33% (10/30) adult subjects and in 50% (4/8) pediatric subjects. Hypersensitivity reactions occurred in adults were pruritus, urticaria, erythema, rash, rash erythematous, eczema, angioedema, and erythema nodosum and in pediatric subjects were urticaria, pruritus, rash, erythema, and localized edema. Anaphylaxis occurred in a 1.5-year-old subject in the pediatric clinical trial and a patient with type A ASMD that received Process B in the managed access program.

Assessment

Although no adult patients developed anaphylaxis in the clinical trials, 33% developed hypersensitivity reactions and 50% of pediatric patients also developed hypersensitivity reactions. More importantly, the pediatric patients that developed anaphylaxis were under age 2 or had Type A ASMD, of which there is minimal safety data.

Conclusion

Hypersensitivity reactions including anaphylaxis are a known risk with ERTs. Anaphylaxis is a serious adverse reaction which could lead to death or serious injury to patients. Due to the minimal safety data in pediatric patients and the known risk of ERT, the review team recommends inclusion of a boxed warning in the labeling about the risk of hypersensitivity reactions including anaphylaxis with treatment of olipudase alfa.

8. Therapeutic Individualization

8.1. Intrinsic Factors

The recommended dosage regimens for olipudase alfa in patients with ASMD are based on individual patient's body weight. Body weight was identified as a significant covariate on clearance of olipudase alfa. Subjects with lower body weight (e.g., younger pediatric subjects) are predicted to have lower exposure compared to subjects with higher body weight (e.g., adults) at the proposed body weight-based dosage regimens. A dose adjustment based on body weight or age is not needed (refer to Section 6.1 and Section 6.3.3). See Appendix 14.5 for the population PK analysis results of the effect of other intrinsic factors on PK of olipudase alfa. The currently

available data do not support a need for further therapeutic individualization based on other intrinsic factors.

8.1.1. Renal and Hepatic Impairment

The effect of renal impairment or hepatic impairment on the PK olipudase alfa has not been studied in dedicated clinical pharmacology studies. Intact olipudase alfa (molecular weight of approximately 76 kDa) is unlikely to be filtered by kidney or excreted in urine. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of therapeutic proteins such as olipudase alfa.

8.2. Drug Interactions

No specific drug-drug interaction studies were conducted with olipudase alfa.

8.3. Plans for Pediatric Drug Development

Not applicable.

8.4. Pregnancy and Lactation

Table 56. Pregnancy and Lactation Labeling

Labeling Section	Recommended Language
8.1 Pregnancy	Animal Data In a study of embryo-fetal development in pregnant mice, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from gestation days (GD) 6 through 15. There was no maternal toxicity that was not attributed to hypersensitivity, which always resulted in maternal mortality. Exencephaly was observed in the fetuses of surviving pregnant mice treated with 10 and 30 mg/kg (1 litter per group). These data are consistent with published literature reports that brief embryonic exposures to sphingomyelin metabolites or a sphingosine-1-phosphate (S1P) receptor modulator produced neural tube defects, including exencephaly, in chicks and mice. The developmental NOAEL is 3 mg/kg; the AUC_{0-24} at this dose is approximately $1/7^{th}$ the exposure associated with the MRHD. The developmental Lowest-Observed-Adverse-Effect Level (LOAEL), 10 mg/kg, is also associated with a safety margin that is less than the clinical exposure at the MRHD In a study of embryo-fetal development in pregnant rabbits, olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg daily from GD 6 through GD 19. There was no maternal or developmental toxicity. Maternal and developmental NOAELs were 30 mg/kg. The AUC_{0-24} associated with this dose was ~10.5-fold the exposure associated with the MRHD. In a study of pre-and postnatal development in mice, olipudase alfa was administered intravenously every other day from GD 6 through 18; then resumed every other day after parturition, from Lactation Day (LD) 1 through LD 19. There was no toxicity to either dams or offspring that was not attributed to maternal hypersensitivity. The maternal and developmental NOAELs are 30 mg/kg. While exposures were not assessed in this study, the animal AUC at this dose is estimated to be ~1.5-fold the MRHD of olipudase alfa.

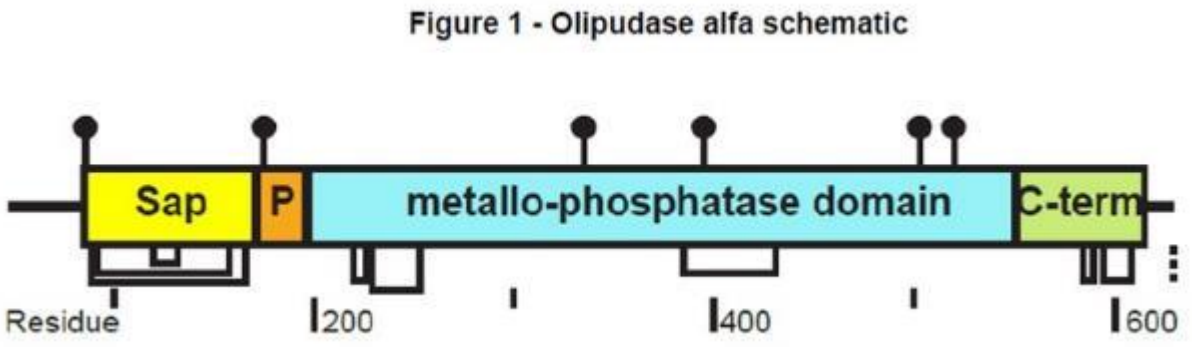
8.2 Lactation	Risk Summary There are no data on the presence of olipudase alfa-rpcp in human milk, the effects on the breastfed infant, or the effects on milk production. Olipudase alfa-rpcp is present in animal milk. *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XENPOZYME and any potential adverse effects on the breastfed infant from XENPOZYME or from the underlying maternal condition. Data Olipudase alfa-rpcp was administered as a single intravenous dose (3 mg/kg) to lactating CD1 mice on post-partum day 7. Milk was not expressed until post-partum day 9, at which time concentrations of olipudase alfa-rpcp detected were approximately 1.3% the estimated maximal plasma concentration on post-partum day 7.
8.3 Females and Males of Reproductive Potential	Because malformations were observed in fetal mice at maternal exposures < those associated with the MRHD, females of reproductive potential should use highly effective contraception while receiving treatment with olipudase alfa. There were no effects on male or female fertility when mice were treated with olipudase alfa. [*See Section 13.1*.]
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	The carcinogenic and mutagenic potential of olipudase alfa were not evaluated. Impairment of Fertility. Intravenous administration of olipudase alfa-rpcp every other day at doses up to 30 mg/kg had no adverse effects in a combined study of fertility in male and female mice. Exposures at this dose, based on the embryo-fetal development study, were estimated to be approximately 1.5-fold those of the MRHD of olipudase alfa-rpcp.

Abbreviations: ASMD, acid sphingomyelinase deficiency; ASMKO, acid sphingomyelinase knockout; AUC, area under the concentration-time curve; IV, intravenous; GD, gestation day; LD, lactation day; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level

9. Product Quality

Xenpozyme (olipudase alfa-rpcp) is a recombinant human ASM developed as an ERT to treat non-CNS manifestations of ASMD in pediatric and adult subjects. Upon treatment, olipudase alfa is internalized by the cells primarily through binding to the cation-independent mannose-6-phosphate receptor with a smaller percentage getting internalized through binding to the mannose receptor. Following internalization and trafficking to lysosomes, olipudase alfa causes breakdown of sphingomyelin, reducing the accumulation of SPM in the affected organs. The drug substance (DS) is a clear and colorless liquid. The DS is (b) (4) (b) (4) Olipudase alfa DP is supplied in (b) (4) single-use vial with nominal strength of 20 mg/vial. The composition of formulation excipients (b) (4) contains (b) (4) mg/mL olipudase alfa, (b) (4) mM sodium phosphate (b) (4) % (w/v) sucrose, and (b) (4) mM (b) (4) methionine at pH 6.5. Olipudase alfa DP is reconstituted with nominal 5.1 mL sterile water for injection and then further diluted before IV infusion.

Figure 38. Olipudase Alfa Schematic



Source: Structure section submitted under module 3.2.S.1.2.
Note: Olipudase alfa contains an N-terminal saposin (Sap) domain, a proline rich linker region, a catalytic metallophosphatase domain, and a helical C-terminal structural domain ending in a cysteine. There are six glycosylation sites depicted by the black circles above the schematic and eight disulfide brackets depicted by the brackets below the schematic.

Olipudase alfa is manufactured in Chinese hamster ovary cells using recombinant DNA technology. (b) (4)
The proposed commercial manufacturing process (Process C (b) (4))consists of (b) (4)
(b) (4)

There were three previous manufacturing processes over the course of development for olipudase alfa DS:

- Process A
- Process B
- Process C (b) (4)

The initial manufacturing process (Process A) was used to initiate the IND. Process A utilized (b) (4) and Process B was developed to (b) (4) Process A and Process B material was demonstrated to be comparable, with improved safety (b) (4) (b) (4) in Process B. Process C (b) (4) was developed to increase manufacturing capacity and improve robustness.

Process C (b) (4) included the transition to the proposed commercial DS manufacturing facility (b) (4) Process C (b) (4) material was demonstrated to have analytical differences from Process B and A material. Specifically, the following changes have been observed:

(b) (4)

(b) (4)

Based on an analysis of the product differences, it is determined that material from Process B and A is not comparable to Process C (b) (4) and Process C (b) (4) from an analytical perspective. This concern was previously communicated during IND development in a meeting held January 25, 2017. At that time, the Applicant agreed to conduct additional clinical studies to evaluate if Process C material had significantly lower efficacy. A decision on whether the differences noted above have clinical impact is deferred to the clinical review teams.

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761261 for Xenpozyme (olipudase alfa-rpcp) manufactured by Genzyme Corporation. The data submitted in this application are adequate to support the conclusion that the manufacture of Xenpozyme (olipudase alfa-rpcp) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

The stability data are sufficient to support an expiration dating period of (b) (4) weeks for olipudase alfa-rpcp DS when stored at (b) (4) °C and an expiration dating period of 24 months for lyophilized olipudase alfa-rpcp DP when stored at 5±3°C.

An inspection of the DS manufacturing facility (b) (4) (b) (4) was performed (b) (4) A recommendation of approval was made for this facility. An inspection of Genzyme Ireland Limited, Waterford, Ireland (FEI: 3003809840) for DP manufacturing operations was waived based on the history of the facility.

All other proposed manufacturing and testing facilities are acceptable based on their current GMP compliance status and recent relevant inspectional coverage.

The Office of Biotechnology Products Immunogenicity team has no bioanalytical assay related approvability issues for olipudase alfa-rpcp. Final determination on the clinical impact of the immunogenicity data is deferred to the Clinical and Clinical Pharmacology teams.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The review of the label/labeling is on-going from the CMC perspective.

Therefore, from the OPQ perspective, this BLA is recommended for “Approval” pending the completion of the label/labeling review.

9.1. Device or Combination Product Considerations

Not applicable

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Human Subjects Protections

As stated by the Applicant, the trials used as a basis for clinical data in this application were conducted in compliance with Good Clinical Practice, as required by the International Council for Harmonization E6 Guideline for Good Clinical Practice. The studies also meet the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Applicant, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC. All studies submitted in this application were conducted according to FDA requirements under IND 012757.

Clinical Site Inspections

FDA clinical site inspections were performed at four sites, two sites each for the pediatric trial DFI13803 (ASCEND-Peds) and adult trial DFI12712 (ASCEND). Three of the four sites are within the United States and one site is in Germany. Both trials appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication. (refer to Section 20.1 for details).

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance Financial Disclosure by Clinical Investigators (February 2013) (see Section 23), and by 21 CFR 54.4.

Of the four covered clinical studies (DFI12712 ASCEND, DFI13803 ASCEND-Peds, LTS13632, and DFI13412), none of the investigators were employed by the Applicant. Nine clinical investigators (six Investigators, three Sub-Investigators) disclosed financial interests and arrangements with the Applicant. The Applicant implemented the following actions to protect studies from potential bias. Spleen and liver imaging data were assessed independently by blinded readers. ECGs were read centrally by an external vendor. A Data Monitoring Committee, independent to the Applicant, reviewed the safety data for all studies periodically. The small number of subjects participated at each site also minimizes the potential for bias.

In conclusion, the likelihood that trial results were biased on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not held for this application. It did not raise challenging efficacy or safety issues that needed external input.

III. Appendices

12. Summary of Regulatory History

The Applicant, Genzyme Corporation (Genzyme), submitted IND 012757 on October 27, 2005, to investigate olipudase alfa, also referred to by the company code name GZ402665, as an enzyme replacement therapy (ERT) for the treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD). Olipudase alfa is a recombinant human acid sphingomyelinase (rhASM) produced by mammalian cell culture technology using a Chinese hamster ovary cell line. The product is to be supplied in lyophilized powder reconstituted for intravenous (IV) infusion and administered (b) (4) according to body weight. Olipudase alfa was granted Orphan Drug designation for the treatment of acid sphingomyelinase deficiency on August 3, 2000.

Following its submission, IND 012757 was placed on full clinical hold on November 30, 2005, due to insufficient pre-clinical and chemistry, manufacturing, and controls (CMC) information. Following the receipt of additional pre-clinical information on March 27, 2006, the clinical hold was partially lifted on May 4, 2006, and Genzyme was permitted to proceed with a single-dose human trial (SPHINGO00605) in adult subjects with Niemann-Pick disease (NPD) type B. A Fast Track designation was granted to olipudase alfa on April 23, 2007.

Genzyme attempted to address the clinical hold through amendments received on October 20, 2008, February 26, 2009, April 24, 2009, December 7, 2009, and a complete response received on January 19, 2010. On February 25, 2010, repeat dose studies were allowed to proceed at a limited dose, interval, and duration, but other investigations remained on clinical hold. A type A meeting was requested with preliminary responses issued on June 14, 2010. Genzyme subsequently requested the meeting be cancelled because the issued comments were deemed to have sufficiently addressed their questions. A complete response to the hold was received November 19, 2010. The partial clinical hold was removed on December 17, 2010, and Genzyme was allowed to proceed with trial SPHINGO00709, then titled "A Phase 2, Randomized, Open-Label, Repeat-Dose, Dose-Comparison, Multi-Center Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of rhASM in Patients With Acid Sphingomyelinase Deficiency (ASMD)."

During the course of olipudase alfa drug development, multiple changes were made to the manufacturing process, including a switch from Process A to Process B, Process B to Process C (b) (4), and from Process C (b) (4) to Process C (b) (4) which is the to-be marketed drug substance (DS) and drug product (DP) manufacturing process. The Applicant and FDA had several interactions to discuss these changes as well as their implications to the olipudase alfa clinical development program.

The first meeting which included discussions of olipudase alfa DS and DP manufacturing changes took place on October 4, 2011, wherein Genzyme informed the FDA that they planned to implement (b) (4) (Process B) to replace (b) (4) (b) (4) (Process A) for the phase 2 studies and future clinical development of olipudase alfa. The meeting minutes were issued on November 4, 2011.

On April 7, 2015, Genzyme met with FDA to discuss their manufacturing process changes from Process B to Process C, (b) (4) for the ongoing phase 2/3 pivotal trial and planned pediatric clinical trial. The FDA requested Genzyme provide additional information to support the comparability between the two processes and raised concerns on the timing of introducing new material to the ongoing clinical studies. The meeting minutes were issued on April 13, 2015.

Multiple interactions also occurred to discuss the clinical development plan. On June 17, 2014, Genzyme met with the FDA to discuss their phase 1/2 clinical trials, and meeting minutes issued for the meeting on July 17, 2014. Other interactions particularly pertained to the pivotal clinical trial SPHINGO00709, revised, and renumbered to DFI12712 on April 17, 2013, and eventually retitled "A Phase 2/3, Multicenter, Randomized, Double-blinded, Placebo-controlled, Repeat-dose, Dose-comparison Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency." Protocol revisions to DFI12712 (ASCEND) were subsequently received on September 29, 2014, December 12, 2014, and April 8, 2015. The FDA provided comments on this protocol on November 14, 2014, January 9, 2015, February 20, 2015, and May 1, 2015.

Olipudase alfa was granted Breakthrough Therapy designation for the treatment of non-neurological manifestations of ASMD on May 26, 2015. Following the breakthrough designation, an initial breakthrough multidisciplinary meeting took place on October 20, 2015, to discuss the overall clinical development plan for olipudase alfa, including the immunogenicity evaluation plan, the primary analysis to support efficacy, the pediatric patient population, and the non-clinical, clinical pharmacology, and CMC data packages. The meeting minutes were issued October 28, 2015.

In response to the FDA's feedback during the breakthrough multidisciplinary meeting, Genzyme submitted a revised protocol for trial DFI12712 (ASCEND) on February 9, 2016, and a statistical analysis plan (SAP) on April 14, 2016. The FDA provided comments, specifically on the proposed endpoints, in an advice letter on February 12, 2016, and on the SAP on June 13, 2016. A clinical outcome assessment meeting took place on August 31, 2016, to discuss the proposed splenomegaly-related score (SRS) patient-reported outcomes (PRO) endpoints for the ongoing pivotal trial DFI12712 (ASCEND). The meeting minutes were issued on September 8, 2016.Additional communication on trial DFI12712 (ASCEND) and the corresponding SAP included an advice letter issued April 13, 2018, and three type C written responses issued on October 9, 2018, February 14, 2019, and August 20, 2019. An amendment for trial DFI12712 (ASEND) and final SAP were received September 6, 2019. Additional amendments for trial DFI12712 (ASCEND) were received April 20, 2020, and February 11, 2021, to incorporate changes related to the COVID-19 pandemic.

On April 13, 2016, Genzyme submitted a proposed proprietary name request for Xenpozyme, which was found conditionally acceptable on May 27, 2016.

A meeting on the manufacturing process took place on January 25, 2017, to discuss the comparability concerns between Process B and Process C, particularly due to the changes in specific activity. The FDA advised that additional clinical data would be needed to evaluate and characterize the impact of these changes. The meeting minutes were issued on January 31, 2017. Additional FDA comments on the incorporation of Process C material into the on-going clinical trials were provided in an advice letter on March 3, 2017.

On July 26, 2017, a meeting took place to discuss the pediatric extrapolation plan for olipudase alfa. The FDA determined (b) (4) (b) (4) challenges for the extrapolation for safety and efficacy. Genzyme proposed to enroll at least 8 additional pediatric subjects (age <12 years) into the open-label DFI13803 (ASCEND-Peds) trial to be initiated with Process C product. The meeting minutes were issued on July 31, 2017.

On May 31, 2018, Genzyme submitted a CMC meeting request to discuss their changes from (b) (4) (b) (4) Process C (b) (4) to (b) (4) Process C (b) (4) intended as the to-be-marketed DS manufacturing process. The FDA issued written responses on July 27, 2018. Additional FDA comments were provided in an advice letter on October 5, 2018.

On May 15, 2019, Genzyme submitted a CMC meeting request to obtain the FDA's feedback on the process performance qualification strategy and shelf-life at registration to support the registration of olipudase alfa. The FDA issued written response on July 15, 2019.

On August 28, 2019, a meeting took place to discuss Genzyme's proposed rolling review Biological License Application (BLA) submission for olipudase alfa. The FDA stated its concerns regarding the format and content of the BLA submission, the proposed datasets, and the timeline given the various manufacturing processes. The meeting minutes were issued September 8, 2019. Genzyme submitted a meeting request to discuss a revised strategy for the rolling submission on September 3, 2019. The FDA issued written responses on October 18, 2019, stating agreement that the proposed rolling review was feasible but reiterated that additional information is needed to establish comparability between Process C (b) (4) and C (b) (4)

On September 13, 2019, Sanofi requested a meeting to obtain the FDA's concurrence on their alternative analysis plan in the PRO SAP for Trial DFI12712 (ASCEND). The FDA granted a type B meeting, which took place on October 28, 2019. The FDA reiterated its concerns on the quantitative analysis results based on a small sample size and stated that the evaluation of clinically meaningful within-subject change in the splenomegaly-related score will be a review issue. The meeting minutes were issued on November 4, 2019.

Genzyme submitted their final reports on the biochemical comparability assessment between Process C (b) (4) and to-be-marketed Process C (b) (4) on September 20, 2019. The FDA issued an advice letter on January 31, 2020, agreeing that the submitted materials supported that Process C (b) (4) and Process C (b) (4) are analytically comparable.

On November 8, 2019, Genzyme requested a meeting to gain agreement with the FDA on their approach for evaluating immunogenicity for olipudase alfa. The meeting was granted to take place on January 16, 2020. After reviewing the FDA preliminary comments provided on January 13, 2020, and the FDA's responses to follow-up questions on February 15, 2020, Genzyme cancelled the meeting on January 16, 2020.

On October 21, 2020, Genzyme submitted a CMC meeting request to discuss their revised plan for the sequence of the lots used for drug substance and DP process performance qualifications and DP stability data to support the marketing application for olipudase alfa. The FDA sent preliminary comments on December 13, 2020. Genzyme found that the preliminary comments sufficiently addressed their questions and on December 15, 2022, cancelled the meeting.

A pre-BLA meeting to discuss the proposed data package to support a marketing application for olipudase alfa took place on March 24, 2021. The discussion focused on the confirmatory

evidence to demonstrate clinically meaningful benefit to the subjects. Particularly, concerns on the failed trial on the PRO splenomegaly-related score endpoint and data needed to support other primary endpoints such as diffusion capacity for carbon monoxide (DL_{CO}), forced vital capacity (FVC), spleen volume, and platelets were discussed. In addition, the FDA reiterated that whether the trial data and results would support the partial extrapolation of efficacy from adult to pediatrics would be a review issue. The meeting minutes were issued on March 26, 2021.

On March 29, 2021, Genzyme submitted an expanded access protocolRHASHC09706 titled "Compassionate Use Program for Olipudase Alfa Enzyme Replacement Therapy for Patients with Chronic Acid Sphingomyelinase Deficiency (ASMD)."

A request from Genzyme for a rolling submission of their BLA was received June 18, 2021. The FDA granted rolling review for olipudase alfa on August 9, 2021.

Genzyme submitted BLA 761261 via the 351(a) pathway in two parts: part 1 consisted of the nonclinical modules and was received on September 8, 2021, and part 2 consisted of the clinical and CMC modules and was received on November 3, 2021. The labeling submitted included the Prescribing Information and carton and container labeling. Genzyme also included a request for the proposed proprietary name Xenpozyme, which the FDA found conditionally acceptable on January 26, 2022. The nonproprietary name, olipudase alfa-rpcp, was found conditionally acceptable on March 18, 2022.

The Division determined that the review classification for the application was priority because olipudase alfa is a drug that treats a serious condition with no approved treatment to date.

On April 20, 2022, a major amendment was received. On May 6, 2022, the FDA informed Genzyme that the user fee goal date was being extended by three months due to the major amendment.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

All nonclinical studies were submitted under IND 012757, with the exception of reproductive and developmental toxicology studies in CD1 mice and New Zealand White rabbits. No genotoxicity or carcinogenicity studies were conducted with olipudase alfa, consistent with International Conference on Harmonisation guidance S6 (R1) *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (June 2011); and Guidance for Industry: *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment* (October 2019). Olipudase alfa is a recombinant human protein and a replacement enzyme and is not expected to exhibit genotoxic or carcinogenic potential.

Studies which have been reviewed for this new drug application are summarized below. These include:

- Pharmacology (including mechanistic studies to understand the toxicity of olipudase alfa on acid sphingomyelinase knockout (ASMKO) mice)
- Safety pharmacology studies in ASMKO mice and cynomolgus monkeys
- Pharmacokinetics and absorption, distribution, metabolism, excretion
- Repeated-dose toxicity studies in ASMKO mice, rats, and cynomolgus monkeys.

13.1.1. Pharmacology

Table 57. The Effects of a Single Administration of Acid Sphingomyelinase (ASM) on the Depletion and Re-Accumulation of Sphingomyelin (SPM) in Niemann-Pick Knockout (KO) Mice

Study Parameter	Study Information
Study no.:	01-0110 PnP
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	February 26, 2001
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	ASM, 9881-116, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase

Key Study Findings

Following administration of 5 mg/kg acid sphingomyelinase (ASM) to groups of ASMKO mice, sphingomyelin (SPM) levels were markedly decreased on days 1-7 in liver (maximum -95%, day 7); in spleen (maximum -80%, day 7); and in kidney (maximum -71%, day 7). Conversely, reductions of levels in lung were of lower magnitude (-43% on day 7). SPM levels began to increase after day 7. Plasma levels of SPM were much lower; these were transiently increased after 24 hours but returned to baseline thereafter.

Study Design

Native ASM was administered to male and female ASMKO mice (source: Genzyme Corporation, 8 to 10 weeks of age) as documented in Table 58.

Table 58. 01-0110 Pnp Study Design and Methods

Group	N	Dose level	Regimen	Route	Day of Sacrifice	Endpoints
1	3-4 per time point*	5 mg/kg	Single dose (Day 1)	IV	[Pre-dose]	Sphingomyelin analysis of liver, lungs, spleen, kidney, plasma
2					2	
3					3	
4					7	
5					21	
6					28	

Source: Review team.
* exact numbers of each sex unspecified
Abbreviations: IV, intravenous; N, total number of subjects.

Results

There were no clinical observations or necropsy observations. Tissue and plasma SPM content are reproduced in Table 59.

Table 59. SPM Reduction and Re-Accumulation Over Time After Administration of a Single Dose (5 mg/kg) ASM to ASMKO Mice

		SPM Content (mg/g Wet Tissue (Mean ± SD)				
Group	Day	Liver	Spleen	Kidney	Lung	Plasma*
1	1	11.12±4.18	19.95±13.78	11.26±4.12	7.51±4.42	41±10
2	2	2.88±0.78	7.00±0.97	7.86±2.79	4.78±3.36	76±4
3	3	2.21±2.11	6.49±3.91	8.63±0.22	5.55±2.71	46±28
4	7	0.53±0.16	4.04±3.16	3.29±0.33	4.25±2.0	36±24
5	21	2.36±0.28	10.69±6.11	18.46±12.86	7.34±3.09	43±39
6	28	5.00±3.09	8.96±10.04	10±11.36	5.83±3.52	46±21

Source: Review Team.
* mcg/mL
Abbreviations: ASM, acid sphingomyelinase; ASMKO, acid sphingomyelinase knockout; SD, standard deviation; SPM, sphingomyelin.

Table 60. The Effects of a Single Administration of Acid Sphingomyelinase (ASM) on the Depletion and Re-Accumulation of Sphingomyelin (SPM) in Niemann-Pick Knockout (KO) Mice

Study Parameter	Study Information
Study no.:	02-0428 PnP
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	April 24, 2002
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	ASM, FD-10544-070, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin.

Key Study Findings

Following administration of 1 mg/kg ASM to groups of Nieman-Pick KO mice, SPM levels were decreased, primarily on day 3, in liver (-76%), in spleen (-67%), and in kidney (-23%). While not run concurrently with study 01-0110 Pnp, considered together these two studies demonstrate that SPM reductions after ASM administration are dose-and duration dependent.

Study Design

Native ASM was administered to male and female Nieman-Pick KO mice (source: Genzyme Corporation, 8 to 10 weeks of age) as documented in Table 61.

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Table 61. 02-0428 Pnp Study Design and Methods

Group	N	Dose level	Regimen	Route	Day of Sacrifice	Endpoints
1	4/time point*	1 mg/kg	Single dose (Day 1)	IV	[Pre-dose]	Sphingomyelin analysis of liver, lungs, spleen, and kidney
2					2	
3					3	
4					7	
5					14	
6					21	
7					28	

Source: Review team.
* exact numbers of each sex unspecified
Abbreviations: IV, intravenous; N, total number of subjects.

Results

There were no clinical observations or necropsy observations. Tissue SPM content are reproduced in Table 62.

Table 62. SPM Reduction and Re-Accumulation Over Time After Administration of a Single Dose (1 mg/kg) ASM

		SPM Content (mg/g Wet Tissue (Mean (SD))			
Group	Day	Liver	Spleen	Kidney	Lung
1	1	13.19 (1.32)	16.59 (1.24)	20.89 (4.09)	10.25 (4.09)
2	2	6.84 (2.50)	9.28 (2.85)	20.18 (9.99)	11.85 (9.99)
3	3	3.17 (1.07)	5.44 (1.38)	16.14 (7.03)	10.87 (7.03)
4	7	3.46 (1.01)	8.61 (2.01)	20.14 (5.43)	5.55 (2.85)
5	14	5.01 (1.44)	16.07 (1.55)	20.72 (4.17)	7.18 (0.6)
6	21	10.15 (0.71)	11.92 (2.43)	22.31 (9.65)	14.6 (9.65)
7	28	14.14 (1.24)	18.13 (4.16)	33.40 (3.71)	10.40 (1.48)

Source: Review team.
Abbreviations: ASM, acid sphingomyelinase; SD, standard deviation; SPM, sphingomyelin.

Table 63. Sub-Therapeutic Dosing and Dose-Response in ASMKO Mice Over a 12-Week Period, Dosing Every Other Week

Study Parameter	Study Information
Study no.:	02-1084 PnP
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	December 9, 2002
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM034, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase

Key Study Findings

Administration of rhASM in ASMKO mice (0.1, 0.3, 1.0) every other week for 12 weeks generally effected dose-related reductions in SPM levels in liver and spleen (maximal -96% and -91%, respectively), relative to those in vehicle-treated animals; and to a lesser extent in kidney. Lung SPM levels were unaffected by treatment. Survival was unaffected at any dose, when compared to that in ASMKO mice that received vehicle. By 14 days after last dose, SPM re-accumulating in liver, spleen, kidney.

Table 64. 02-1084 Pnp Study Design and Methods

Group	N	Dose (mg/kg)	Regimen	Route of Administration	Samples Collected at Necropsy 1 or 2 weeks After 6th Dose
1	8*	0	Every other week for 6 doses	IV	Liver, kidneys, spleen, lung (SPM content** and histopath) Heart, brain***
2		0.1			
3		0.3			
4		1.0			Blood, processed to serum

Source: Review team.
*exact number of males and females unspecified
**SPM content determined by enzymatic assay with ASM, and tissue staining with tannic acid/toluidine blue
***for possible future analysis
Abbreviations: IV, intravenous; N, total number of subjects; SPM, sphingomyelin.

Results

One mouse in the 0.3 mg/kg group died on day 3. The cause of death was determined to be disease progression (i.e. SPM accumulation due to sphingomyelinase deficiency). One mouse in the 1 mg/kg group died due to anaphylaxis shortly after the second dose. Clinical signs related to disease progression were observed (e.*g. ocular discharge and closure).* However, no eye abnormalities were observed in the 1 mg/kg group. Bodyweight was increased by approximately 13%, 10%, and 13% in the 0.1, 0.3, and 1 mg/kg groups, respectively, as compared to 9% in the [untreated ASMKO] control group.

SPM levels 1- and 2-weeks following administration of the last (6th) dose are reproduced below, in Table 65.

Table 65. SPM Levels (mg/g Tissue) in Selected Tissues After 12 Weeks of Treatment With rhASM

	SPM Levels in Liver		SPM Levels in Spleen		SPM Levels in Kidney		SPM Levels in Lungs	
Dose (mg/kg)	1 Wk After Last Dose	2 Wks After Last Dose	1 Wk After Last Dose	2 Wks After Last Dose	1 Wk After Last Dose	2 Wks After Last Dose	1 Wk After Last Dose	2 Wks After Last Dose
0 (Vehicle)	52.2±8.2	50.8±10.6	74.0±12.7	52.6±7.4	54.9±10.6	62.9±32.1	38.3±10.2	41.8±10.9
0.1	27.3±9.1	29.2±7.8	36.2±12.6	44.0±4.0	60.9±10.0	56.0±8.9	30.4±14.6	43.6±10.1
0.3	6.9±2.6	12.2±0.4	17.9±4.6	21.7±7.7	37.9±9.9	42.8±9.8	45.4±5.9	44.2±2.6
1.0	2.3±0.7	9.5±2.8	6.5±1.1	12.5±0.6	27.7±2.3	34.5±2.9	36.4±9.7	32.6±14.1

Source: Review team.
Abbreviations: rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin; Wk, week

Table 66. The Effects of a Debulking Dosing Scheme on the Quantity of SPM in Various Tissues From ASMKO Mice

Study Parameter	Study Information
Study no.:	03-0788 Pnp
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	December 15, 2003
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049 IRS, purity unspecified

Source: Review Team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin.

Key Study Findings

Unexpectedly, administration of a single 30 mg/kg dose of rhASM to ASMKO mice resulted in moribundity and death of all animals treated. Minor increases in serum cholesterol (mean 1.62x upper limit of normal (ULN)), alanine aminotransferase (ALT) (mean 2.4x ULN) and aspartate aminotransferase (AST) (1.23x ULN) were reported in some animals from the second cohort tested.

Table 67. 03-0788 Pnp Study Design and Methods

Group	N	Dose (mg/kg) rhASM	Route and Regimen	Tissue Collection and Comments
1	9	30	IV, single dose	No tissues were collected. All animals in group 1 were found dead 24h after dose administration. Lethargy and rapid breathing noted after 2-3h in some animals, with most exhibiting lethargy by 6 h. In group 2, 5/6 animals euthanized by 6h post dose. Clinical chemistry conducted on animals in Group 2 demonstrated minor increases in cholesterol in 3 animals (mean 194 mg/dL, reference range 50-120); minor increases in ALT 3 animals (333 U/L, reference range 24-140 U/L); and minor increases in AST in 3 animals (355 U/L, reference range 72-288 U/L). The same 3 animals were not invariably affected.
2	6	30	IV, single dose	

Source: Review team.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; N, total number of subjects; rhASM, recombinant human acid sphingomyelinase.

Table 68. Acute Toxicity Study in ASMKO and C57BL/6 Mice Following a Single Intravenous Administration of rhASM

Study Parameter	Study Information
Study no.:	04-0025 Pnp
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	January 26, 2004
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practices; MA, Massachusetts; No, number; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

Mortality/euthanasia was reported in 5 of 12 ASMKO mice, although not wild type (WT) animals, given a single 10 mg/kg dose of rhASM. Serum chemistry findings included increases in cholesterol, AST, ALT, and bile acids. Histopathology identified liver and adrenals as target organs, with degeneration/necrosis reported in both, at both 3 and 10 mg/kg. A no observed adverse effect level (NOAEL) was not identified.

Reviewer's Comments: Liver and adrenal pathology identified in this study were subsequently determined to be secondary to hypotension/hypoperfusion.

Table 69. 04-0025 Pnp Study Design and Methods

Group	N		Strain	Dose (mg/kg)	Clinical Observations and Mortality
	Males	Females			
1	5	3	C57BL/6	0	-
2	4	4		3	-
3	4	4		10	-
4*	4	4		10	-
6**	4	4	ASMKO	3	-
7	4	4		10	1/8 found dead at 53h post-dose without antecedent clinical observations. 2/8 additional animals with initial mild-moderate lethargy euthanized 53 h post-dose.
8*	2	2		10	2/8 animals euthanized at 46h after onset of mild lethargy between 26-46h post dose.

Source: Review team.
* Due to deaths in the 10 mg/kg dose groups, the original intention to dose groups 4 and 8 with 20 mg/kg was amended to 10 mg/kg.
**Group 5 animals repurposed to another study.
Abbreviations: ASMKO, acid sphingomyelinase knockout; h, hour; N, total number of subjects.

Results

Significant reductions in mean body weight change at 24 and 72 hours post-dose in groups 6 to 8. A reduction in mean body weight change was reported in group 4, but not group 3; this was dismissed. There were no changes in limited clinical chemistry (serum cholesterol, AST, ALT, bilirubin, bile acids) in WT mice. Dose-related increases in ALT and AST were noted at 24 and 72 hours in groups ASMKO mice. Bile acids were increased 158-fold in ASMKO mice that received 10 mg/kg rhASM. Increased cholesterol was reported at 24 hours in mice in group 6, and 24 and 72 hours in mice in groups 7 to 8.

The liver and adrenal were target organs. Liver observations included hepatic ballooning degeneration, hepatic inflammation, hepatocellular apoptosis. Adrenal observations included cortical degeneration/necrosis and apoptosis, as well as zona fasciculata necrosis. Findings were reported at both 3 and 10 mg/kg dose levels. A NOAEL was not identified.

Table 70. The Acute Toxicity of rhASM, Lot SM049, at Doses of 10 and 20 mg/kg to ASMKO Mice

Study Parameter	Study Information
Study no.:	04-0047 Pnp
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	January 21, 2004
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

IV administration of single doses of 10-20 mg/kg to ASMKO mice resulted in death/euthanasia for all animals. Minor increases in serum cholesterol and ALT were reported.

Table 71. 04-0047 Pnp Study Design and Methods

Group	N	Dose (mg/kg)	Route and Regimen	Clinical pathology Endpoints and Tissue Collection	Mortality/Comments
1	4	20	IV, single dose	Cholesterol, bile acids, ALT, AST Saline perfusion to collect liver, spleen, kidney, lung; then 10% NBF for remaining organs for possible future analysis	2 animals found dead 24h after dosing. 2 animals with severe lethargy 15-17h after dosing were euthanized. No gross pathology associated with treatment.
2	2	10	IV, single dose		Mild lethargy 15-21h post dose, euthanasia following subsequent [unspecified] adverse clinical observations. No gross pathology associated with treatment.

Source: Review team.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; NBF, neutral buffered formalin.

Results

Blood samples for clinical chemistry were collected from animals not found dead (N=4). Elevations in serum cholesterol (3 mice, mean 1.7x ULN) and ALT (3 mice, mean 1.9x ULN) were reported; findings were variable, and unrelated to dose.

Table 72. The Effect of a Low Dose Followed Five Days Later With a High Dose on the Toxicity of rhASM in ASMKO Mice

Study Parameter	Study Information
Study no.:	04-0099 Pnp
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	February 2, 2004
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049 IRS, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

These results suggest that the lethality of rhASM previously associated with administration of single doses of 20 and 30 mg is mitigated by pretreatment with a tolerated dose. The microscopic lesions in the 3/20 and 3/30 mg/kg groups were similar to those present in the 3/0 mg/kg group, although reduced in severity among pretreated animals.

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Table 73. 04-0099 Pnp Study Design and Methods

		Dose (mg/kg)			
Group	**N**	**Day 1**	**Day 6**	**Tissues Collected**	**Comments**
1	1/sex	3	vehicle	Liver, adrenal, spleen, lung, kidney, pancreas, brain, heart, small intestine, descending aorta	No clinical observations. All animals survived until 24h after dose administration on Day 6. All groups reported with random ballooning hepatocellular/Kupffer cell degeneration, and apoptotic parenchymal foci with some inflammatory foci; ballooning degeneration reduced among pre-treated animals.
2	2/sex	3	20		
3	2/sex	3	30		

Source: Review team.
Abbreviations: h, hour.

Table 74. Evaluation of rhASM Toxicity in ASMKO Mice Using a Tolerated Dose Followed Several Days Later With Known Lethal Doses*

Study Parameter	**Study Information**
Study no.:	04-0505 Pnp
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	September 10, 2004
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049DP, purity unspecified

Source: Review team.
* Known lethal doses are discussed in previous studies.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

Pretreatment of ASMKO mice with a single 3 mg/kg dose of rhASM did not prevent mortality with subsequent administration of known lethal doses. However, the time to death/ moribund sacrifice after dosing with 30 mg/kg (48 hours) exceeded that previously reported with administration of a single lethal dose (5 to 14 hours), suggesting that pretreatment with 3 mg/kg produced delayed the onset of mortality/moribundity.

Table 75. 04-0505 Pnp Study Design and Methods

		Dose (mg/kg)				
Group	**N**	**1st (Day 1)**	**2nd (Day 6 or 8)**	**3rd (Day 11)**	**Scheduled Endpoints and Tissues**	**Comments**
1	6	None			Blood for clinical chemistry. Liver, spleen, kidney, lung planned; expanded to include adrenals, brain, heart	Necropsy day 12
2	6	3	10	10		1 animal moribund ~48h after first 10 mg dose (day 8), remaining animals lethargic/moribund by days 10-11. All euthanized after 3rd dose.
3	6	3	30	NA		4 animals died without antecedent clinical observations ~48h after 30 mg dose; remaining were euthanized in moribund condition

Source: Review team.
Abbreviations: h, hour; N, total number of subjects; NA, not applicable.

Results

Clinical Chemistry

No clinical chemistry samples collected (due to moribundity).

Gross Pathology

No abnormalities.

Histopathology

Limited evaluations in group 3 mice sacrificed in moribund condition. Heart: moderate numbers of marginated neutrophils within one large coronary artery. Kidneys: Tubular necrosis with cellular debris and casts within the tubules, and tubular mineralization. Liver: foci of ballooning degeneration, mild inflammation, and neutrophilic inflammatory foci. Other hepatic lesions included portal stroma with mixed-cell inflammatory infiltrates, neutrophils within the sinusoids, apoptotic and/or necrotic hepatocytes.

Table 76. The Acute Toxicity of Dosing 5 mg/kg of rhASM to ASMKO Mice Every 2 Hours for a Total of 6 Hours

Study Parameter	Study Information
Study no.:	04-0506 Pnp
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	September 7, 2004
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049DP, purity unspecified

Source: Review Team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin.

Key Study Findings

Female ASMKO mice (n = l0) received 5 mg/kg of rhASM every 2 hours, for a total dose of 20 mg/kg over the course of 6 hours. All animals were found dead 24 hours following the first rhASM administration. There were no antecedent adverse clinical observations immediately prior to nor following individual dose administrations. Gross necropsies could not be conducted, due to extensive organ/tissue autolysis.

Table 77. 04-0506 Pnp Study Design and Method

Group	N	Dose (mg/kg)	Route and Regimen	Tissues	Comment
1	10	5	IV, at t =0, 2, 4, 6h	Carcasses in NBF	All animals found dead 24h after first dose administration. No antecedent clinical signs. Gross necropsies not conducted.

Source: Review Team.
Abbreviations: h, hours; IV, intravenous; N, total number of subjects; NBF, neutral buffered formalin.

Table 78. The Evaluation of Tissue SPM Levels From the Repeat Dose Toxicity Study in ASMKO Mice

Study Parameter	Study Information
Study no.:	04-0813 Pnp*
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	January 7, 2005
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049DP, purity unspecified

Source: Review team.
* Tissue SPM levels from organs removed in Study 04005.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin.

Key Study Findings

Administration of rhASM in ASMKO mice (0.3, 1.0, 3.0 mg/kg IV) every other week for 12 weeks effected profound reductions in SPM levels in liver (93-99%, unrelated to dose) and spleen (dose-related, 83 -100%); there were lesser, dose-related reductions in lung SPM content (17-62%). Survival was unaffected at any dose, when compared to that in ASMKO mice that received vehicle.

Study design and methods are outlined with the review of repeated-dose toxicity study Genzyme 04005.

Results

Tissue SPM levels are reproduced in Table 79.

Table 79. Tissue SPM Levels After 12 Weeks rhASM Treatment

Dose (mg/kg)	Liver	Spleen	Lung
Necropsy at End of Dosing, SPM (mg/g Tissue)			
0 (vehicle)	91.52±13.8	67.3±14.9	34.0±6.5
0.3	2.3+4.0	11.6+3.0	23.0+3.1
1.0	5.6±8.0	0.8±1.7	13.4±2.8
3.0	6.2+7.7	BLD	14.3±7.1
Necropsy 4 Weeks Following End of Dosing, SPM (mg/g Tissue)			
0 (Vehicle)	108.4±13.8	76.5±13.4	27.1±7.1
3.0	31.8±9.7	13.7±3.4	29.2±3.9

Source: Review team.
Abbreviations: BLD, below limit of detection; rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin.

Table 80. The Effects of Dosing rhASM, Dosed Every Other Day at 3 mg/kg for a Total of Four Doses, Then Dosed at 20 mg/kg 72h Following the Final 3 mg/kg Dose

Study Parameter	Study Information
Study no.:	04-0889 Pnp
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	January 7, 2005
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049DP, purity unspecified

Source: Review team.
Abbreviations: GLP, good laboratory practices; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

Administration of repeated doses (3 mg/kg) rhASM prior to the administration of a dose known to be lethal (20 mg/kg) prevented adverse clinical observations, mortality, and previously-associated histopathological findings consistent with hypotension and shock.

Table 81. 04-0889 Study Design and Methods

Group	N	Doses (mg/kg), Regimen	Tissues Collected	Comments
1	6	3 on days 1,4,6,8 20 on Day 11	Liver, spleen, kidney, lung, adrenal, heart, brain	Necropsies scheduled for Study Days 15 (N=4) and 18 (N=2). All animals survived to necropsy; there were no adverse clinical observations and no necropsy observations. Results of histopathological evaluation were limited to small numbers of inflammatory cell clusters in the liver: leukocytes were noted around and migrating through the central vein; there was no evidence of vasculitis, nor lesions suggestive of hypotension (e.g., adrenal cortical necrosis, renal tubular necrosis).

Source: Review team.
Abbreviations: N, total number of subjects.

Table 82. The Analysis of Serum and Tissue Samples From Acid ASMKO Mice for Cytokine Levels Following Administration of rhASM

Study Parameter	Study Information
Study no.:	05-0127 Pnp
Study report location:	001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	February 23, 2005
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, Lot SM049DP, purity unspecified

Source: Review Team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

Administration of a single, lethal dose of rhASM (20 mg/kg) to ASMKO mice produced marked increases in granulocyte colony stimulating factor (G-CSF) and interleukin (IL)-6, beginning at the 3 hour timepoint. Whether these increased levels are causally-related to rhASM toxicity in ASMKO mice was not determined in this study. Minor increases in nitric oxide (NO) end products (NS) were reported, although sample sizes were small and inter-individual variability was high at 1, 3, 4, and 6 hour timepoints.

Table 83. 05-0127 Study Design and Methods

Group	N	Dose (mg/kg)	Time (h)	Tissues Collected	Comments
1	3	0	0	Blood for serum; Liver, spleen for cytokine; liver, spleen, lung for biochem; liver, spleen, lung adrenal for EM/histopath	No clinical observations. No cytokine elevations.
2	4	20	1		No clinical observations. No cytokine elevations
3	4		2		No clinical observations. No cytokine elevations.
4	4		3		No clinical observations. Significant increases in IL-6>10,000 pg/mL), G-CSF (10000-100000 pg/mL); lesser increases in IL-1α, IL-1β, MIP-1α.
5	4		4		No clinical observations. Significant increases in IL-6>10,000 pg/mL), G-CSF (10000-100000 pg/mL); lesser increases in IL-1α, IL-1β, MIP-1α.
6	4		6		Mice began to show signs of lethargy. Significant increases in IL-6>10,000 pg/mL), G-CSF (10000-100000 pg/mL); lesser increases in IL-1α, IL-1β, MIP-1α. 2-fold increase in serum nitrate/nitrite levels (evidence of NO-vasodilatory mediation?).

Source: Review team.
Abbreviations: EM, electron microscopy; G-CSF, granulocyte colony-stimulating factor; h, hour; IL, interleukin; MIP, ; N, total number of subjects; NO, nitric oxide.

Results

See Table 84 below. Briefly, serum concentrations of several cytokines were increased, with the greatest increases observed for G-CSF (1331-fold) and IL-6 (258-fold). The increases in G-CSF and IL-6 were first observed at 2 hours, well before the first overt signs of toxicity (6 hours). Keratinocyte chemoattractant (KC) was increased by 14.8-fold. Much smaller increases (1.6- to 3.9-fold) were observed for IL-1α, IL-1β, IL-3, IL-10, IL-12 (p40), tumor necrosis factor (TNF)-α, macrophage inflammatory protein-1 (MIP-1)α, and RANTES. Increased levels of IL-1α, IL-1β, IL-6, and G-CSF are consistent with an acute phase inflammatory response.

To determine whether cytokine production was associated with potential vasoactive mediators that might contribute to hypotension, serum NO levels were estimated through measurement of the NO metabolites nitrite and nitrate. No statistically significant changes in serum levels of NO or C-reactive protein (CRP) were observed. However, the NO concentration at 6 hours was 2.3-fold higher than the control value. The results are shown in Table 85 below.

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Table 84. Concentrations of Cytokines Examined After Administration of a Single Dose (20 mg/kg) rhASM to ASMKO Mice Over a 6h Time Course

	Serum Concentration (pg/ml)					
Cytokine	Vehicle Control	1 hr	2 hr	3 hr	4 hr	6 hr
IL-1α	71.8 ± 40.6	41.2 ± 3.3	62.9 ± 19.8	226.3 ± 37.6*	261.1 ± 27.4*	200.7 ± 22.9*
IL-1β	94.6 ± 16.0	82.9 ± 25.6	142.9 ± 38.0	355.4 ± 67.4*	366.8 ± 57.3*	241.6 ± 41.1*
IL-2	31.2 ± 5.5	28.6 ± 5.8	42.2 ± 12.2	31.6 ± 5.6	37.8 ± 12.7	33.0 ± 12.6
IL-3	12.3 ± 7.4	6.2 ± 2.8	14.3 ± 5.4	28.9 ± 4.5*	38.4 ± 11.4*	23.7 ± 11.8
IL-4	2.2 ± 0.7	1.0 ± 0.4	2.3 ± 0.9	2.9 ± 0.5	3.6 ± 1.2	2.0 ± 0.7
IL-5	27.4 ± 7.6	13.0 ± 4.8*	19.3 ± 4.8	35.2 ± 4.3	37.8 ± 8.4	33.4 ± 7.3
IL-6	117.3 ± 21.3	103.8 ± 22.3	1762 ± 606*	22011 ± 14603 [a]	30294 ± 22749 [a]	12249 ± 2189*
IL-10	206.5 ± 26.8	165.1 ± 31.3	237.9 ± 70.5	258.8 ± 28.4	341.7 ± 74.2*	332.3 ± 98.5
IL-12 (p40)	677.4 ± 155.6	517.2 ± 65.9	962.5 ± 289.2	1360 ± 437	1418 ± 272*	1043 ± 285
IL-12 (p70)	169.4 ± 118.2	98.6 ± 20.9	131.9 ± 40.4	197.4 ± 22.2	260.1 ± 81.4	206.7 ± 73.7
IL-17	93.4 ± 20.3	78.4 ± 15.2	115.2 ± 37.6	64.9 ± 5.8	83.6 ± 41.3	76.2 ± 47.4
G-CSF	62.2 ± 8.3	93.8 ± 75.8	104.9 ± 26.8*	8783 ± 5056*	82810 ± 51175[a]	47318 ± 4601[a]
GM-CSF	1496 ± 1	1495 ± 2	1499 ± 3	1504 ± 1*	1507 ± 1*	1504 ± 1*
IFN-γ	174.5 ± 30.0	156.1 ± 25.7	292.1 ± 110.0	141.2 ± 19.8	197.8 ± 126.3	155.2 ± 96.0
TNF-α	387.2 ± 113.5	368.8 ± 68.4	607.7 ± 233.9	509.4 ± 65.6	625.7 ± 190.0	443.8 ± 202.6
KC	63.4 ± 14.9	41.1 ± 6.6*	941.8 ± 437.8*	ND	ND	ND
MIP-1α	136.7 ± 18.7	121.6 ± 29.22	234.7 ± 46.2*	359.2 ± 51.9*	444.0 ± 68.6*	402.0 ± 62.5*
RANTES	241.9 ± 146.9	150.3 ± 27.1	190.9 ± 61.0	363.2 ± 25.4	419.2 ± 112.8	320.4 ± 71.9

Values are the mean ± S.D. of 4 mice/time-point.
ND: not determined due to values that exceeded the standard range
a: extrapolated values that exceeded the standard range
*$p < 0.05$

Source: IND 012757 Review, pg. 58.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; hr, hour; IFN, interferon; IL, interleukin; KC, keratinocyte chemoattractant; MIP, macrophage inflammatory protein; ND, not determined due to values that exceeded the standard range; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; SD, standard deviation; TNF, tumor necrosis factor.

Table 85. Concentrations of Serum NO and CRP After Administration of a Single Dose (20 mg/kg) rhASM to ASMKO Mice Over a 6h Time Course

Serum Analyte	Vehicle Control	1 hr	2 hr	3 hr	4 hr	6 hr
Nitric oxide (µM)	28.4 ± 3.6	52.9 ± 27.2	24.2 ± 3.1	46.2 ± 15.0	39.6 ± 10.5	66.2 ± 26.7
CRP (µg/ml)	12.0 ± 0.5	14.3 ± 8.8	16.4 ± 4.8	15.6 ± 4.9	10.6 ± 2.8	16.8 ± 6.6

Values are the mean ± S.D. of 4 mice/time-point.

Source: IND Review, pg. 59.
Abbreviations: CRP, C-reactive protein; hr, hour; NO, nitric oxide.

Table 86. The Analysis of Cytokine Profiles of Various Doses of rhASM to ASMKO Mice

Study Parameter	Study Information
Study no.:	05-0374 Pnp
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	April 21, 2005
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM049DP, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

Single administrations of three dose levels of rhASM to ASMKO mice evoked dose-related increases in two cytokines (G-CSF and IL-6) at three and four hours post-dose. IL-1α, IL-1β ~ and MIP-1 α were increased relative to levels in untreated animals, but increases were unrelated to dose. There were no group mean increases in TNF-α at any dose or time point.

Reviewer's Comments: At the time of IND review, Keratinocyte chemoattractant (KC) values were labeled as out of range. The report was subsequently amended to indicate that KC was increased by doses 3 and 10 mg/kg at 9 hours; and, additionally, by the 10 mg/kg dose at 3, 4, and 6 hours.

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Table 87. 05-0374 Study Design and Methods

Group	N	Dose (mg/kg)	Blood Collection	N per Timepoint	Tissues Collected	Comments
1	3	0	Pre-dose	3	Blood;	[baseline cytokine levels]
2	15	0.3	2,3,4,6,9h		Liver, spleen, lungs, adrenal for cytokines	No increases in cytokine levels
3	15	3.0			Liver, spleen, lungs	Dose-related increases in
4	15	10			frozen	G-CSF and IL-6 at 3, 4h; comparable increases at 9h. Increases in the other cytokines at 3,4,6h relative to baseline. 10 mg/kg evoked increases in KC at 3,4,6h; 3 and 10 mg/kg evoked increases at 9h.

Source: Review team.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; h, hour; IL, interleukin; KC, keratinocyte chemoattractant; N, total number of subjects.

Results

Cited directly from the IND Safety Review (pp 63-64):

> The most notable effect in the 0.3 mg/kg group was the increased IL-6 concentrations, which were 43-244% greater than the control values at 2-6 hr post-dose. [Additional] Cytokine increases that were limited to single time points were observed for IL-1α (42% at 9 hr), IL-3 (129% at 3 hr), IL-5 (4.7-fold at 6 hr), IL-12 (p40) (58% at 3 hr), G-CSF (81% at 6 hr), TNF-α (3.4-fold at 3 hr), and RANTES (40% at 3 hr).
>
> In the 3 mg/kg group, the greatest increases were observed for G-CSF (106-fold), KC (104-fold), and IL-6 (64-fold). Other cytokines that were increased include the following: IL-1α (126-164% at 6-9 hr), IL-1β (116% at 6 hr), IL-3 (119% at 3 hr), IL-4 (103% at 3 hr), IL-10 (42-57% at 3-9 hr), IL-12 (p40) (132-171% at 6-9 hr), IL-12 (p70) (106% at 3 hr), IL-17 (55% at 3 hr), GM-CSF (46-59% at 3-9 hr), IFN-γ (75% at 3 hr), TNF-α (113% at 3 hr), MIP-1α (62-90% at 3-9 hr), and RANTES (42% at 3 hr).
>
> The cytokine profile in the 10 mg/kg group was generally comparable to that of the 3 mg/kg group. It is noteworthy that 10 mg/kg was established as the minimum lethal dose in ASMKO mice. IL6, G-CSF, and KC were increased by up to 536-fold, 93-fold, and 64-fold, respectively. The IL-6 levels at 10 mg/kg were substantially greater than that observed at 3 mg/kg, whereas G-CSF and KC levels were similar at these doses. Thus, IL-6 may be the most important indicator of acute toxicity among the cytokines measured in this study. Other cytokines that were increased include the following: IL-1α (104% at 6 hr), IL-1β (65-82% at 3-4 hr), IL-3 (126% at 3 hr), IL-10 (46-66% at 2-6 hr), IL-12 (p40) (57% at 6 hr), TNF-α (52-83% at 2-3 hr), and RANTES (53% at 3 hr). Transient decreases in IL-2, IL-5, IL-12 (p70), IL-17, and IFN-γ were also observed.

Values for all cytokines **(exception: discount KC values)** at 3 mg/kg are reproduced in Table 88. Values for all cytokines at 10 mg/kg **(exception: discount KC values)** are reproduced in Table 89. Amended report values for KC are reproduced in Table 90.

Table 88. Serum Cytokine Concentrations After Administration of rhASM 3 mg/kg

	Serum Concentration (pg/ml) after Treatment with 3 mg/kg					
Cytokine	Vehicle Control	2 hr	3 hr	4 hr	6 hr	9 hr
IL-1α	90.9 ± 15.9	91.3 ± 37.7	148.3 ± 63.3	89.7 ± 12.2	240.3 ± 64.8*	206.0 ± 53.6*
IL-1β	124.2 ± 23.7	115.0 ± 54.3	180.2 ± 114.0	123.9 ± 43.4	268.1 ± 33.1*	252.1 ± 87.4
IL-2	61.8 ± 11.3	56.0 ± 19.8	86.4 ± 32.1	52.7 ± 0.7	49.3 ± 10.8	66.1 ± 22.6
IL-3	22.8 ± 4.6	17.8 ± 8.5	50.0 ± 28.7	20.5 ± 4.3	31.7 ± 3.4	37.2 ± 16.9
IL-4	3.3 ± 0.8	1.9 ± 0.7	6.7 ± 3.5	3.0 ± 0.4	3.3 ± 1.3	4.1 ± 1.8
IL-5	58.0 ± 8.9	54.5 ± 10.9	70.6 ± 25.1	48.8 ± 2.4	49.2 ± 8.9	67.2 ± 28.7
IL-6	126.4 ± 26.0	140.0 ± 39.1	2602 ± 1070*	7736 ± 2644*	ND	8044 ± 3023*
IL-10	138.0 ± 26.5	115.4 ± 48.2	216.3 ± 127.6	145.4 ± 16.9	196.7 ± 17.5*	216.5 ± 92.6
IL-12 (p40)	1653 ± 160	1211 ± 378	1629 ± 375	2166 ± 1059	4474 ± 501*	3831 ± 958*
IL-12 (p70)	1103 ± 212	1239 ± 784	2282 ± 1075	1292 ± 342	1342 ± 573	1739 ± 580
IL-17	989.2 ± 167.3	1025 ± 366	1534 ± 608	911.0 ± 123.3	701.2 ± 267.5	903.9 ± 204.7
G-CSF	172.5 ± 98.7	109.6 ± 24.5	389.4 ± 286.6	836.4 ± 522.1	16487 ± 607*	18297 ± 392*
GM-CSF	98.4 ± 15.2	90.1 ± 30.2	148.1 ± 51.7	105.9 ± 7.3	143.6 ± 10.6*	156.9 ± 47.2
IFN-γ	161.2 ± 35.3	158.8 ± 63.1	281.7 ± 118.6	169.3 ± 18.6	153.1 ± 51.7	188.2 ± 61.2
TNF-α	654.7 ± 189.6	642.5 ± 303.1	1393 ± 686	807.9 ± 213.7	814.3 ± 187.1	991.0 ± 456.5
KC	84.2 ± 16.2	70.8 ± 3.9	1498 ± 1487	3257 ± 1136*	ND	8774 ± 6940
MIP-1α	216.2 ± 39.2	183.0 ± 55.1	351.3 ± 121.6	238.2 ± 11.8	372.0 ± 21.9*	411.9 ± 119.6
RANTES	477.6 ± 86.1	425.6 ± 150.3	680.6 ± 69.1*	456.3 ± 53.2	529.4 ± 70.5	641.9 ± 257.4

Values are the mean ± S.D. of 3 mice/time-point.

Source: IND 012757 review, pg 62.
* Statistically significant
Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; hr, hour; IFN, interferon; IL, interleukin; KC, keratinocyte chemoattractant; MIP, macrophage inflammatory protein; ND, not determined due to values that exceeded the standard range; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; SD, standard deviation; TNF, tumor necrosis factor.

Table 89. Serum Cytokine Concentrations After Administration of rhASM 10 mg/kg

	Serum Concentration (pg/ml) after Treatment with 10 mg/kg					
Cytokine	Vehicle Control	2 hr	3 hr	4 hr	6 hr	9 hr
IL-1α	90.9 ± 15.9	120.8 ± 38.7	89.6 ± 18.7	158.9 ± 48.4	185.9 ± 59.9	124.4 ± 32.9
IL-1β	124.2 ± 23.7	187.6 ± 54.9	205.1 ± 30.1*	226.2 ± 76.6	225.1 ± 41.0*	159.8 ± 30.9
IL-2	61.8 ± 11.3	87.4 ± 24.3	49.6 ± 16.7	32.4 ± 4.0*	48.6 ± 16.9	48.7 ± 3.5
IL-3	22.8 ± 4.6	36.3 ± 13.6	51.6 ± 44.3	16.8 ± 6.3	22.6 ± 7.2	16.9 ± 5.7
IL-4	3.3 ± 0.8	5.4 ± 2.3	3.5 ± 1.0	1.8 ± 0.5	2.6 ± 1.7	2.7 ± 0.4
IL-5	58.0 ± 8.9	72.6 ± 19.0	57.3 ± 13.7	32.6 ± 6.1*	55.7 ± 17.0	94.5 ± 37.0
IL-6	126.4 ± 26.0	1472 ± 893	12180 ± 2509*	67758 ± 60099	26229 ± 14185*	18521 ± 9609*
IL-10	138.0 ± 26.5	216.0 ± 73.8	228.6 ± 16.5	223.1 ± 81.3	202.2 ± 18.5*	171.4 ± 5.0
IL-12 (p40)	1653 ± 160	1674 ± 541	1858 ± 184	2010 ± 924	2603 ± 489*	2530 ± 97.5*
IL-12 (p70)	1103 ± 212	1973 ± 775	1272 ± 397	551.5 ± 270.0*	945.7 ± 367.7	899.1 ± 243.2
IL-17	989.2 ± 167.3	1281 ± 226	736.2 ± 313.8	290.6 ± 100.1*	588.3 ± 424.9	500.9 ± 101.6*
G-CSF	172.5 ± 98.7	128.0 ± 27.0	925.0 ± 346.7*	12311 ± 3848*	15527 ± 629*	16033 ± 1206*
GM-CSF	98.4 ± 15.2	131.9 ± 33.5	113.2 ± 20.8	112.8 ± 22.8	124.6 ± 22.7	120.7 ± 10.8
IFN-γ	161.2 ± 35.3	248.0 ± 82.6	139.0 ± 54.2	59.5 ± 15.9*	119.9 ± 58.1	104.7 ± 19.5
TNF-α	654.7 ± 189.6	1199 ± 604	996.8 ± 293.7	359.2 ± 74.4	564.0 ± 339.2	453.4 ± 54.3
KC	84.2 ± 16.2	216.8 ± 116.9	5429 ± 1018*	4398 ± 137*	3557 ± 351*	3275 ± 426*
MIP-1α	216.2 ± 39.2	250.2 ± 50.3	238.3 ± 44.7	213.4 ± 38.7	263.2 ± 28.5	273.5 ± 29.7
RANTES	477.6 ± 86.1	514.4 ± 35.5	732.7 ± 428.3	407.2 ± 325.3	464.7 ± 118.7	441.5 ± 133.0

Values are the mean ± S.D. of 3 mice/time-point.

Source: IND 012757 review, pg 63.
* Statistically significant.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; hr, hour; IFN, interferon; IL, interleukin; KC, keratinocyte chemoattractant; MIP, macrophage inflammatory protein; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; SD, standard deviation; TNF, tumor necrosis factor.

Table 90. Time Course of Keratinocyte Chemoattractant (KC) Levels Following Administration of 3 Dose Levels of rhASM

Cytokine	Vehicle	Dose	2h	3h	4h	6h	9h
KC	[84.2±16.2]	0.3	52.12.±12.66	21.49±0.71	64.43±17	112.2±2.98	79.29±18.46
		3	70.78±3.88	1497.71±1496.92	3257±1136	[out of range]	8774±6940
		10	216.79±116.89	5248.71±1018.14	4398±137	3557±351	3725±426

Source: Review team.
* Out of range.

Table 91. The Cytokine Profile of ASMKO Mice After Every Other Day Dosing of rhASM at 3 mg/kg Followed by 20 mg/kg or rhASM

Study Parameter	Study Information
Study no.:	05-0437 Pnp
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	June 3, 2005
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	SM049

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

When administered to ASMKO mice every other day, 3 mg/kg rhASM produced increases in pro-inflammatory cytokines comparable to those previously described after the first, although not subsequent, 3 mg/kg doses. When this series was followed by a single 20 mg/kg dose, there was no further release of cytokines, nor mortality through 12 hours after administration of this known lethal dose.

Table 92. 05-0437 Study Design and Methods

Group #	# of Animals	Dose mg/kg	Days of Dosing	Time Point After Last Dose	Route of Administration	Tissue Collection
1	6	3mg/kg rhASM	Study Day 1	4, 9 hours	IV	Blood was collected for serum and plasma and stored frozen at -80°C Liver, Spleen and Lungs were frozen in liquid nitrogen and stored at -80°C. All tissues were taken for possible future analysis.
2	6	3,3mg/kg rhASM	Study Day 1 and 4	4, 9 hours		
3	6	3,3,3mg/kg rhASM	Study Day 1, 4, and 6	4, 9 hours		
4	6	3,3,3,3mg/kg rhASM	Study Day 1, 4, 6, and 8	4, 9 hours		
5	3	3,3,3,3,20mg/ kg rhASM	Study Day 1, 4, 6, 8, and 11	3 hours		
6	3	3,3,3,3,20mg/ kg rhASM	Study Day 1, 4, 6, 8, and 11	4 hours		
7	3	3,3,3,3,20mg/ kg rhASM	Study Day 1, 4, 6, 8, and 11	6 hours		
8	3	3,3,3,3,20mg/ kg rhASM	Study Day 1, 4, 6, 8, and 11	9 hours		
9	3	3,3,3,3,20mg/ kg rhASM	Study Day 1, 4, 6, 8, and 11	12 hours		

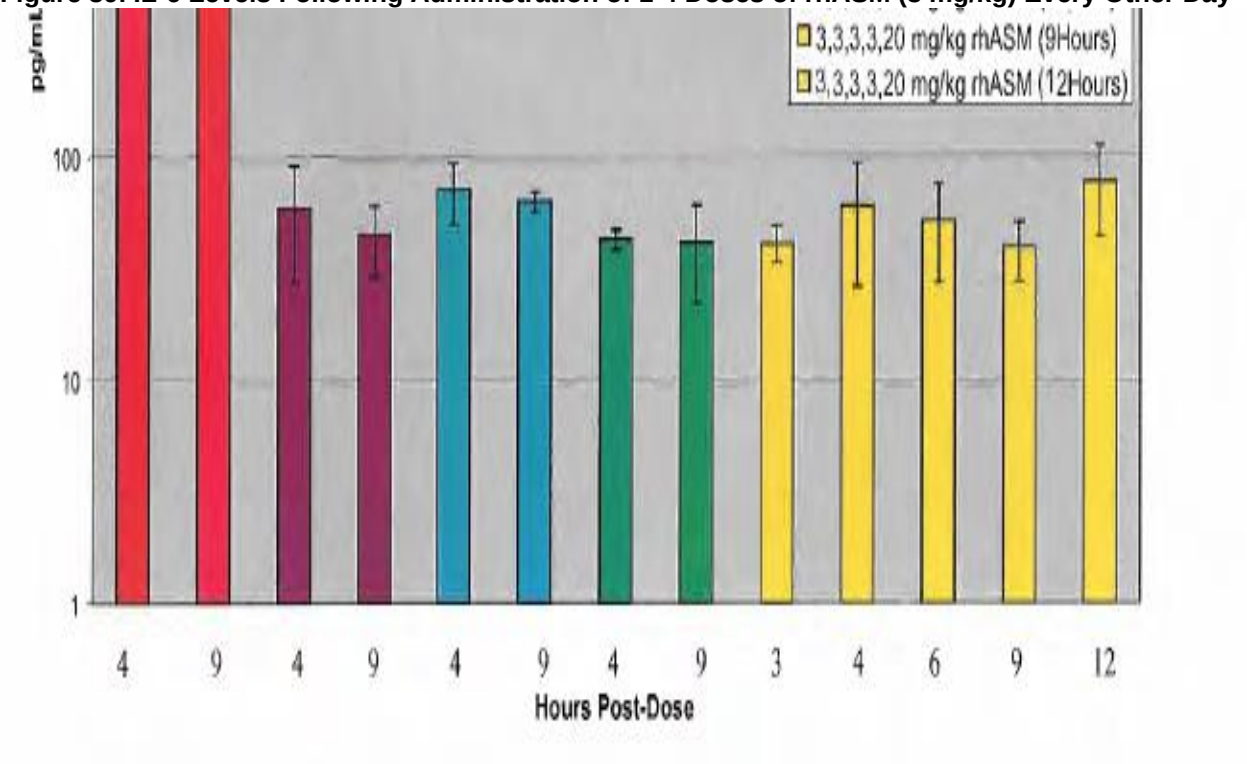
Source: Genzyme, Study Report 05-0437.
Abbreviations: IV, intravenous; rhASM, recombinant human acid sphingomyelinase.

Results

Serum samples showed an increase in pro-inflammatory cytokines (IL-6, IL-1α and β, G-CSF, M1p1 α , etc.) as previously reported, albeit only following administration of the first 3 mg/kg dose. Thereafter cytokine levels were not elevated, despite subsequent doses of 3 mg/kg; nor were cytokine levels increased after administration of a 20 mg/kg dose. A sample profile (IL-6) is included below in Figure 39.

The same temporal profile was observed for all cytokines previously reported to be increased following rhASM administration. Notably, mice dosed with rhASM 20 mg/kg survived for 12 hours after administration of a known lethal dose.

Figure 39. IL-6 Levels Following Administration of 1-4 Doses of rhASM (3 mg/kg) Every Other Day



Source: Genzyme, Study Report 05-0437 Pnp, pg 7.
Abbreviations: IL, interleukin; rhASM, recombinant human acid sphingomyelinase.

Table 93. A Study to Evaluate the Effects of rhASM on Cardiovascular Hemodynamics in Conscious Telemeterized ASMKO Mice

Study Parameter	Study Information
Study no.:	05-0533 Pnp
Study report location:	001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 12, 2005
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, 12409-017, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; (b) (4) N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

This study examined hemodynamic parameters following: 1). administration of a single dose of rhASM (0, 10, or 20 mg/kg) to conscious, instrumented ASMKO mice from time of administration to death/unscheduled euthanasia of animals in rhASM-treated groups – designated Subset 1; 2). Sequential administrations of vehicle/rhASM (0, 3, 3 mg/kg) on study days 1, 5, 9 – designated Subset 2. (A single animal that received 10 mg/kg from subset 1 survived and was dosed again on study day 9.)

rhASM produced dose-related peak reductions in heart rate (3 mg/kg and higher) and blood pressure (10 and 20 mg/kg). The onset of these effects was delayed for 1 to 3 hours after dosing, which suggests the involvement of a product/products generated by acid sphingomyelinase (ASM) activity, or a catabolite of rhASM degradation. Hemodynamic parameter declines were generally monotonic among animals found dead.

All subset 1 animals survived to scheduled euthanasia.

Reviewer's Comments: There were no clear differences in effects on systolic or diastolic blood pressure measurements. As such, mean arterial pressure is used to denote changes in blood pressure.

Table 94. 05-0533 Study Design and Methods

Subset	Group	N	Prior to Study Initiation	Tx (mg/kg) (Day 1)	Tx (mg/kg) (Day 5)	Tx (mg/kg) (Day 9)	Comment
2*	1	4	ASMKO mice instrumented prior to study start to record C-V parameters	0 (vehicle)	3	3	Animals survived until scheduled sacrifice. Time course of HR: see Figure 40. Time Course of MAP: see Figure 45.
1	2	4		10	-	10-	3 of 4 animals found dead/euthanized from 56-75 h post dosing. Time Course of HR: see Figure 40 and Figure 42. Time course of MAP: see Figure 41 and Figure 43. A 2nd attenuation of MAP reductions after 48h did not resume normal circadian variation (not shown). The 4th animal that survived dosing on day 1 was re-dosed on day 9; declines in hemodynamic parameters were attenuated, relative to those on day 1 (data not shown).

Subset	Group	N	Prior to Study Initiation	Tx (mg/kg) (Day 1)	Tx (mg/kg) (Day 5)	Tx (mg/kg) (Day 9)	Comment
1	3	4		20	-	-	All animals found dead/euthanized by 43h after dosing. Time Course of HR: see Figure 40 and Figure 42. Time course of MAP: see Figure 41 and Figure 43. Death/euthanasia in 3/4 animals between 14-21h post-dose.

Source: Review team.
* Applicant designation of Group 1 as Subset 2, and Groups 2 and 3 as Subset 1.
Abbreviations: ASMKO, acid sphingomyelinase knockout; C-V, coefficient of variation; h, hour; HR, heart rate; MAP, mean arterial pressure; Tx, treatment.

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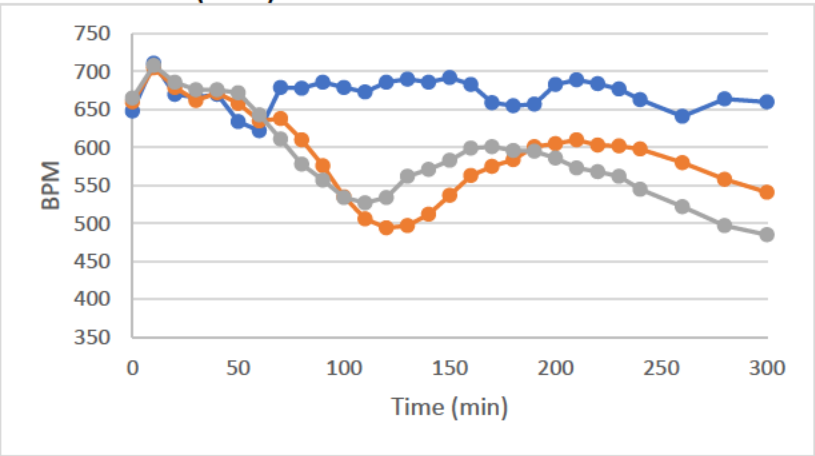
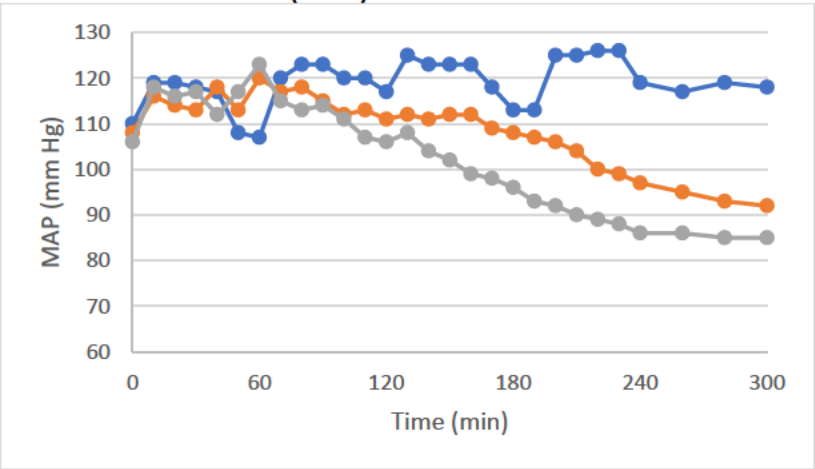
Figure 40. Heart Rate following 0, 10, 20 mg/kg rhASM Administration (0-5 h)



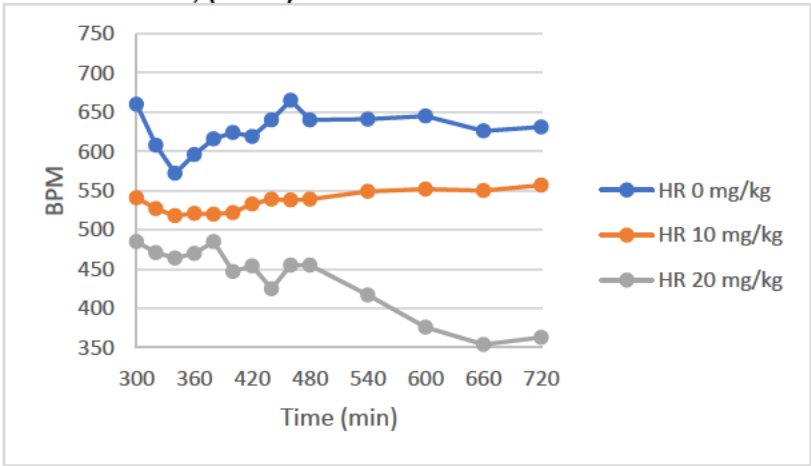
Source: Review team.
Abbreviations: BPM, beats per minute; h, hours; rhASM, recombinant human acid sphingomyelinase.

Figure 41. Mean Arterial Pressure Following 0, 10, 20 mg/kg rhASM Administration (0-5 h)



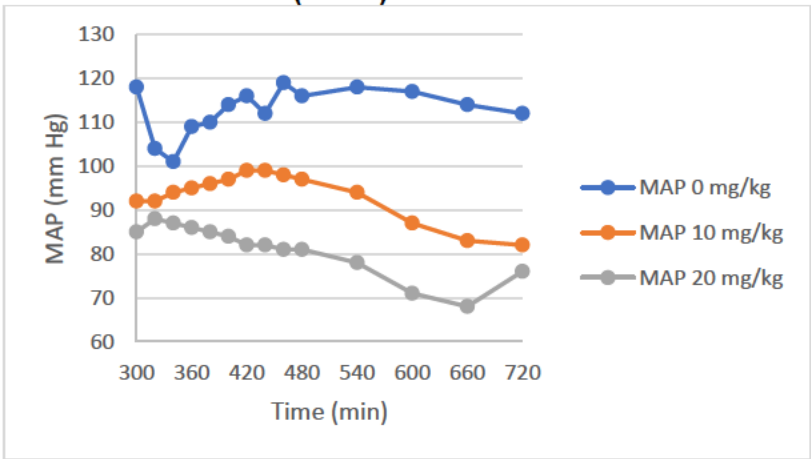
Source: Review team.
Abbreviations: MAP, mean arterial pressure; h, hours; rhASM, recombinant human acid sphingomyelinase.

Figure 42. Heart Rate following 0, 10, 20 mg/kg rhASM Administration, (5-12h)



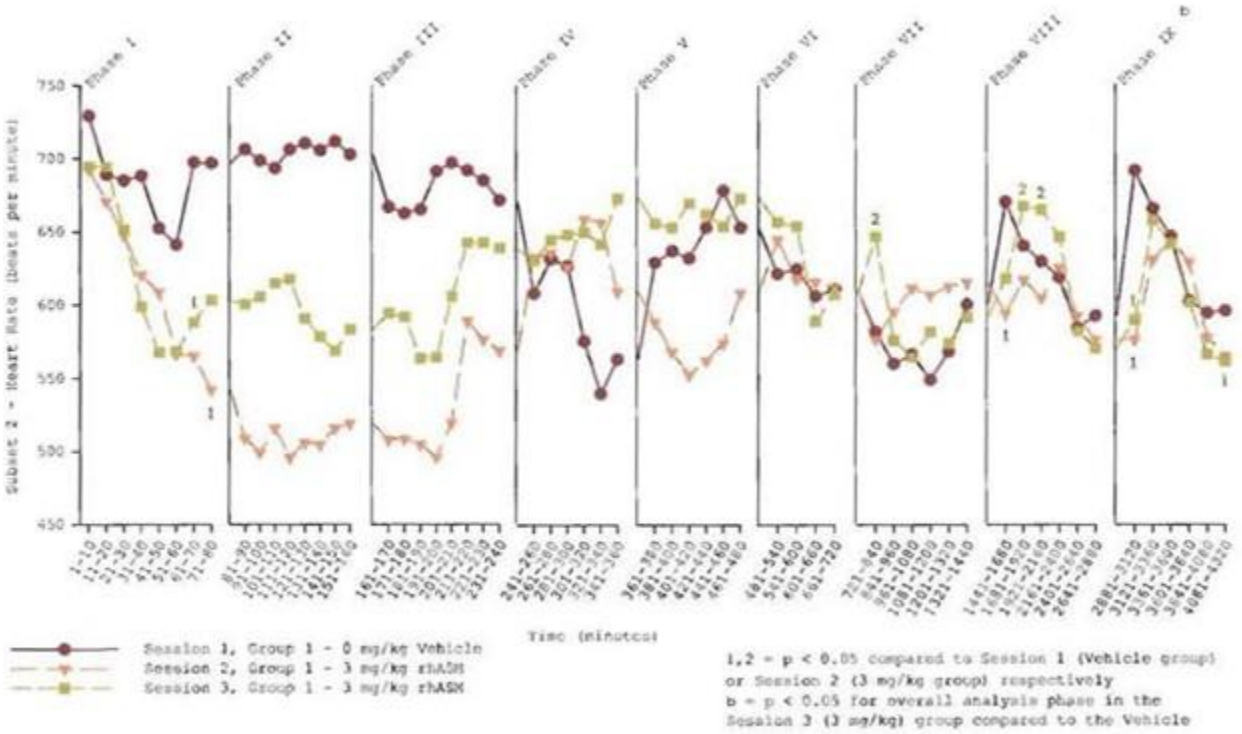
Source: Review team.
Abbreviations: BPM, beats per minute; h, hours; rhASM, recombinant human acid sphingomyelinase.

Figure 43. Mean Arterial Pressure following 0, 10, 20 mg/kg rhASM Administration (5-12 h)



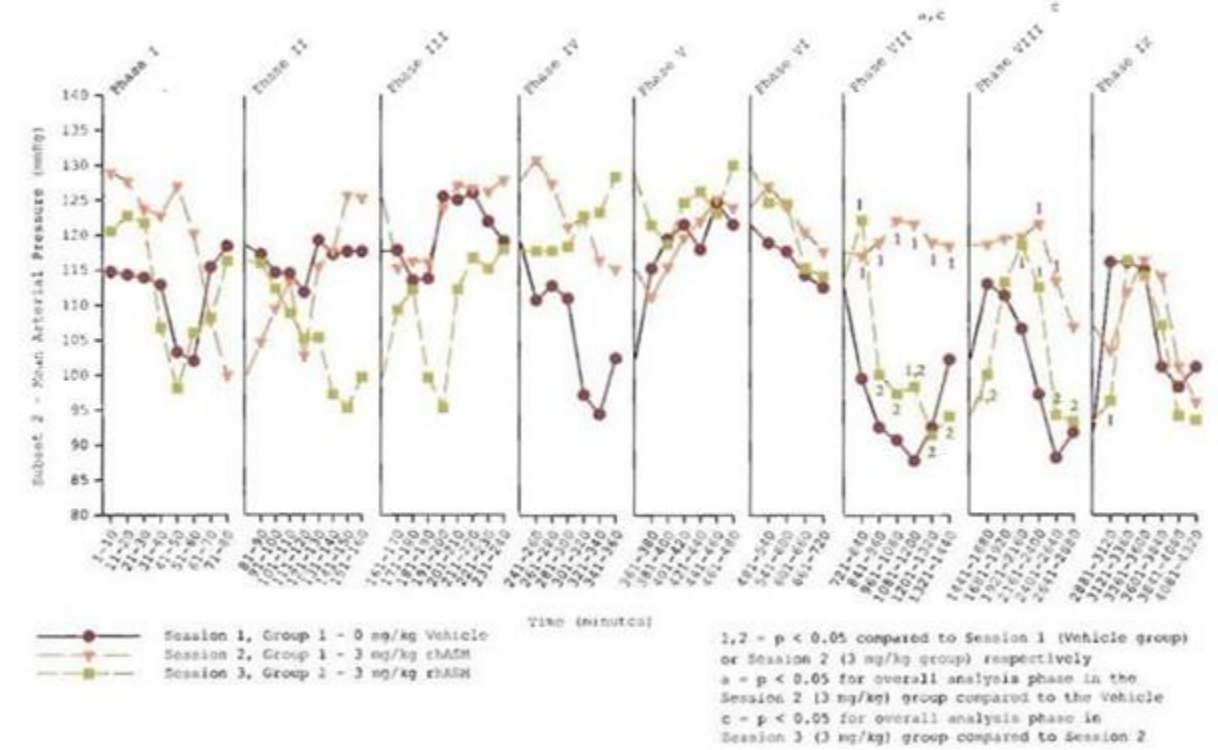
Source: Review team.
Abbreviations: MAP, mean arterial pressure; rhASM, recombinant human acid sphingomyelinase

Figure 44. Heart Rate Following Sequential Administration of 0, 3, 3 mg/kg (on Study Days 1, 5, 9)



Source: Applicant-generated. Final Report 05-0533 Pnp, pg. 26.

Figure 45. MAP Following Sequential Administration of 0, 3, 3 mg/kg (on Study Days 1, 5, 9)



Source: Applicant generated. Final Report 05-0533 Pnp, pg 27.

Table 95. The Collection of Serum and Tissues at Various Time Points Following a Single Dose of 20 mg/kg rhASM in ASMKO Mice

Study Parameter	Study Information
Study no.:	05-1008 Pnp
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	February 2, 2006
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM078, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

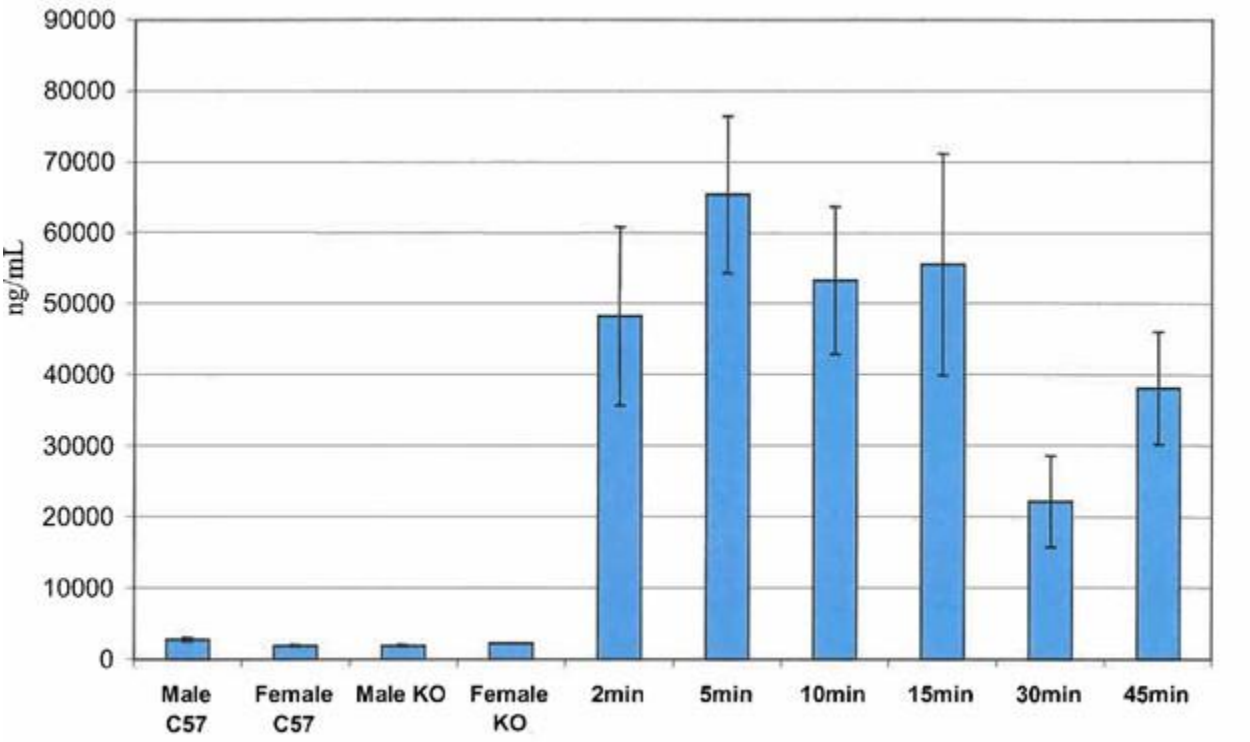
Serum cytokines, ceramide, sphingosine, and sphingosine-1-phosphate were profiled in untreated animals, and likewise from 2 to 45 min following administration of a single dose of rhASM (20 mg/kg) to ASMKO mice. Ceramide increases were rapid and large (from 2 to 15 min, ceramide levels >40,000 ng/mL); baseline levels in untreated animals were <300 ng/m. Serum ceramide may serve as an early marker of rhASM toxicity.

Table 96. 05-1008 Study Design and Methods

Group	N	Dose (mg/kg)	Time (min)	Tissues Collected	Comments
1	5	-	-	*	
2	5	20	2	Blood for serum cytokines, ceramide, sphingosine and S1P. Liver, spleen kidney, lung, heart frozen for potential future analysis	No treatment-related clinical observations, no changes in IL-6, GM-CSF, IL-1β, TNF-α. Large, rapid, increases in ceramide (at least 4 isoforms, of which C24:1 predominates) from 2-15 min; these fell off somewhat thereafter. See Figure 46. The Applicant states that serum Sphingosine, although not S1P1, may likewise be elevated; that said, the raw data depict the inverse. Since this experiment will be repeated 3 more times, the remaining data should clarify.
3	5		5		
4	5		10		
5	5		15		
6	5		30		
7	5		45		

Source: Review team.
* Necropsy conducted prior to dosing of treated animals.
Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; N, total number of subjects; S1P1, sphingosine-1-phosphate receptor 1; TNF, tumor necrosis factor.

Figure 46. Serum Ceramide Concentrations Shortly Following Administration of rhASM (20 mg/kg) to WT or ASMKO mice



Source: Genzyme Study Report 05-1008 PnP.
Abbreviations: ASMKO, acid sphingomyelinase knockout; KO, knockout; rhASM, recombinant human acid sphingomyelinase; WT, wild type.

Table 97. The Cytokine Profile and Acute Toxicity of ASMKO Mice Following a 3 mg/kg Dose of rhASM on Day 1 and 20 mg/kg on Day 3

Study Parameter	Study Information
Study no.:	05-1009 PnP
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	January 23, 2006
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM078, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Reviewer's Comments: This study used cytokine profiles reported in untreated ASMKO mice (see 05-0374, Group 1) as baseline data for comparisons with ASMKO mice treated on Study day 1 with 3 mg/kg, followed by 20 mg/kg on Study day 3. Further, results are herein contrasted to those in study 05-0127, in which rhASM (20 mg/kg) was administered to ASMKO mice, and temporal cytokine profiles were generated.

Key Study Findings

Cytokine profiles following treatment with rhASM 3 mg/kg and 20 mg/kg on study days 1 and 3, respectively, at hours 4 and 8-9 post-dose on study day 3, were generally comparable to those of untreated animals (see 05-0374); and in marked contrast to those reported in 05-0127, in which significant increases in IL-6 (>10,000 pg/mL), G-CSF (10000-100000 pg/mL), and lesser increases in IL-1α, IL-1β, MIP-1α were reported, prior to the onset of adverse clinical signs. It is

concluded that administration of a tolerated dose (3 mg/kg) 48 hours prior to administration of 20 mg/kg (a known lethal dose) precludes mortality in ASMKO mice. Further, neither the lethality noted in previous studies, nor the associated cytokine profile, were observed.

Table 98. 05-1009 Study Design and Methods

Group	N	Dose	Time of Nx	Samples collected	Comments
1 2	3 3	3, 20 mg/kg on Days 1, 3	4h Day 3 8-9h Day 3	Blood for serum cytokines. Liver, spleen, kidney, lung, heart frozen	After evoking an inflammatory cytokine response (day 1), all cytokine levels in groups 1 and 2 at 4 and 8-9h post 20 mg/kg administration on Study Day 3 were comparable to baseline levels from untreated animals in study 05-0374. [These are contrasted with increased levels reported from Study 05-0127 (see Table 84).]
3 4	3 3	3, 20 mg/kg on Day1,3	Day 28	None	Animals survived to Study Day 28. No further tissues were collected, nor was serum analyzed for cytokines.

Source: Review team.
Abbreviations: h, hour; N, total number of subjects; Nx, necropsy.

Table 99. The Cytokine Profile and Acute Toxicity in ASMKO Mice Following a 3 mg/kg Dose of rhASM on Day 1 and 20 mg/kg on Day 6

Study Parameter	Study Information
Study no.:	05-1240 Pnp
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	February 15, 2006
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, DM078DP, Purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

Cytokine profiles generated after treatment with rhASM 3 mg/kg and 20 mg/kg on study days 1 and 6, respectively, at hours 4 and 9 post-dose on study day 6, did not resemble those reported in 05-0127, in which significant increases in IL-6 (>10,000 pg/mL), G-CSF (10000-100000 pg/mL), and lesser increases in IL-1α, IL-1β, MIP-1α were reported. It is concluded that administration of a tolerated dose (3 mg/kg) 120 hours prior to administration of 20 mg/kg (a known lethal dose) precludes mortality in ASMKO mice and does not produce the cytokine profile associated with lethality in previous studies.

Table 100. 05-1240 Pnp Study Design and Methods

Group	N	Dose	Time of Nx	Samples Collected	Comments
1 2	6 (3/sex) 6 (3/sex)	3. 20 mg/kg on Days 1, 6	4h Day 6 9h Day 6	Blood for serum cytokines.	One mouse in group 1 found dead immediately following 20 mg/kg dose on day 6*. Another group 1 mouse observed with head tilt after at 4h after 20 mg/kg dose. After evoking an inflammatory cytokine response (day 1), all cytokine levels in groups 1 and 2 at 4 and 9h post 20 mg/kg administration on Study Day 6 were not elevated, when compared to increased levels reported from Study 05-0127 (see Table 84).

Source: Review team.
* Air bubbles detected in dosing solution; mortality not attributed to rhASM administration.
Abbreviations: h, hour; N, total number of subjects; Nx, necropsy; rhASM, recombinant human acid sphingomyelinase.

Table 101. 06-0129 Pnp Study Design and Methods

Group	N	Dose mg/kg	Time of Sampling (h)	Samples Taken	Comment
1 2 3 4 5 6	7	None 20	[Baseline] 0.083 0.5 1 4 9	Blood for plasma, serum ceramide, sphingosine, S1P. Liver, spleen kidney, lungs, heart frozen	To state the obvious: reliance on time course information is dependent on time points at which samples were collected. Whether ceramide release is truly biphasic is difficult to determine, given that no blood was collected between 1 and 4h; and that ceramide levels continue an apparent upward trajectory at 4 and 9h. See Figure 47 and Figure 48.

Source: Review team.
Abbreviations: h, hour; N, total number of subjects; S1P, sphingosine-1-phosphate.

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Figure 47. Plasma Ceramide Levels Following Administration of rhASM 20 mg/kg

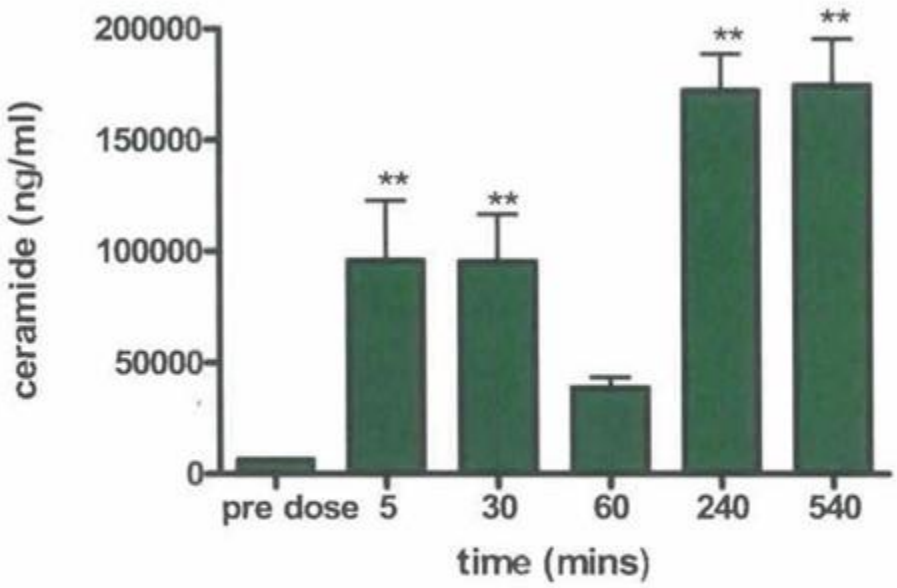


Figure 1: Time course measurement of the effect of rhASM (20 mg/kg) on plasma ceramide levels in ASMKO mice. Values are mean ± SD (n=5). Asterisks indicate significance compared to untreated ASMKO plasma.

Source: Genzyme report 06-0129 PnP, page 7.
Abbreviations: ASMKO, acid sphingomyelinase knockout; rhASM, recombinant human acid sphingomyelinase.

Figure 48. Plasma SPM, S1P Levels Following Administration of rhASM 20 mg/kg

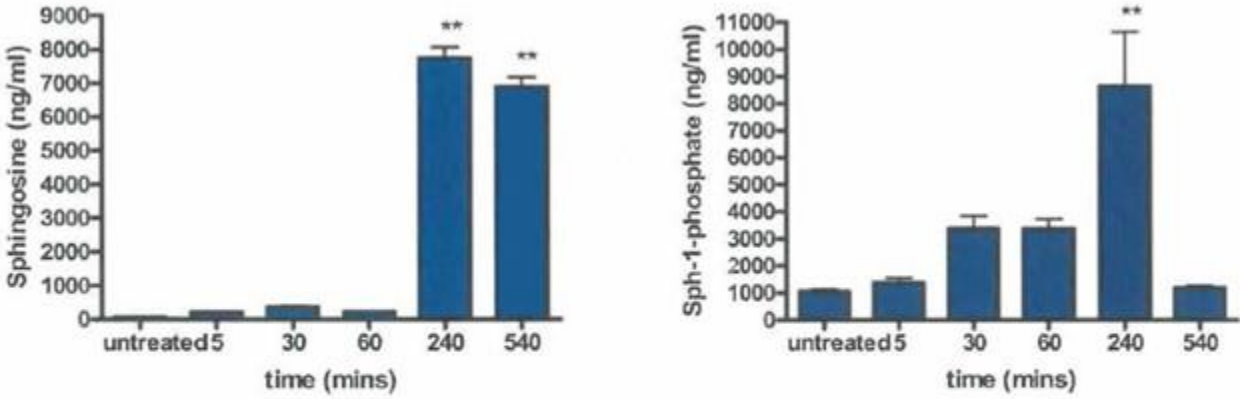


Figure 2: Time course measurement of the effect of rhASM (20 mg/kg) on plasma sphingosine and sphingosine-1-phosphate levels in ASMKO mice. Values are mean ± SD (n=5). Asterisks indicate significance compared to untreated ASMKO plasma.

Source: Genzyme report 06-0129 PnP, page 8.
Abbreviations: ASMKO, acid sphingomyelinase knockout; rhASM, recombinant human acid sphingomyelinase; S1P, sphingosine 1-phosphate; SD, standard deviation; SPM, sphingomyelin.

Table 102. An Investigation to Correlate Changes in Ceramide to Lethality in ASMKO Mice Administered rhASM

Study Parameter	Study Information
Study no.:	07-1346
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	May 22, 2007
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, lot SM049, purity unspecified

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

A late study amendment (2021) refuted the original conclusions of the study, which averred that increased levels of total plasma ceramide and the C16 isoform correlated with lethality and adverse clinical outcome after administration of intravenous olipudase alfa 10 or 20 mg/kg. Instead, C16 ceramide levels correlated with toxicity associated with 20 mg/kg, although not 10 mg/kg.

Table 103. An Evaluation of rhASM (Process C) Compared to rhASM (Process B) Following a Single Intravenous Administration at 1 and 3 mg/kg in ASMKO Mice

Study Parameter	Study Information
Study no.:	15-06259
Study report location:	0001
Conducting laboratory and location:	Genzyme/Sanofi, Framingham MA
Date of study initiation:	April 27, 2015
GLP compliance:	*
QA statement:	*
Drug, lot #, and % purity:	rhASM Process B, 14CT075, 4.0 mg/mL rhASM Process C, 105748: (b) (4) 3.89 mg/mL:

Source: Review team.
Note: Inclusion of a Regulatory Compliance Statement limited to the following description: "The study was conducted according to Sanofi's Global Quality Directive on Good Research Practices."
* No inspection page / dates for any study procedures.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

After administration of single doses of vehicle or rhASM 1 mg/kg or 3 mg/kg to ASMKO mice from manufacturing Processes B or C, plasma ceramide levels were elevated in 3 mg/kg groups from both processes at 540 minutes and 72 hours post-dosing, relative to vehicle-treated blood ceramide contents at these timepoints. (Comparisons were not conducted for 1 mg/kg dose groups.) Tissue SPM levels in liver, spleen and kidney were reduced in all rhASM-treated groups, relative to SPM levels in these tissues in vehicle-treated animals.

Reviewer's Comments: Considering the significant changes in manufacturing processes undergone over the course of development, this qualification study is de minimis. Further, statistical comparisons for blood ceramide content in experimental groups should be compared between Processes B and C; instead, the comparisons made were between each 3 mg/kg dose group and its respective vehicle-treated value. It is likely that the inherent variability in the data, when coupled with the low N, precludes detection of a statistically-significant difference in

plasma ceramide levels at 540 min (the timepoint with maximal ceramide levels), although mean data hint that rhASM from Process C is less potent than that from Process B for this endpoint.

Table 104. 15-06259 Study Design and Methods

Group	N (M/F)	Test article	Dose	Route of Administration and Regimen	Ceramide Blood Sample Timepoints	Tissue SPM Content 72h After Dosing
1	8/4	Process B Vehicle	0	IV, Single Dose	Analyses limited to groups 1, 2, 5, 6 at any timepoint. Day 0: 10, 45, 120, 540 min post-dose. Day 3: immediately prior to euthanasia.	All groups: liver (large lobe) spleen, kidney (left) harvested for SPM content analysis
2	8/4	Process C Vehicle	0			
3	7/5	Process B rhASM	1			
4	7/5	Process C rhASM	1			
5	7/5	Process B rhASM	3			
6	7/5	Process C rhASM	3			

Source: Review team.
Abbreviations: F, female; h, hour; IV, intravenous; M, male; N, total number of subjects; rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin.

ASMKO mice were 8 to 14 weeks at the time of dosing. Body weights were collected prior to dosing. Animals were anaesthetized to permit retro-orbital sinus blood collections using dried-blood-spot technology for blood ceramide content. Animals were euthanized by CO2 asphyxiation 72 hours after dosing.

Results

There were neither treatment-related clinical nor necropsy observations. Blood ceramide concentrations were comparable among experimental groups at 10, 45 and 120 minutes post-dose, although significantly elevated in both Process B and Process C groups at 540 minutes and 72 hours post-dose, as documented below in Table 105 Tissue SPM content is reproduced below in Table 106.

Table 105. Blood Ceramide Content Over Time After Administration of Single IV Doses (3 mg/kg) of Vehicle or rhASM From Processes B and C

	Blood Ceramide (µg/mL)*				
Group	10 min	45 min	120 min	540 min	72h
1	6.1±10.8	5.7±0.9	7.4±1.4	6.9±1.2	8.6±1.9
2	6.2±0.8	6.3±1.3	7.2±1.8	6.7±1.6	6.9±2.0
5	5.8±1.0	5.8±1.0	8.6±1.6	29.7±10.2****	14.6±5.3***
6	6.1+1.1	5.8±1.0	8.2±1.6	37.2±11.3****	14.5±5.4**

Source: Review team.
* Values represent 10-12 samples per time point.
** Represents statistical significance of unpaired t-tests at the level of p≤0.01.
*** Represents statistical significance of unpaired t-tests at the level of p≤0.001.
**** Represents statistical significance of unpaired t-tests at the level of p≤0.0001.
Note: Statistical comparisons are not between ceramide content in groups 5 and 6, but comparisons of group 5 with group 1, and group 6 with group 2.
Abbreviations: h, hour; IV, intravenous; rhASM, recombinant human acid sphingomyelinase.

Table 106. Tissue SPM Content After Administration of rhASM From Processes B and C (Mean ± SD)

Group	Liver*	Spleen*	Kidney*
1	41.0±8.7	24.6±6.8	20.2±2.6
2	40.3±9.8	25.0±7.1	19.0±3.9
3	8.9±5.1	11.8±4.3**	17.9±4.2**
4	6.8±4.9	9.7±4.2**	17.4±3.3**
5	5.2±3.8	8.0±3.5**	12.3±3.3**
6	4.5±1.8	7.0±1.5**	13.9±2.9**

Source: Review team.
* Values represent 10-12 samples per time point
** Represents statistical significance of unpaired t-tests at the level of p≤0.0001.
Note: Statistical comparisons are not between process B and C SPM contents for vehicle or rhASM-dosed groups, but comparisons of rhASM groups with Process B and C vehicle-treated groups.
Abbreviations: rhASM, recombinant human acid sphingomyelinase; SD, standard deviation.

13.1.2. Safety Pharmacology

Table 107. The Collection of Baseline Electrocardiogram Data From ASMKO Mice Using the ECGenie to Measure Heart Rate in Response to rhASM

Study Parameter	Study Information
Study no.:	06-0302
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	June 12, 2006
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	SM049 and SM078

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

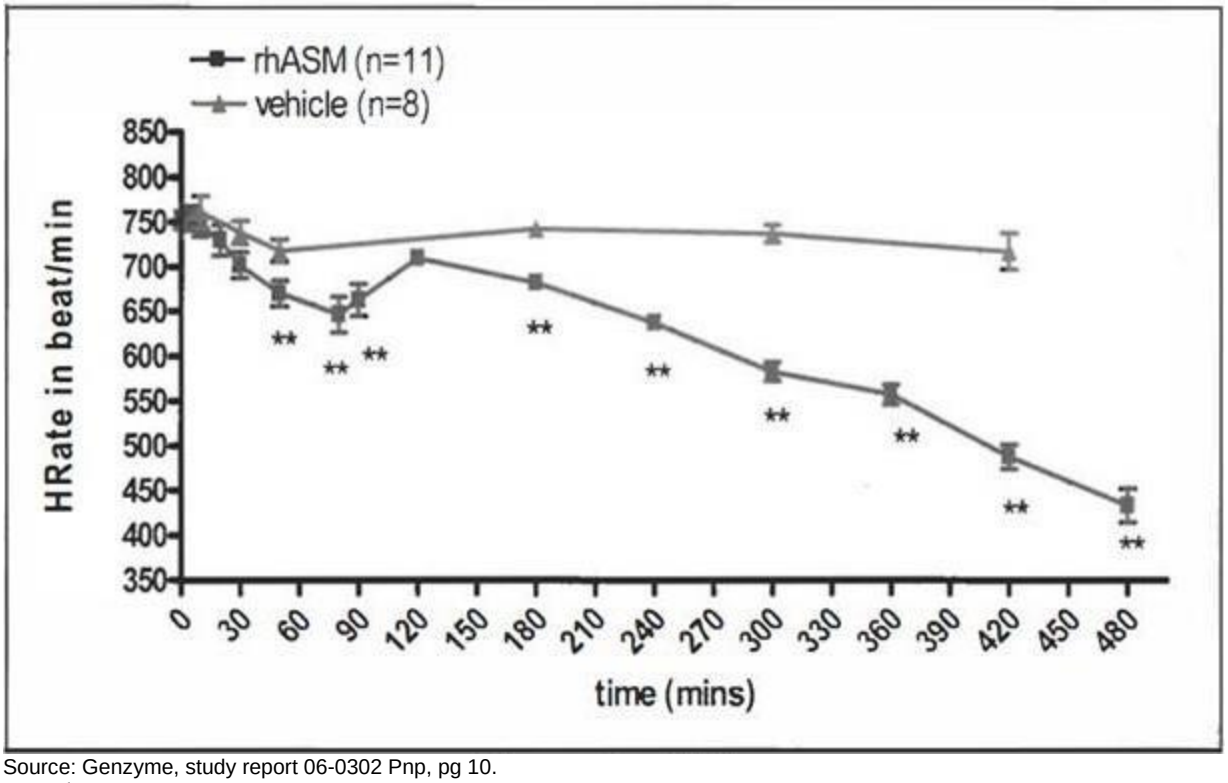
This is the first study to examine effects of rhASM dosing on the QT interval. After collection of baseline electrocardiogram (ECG) data, rhASM (0, 20 mg/kg) was administered to conscious ASMKO mice. Initially, the time course of bradycardia and Q-T prolongation were not coupled – the time course of the former preceded the latter. After ~4 hours, as the animals became lethargic and moribund, heart rate reductions were accompanied by persistent QT prolongation.

Table 108. 06-0302 Study Design and Methods

Group	N	Dose	Comment
1	20	-	Baseline ECG collected for unspecified period
	8	0	See Figure 49 and Figure 50.
	12	20	HR diverges from baseline of 750 bpm at ~t =45 min after dosing (650 bpm); partial recovery 90-180 min(600-700 bpm); further decline thereafter until death/euthanasia at 480 min (<500 bpm). QT prolongation first observed~80-90 min post-dose; diverges from vehicle QT at times ≥240 min

Source: Review team.
Abbreviations: BPM, beats per minute; ECG, electrocardiogram; N, total number of subjects; QT, electrocardiogram interval.

Figure 49. Time Course of rhASM Effects on HR in ASMKO Mice



Source: Genzyme, study report 06-0302 Pnp, pg 10.
** p-value<0.01
Abbreviations: ASMKO, acid sphingomyelinase knockout; HR, heart rate; HRate, heart rate; n, number of subjects in category; rhASM, recombinant human acid sphingomyelinase.

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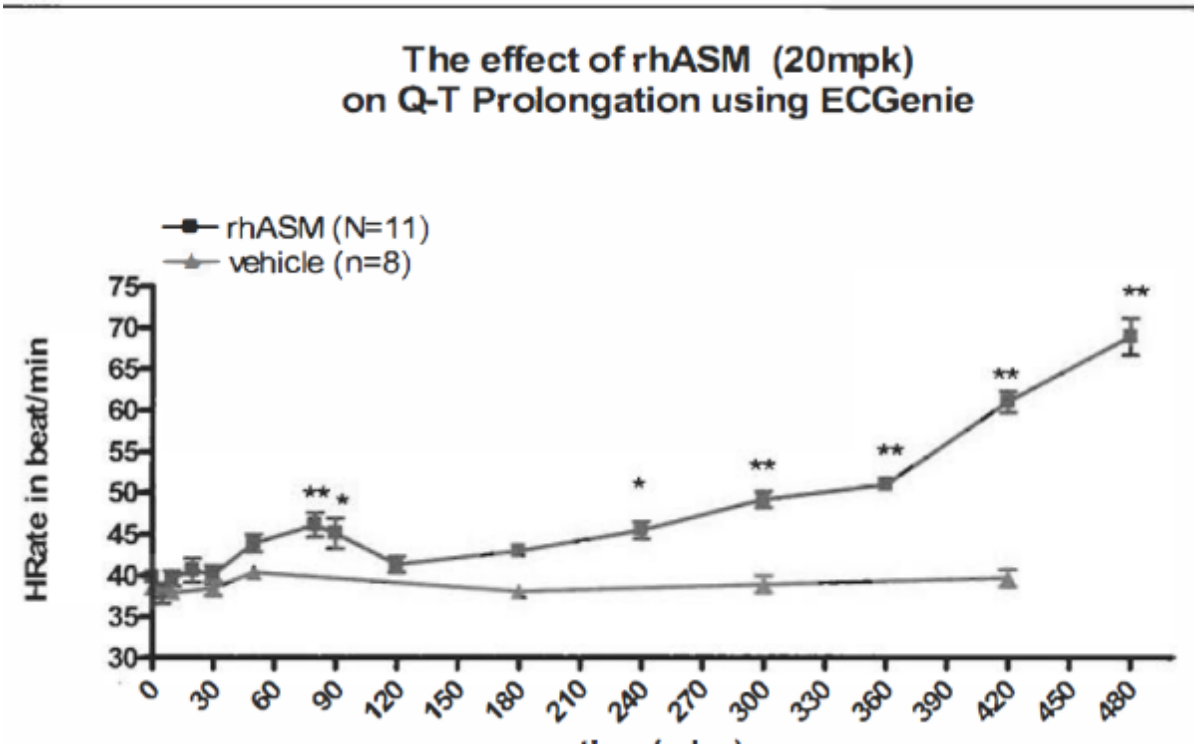
Figure 50 Time Course of rhASM Effects on Q-T Interval*



Source: Genzyme, study report 06-0302 Pnp, pg 10.
* p-value<0.05
** p-value<0.01
Note: Y axis erroneously labeled.. This is not heart rate, it is QT interval.
Abbreviations: ECG, electrocardiogram; HRate, heart rate; N, total number of subjects; n, number of subjects in category; rhASM, recombinant human acid sphingomyelinase.

Table 109. Recombinant Human Acid Sphingomyelinase (rhASM): A Cardiovascular and Respiratory Assessment in Cynomolgus Monkeys

Study Parameter	Study Information
Study no.:	08002
Study report location:	Module 4.2.1.3.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/20/08
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SM078, 97.9%

Source: Review team.
Abbreviations: GLP, good laboratory practice; (b) (4) QA, quality assurance.

Study Design

This study was conducted to examine the effects of IV doses of rhASM on hemodynamic and respiratory parameters and electrocardiographic (ECG) activity in conscious, telemetered cynomolgus monkeys. There were three groups. The Group 1 animals received the positive control, morphine, via a single subcutaneous injection at a volume of 0.033 mL/kg, on day 1. The Group 2 animals received the vehicle (b) (4) mM NaPO4, (b) (4) (b) (4) M (b) (4) methionine (b) (4) % sucrose, pH 6.5) or the test article, rhASM, at a dose of 30 mg/kg,

via a 30-minute IV infusion via a syringe pump at a volume of 7.7 mL/kg on days 1 and 4/5, respectively.

- Hemodynamic parameters, ECGs, and core body temperature were recorded from the Group 2 animals via telemetry for at least 2 hours before each dosing through 24 hours after each dosing. ECG waveforms were qualitatively evaluated for any abnormalities (PR, QRS, RR, QT, and QTcB [Bazett's] intervals).
- Respiratory parameters (respiratory rate and tidal volume) were also recorded for the Group 2 animals via the LifeShirt system for approximately 2 hours before dosing through approximately 20 hours after each dosing.
- Arterial blood samples were collected from the Group 2 animals and analyzed for pH, partial pressure of carbon dioxide (pCO2), partial pressure of oxygen (pO2), saturated oxygen (SO2), and blood bicarbonate (HCO3-).
- Blood samples were collected from the Group 2 animals.
- Serum samples collected during Session 3 (30 mg/kg rhASM) were analyzed for test article concentration. Clinical observations were recorded at protocol specified time points, and body weights were collected.

Table 110. Study 08002 Experimental Design

Session Number[a]	Group Number	Number of Animals[b]		Test Material	Dosage Level (mg/kg)[c]	Dose Conc. (mg/mL)	Dosage Volume (mL/kg)	Dosing Regimen	Monitoring Period
		Males	Females						
1	1	2	2	Positive Control	0.5	15	0.033	Subcutaneous injection	2 hours before each dose through 24 hours after each dose
2	2	3	3	Vehicle	0	0	7.7	30-minute intravenous infusion once for each session	
3				rhASM	30	3.9			

[a] Dose Sessions 2 and 3 were separated by at least 48 hours. Dosing ended after the completion of Session 3.
[b] The same animals were dosed in each session (Sessions 2 and 3), with the exception of the positive control animals (Group 1) in Session 1, who represent a different cohort of animals.
[c] rhASM at 10 and 3 mg/kg was not administered as there were no quantitative clinical effects observed after the 30 mg/kg dose.

Source: Review team.
Abbreviations: rhASM, recombinant human acid sphingomyelinase.

Toxicokinetic analyses

See Table 111.

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Table 111. Toxicokinetic Parameters for a 30-min Infusion of rhASM to Cynomolgus Monkeys

Parameter	All Animals (n=5)	Males (n=2)	Females (n=3)
$\alpha t_{1/2}$ (hr)	0.21 ± 0.04	0.26 ± 0.03	0.18 ± 0.01
$\beta t_{1/2}$ (hr)	7.31 ± 0.43	7.52 ± 0.03	7.17 ± 0.55
Cl (ml/hr)	28.6 ± 3.31	28.9 ± 2.51	28.4 ± 4.31
V_{ss} (ml)	233 ± 36.6	242 ± 29.3	228 ± 46.3
AUC (µg X hr/ml)	3378 ± 415	3552 ± 461	3262 ± 434
C_{max} (µg/ml)	1521 ± 191	1512 ± 282	1527 ± 183

Values represent mean ± SD.

Source: Genzyme report 08002, pg. 125.

Study Findings

- IV administration of rhASM at 30 mg/kg was well tolerated in all of the study animals.
- No effect of rhASM were observed on blood pressure, heart rate, body temperature, ECG intervals, respiratory rate, tidal volume, or blood gas parameters.
- The NOAEL was considered 30 mg/kg rhASM, a dose associated with an area under the concentration-time curve (AUC) =3378 µg*h/mL, and a maximum plasma concentration (C_{max}) of 1521 µ/mL.

13.1.3. Pharmacokinetics, Biodistribution, and Toxicokinetics

The pharmacokinetic (PK) and biodistribution properties of olipudase alfa were investigated in both wild type and ASMKO mice, in single dose studies that evaluated doses ranging from 1 to 10 mg/kg. A single-dose of olipudase alfa (5 mg/kg) administered to ASMKO mice characterized the time course of tissue SPM levels (liver, spleen, kidney, and lung). A single dose ^{125}I radiolabeled study (5 mg/kg) in ASMKO mice also evaluated brain for evidence of CNS distribution.

Toxicokinetic (TK) was evaluated following a single IV administration of olipudase alfa in rats (as well as liver biodistribution), beagle dogs at 3, 10, and 30 mg/kg and in cynomolgus monkeys at 30 mg/kg. Toxicokinetic parameters following repeated IV administration of olipudase alfa was also evaluated in cynomolgus monkeys, pregnant CD-1 mice, and pregnant New Zealand White rabbits at 3, 10, and 30 mg/kg.

Standard deviation (SD) PK parameters in mice, as well as C_{max} and AUC values for olipudase alfa 30 mg/kg doses in all nonclinical toxicology species, are reproduced in Table 112 and Table 113. Further details of repeated-dose TK parameter values are included in reviews of studies 02027, 07007, TER0694 and TER0698.

Table 112. PK Parameters After Administration of Single Doses rhASM (1-10 mg/kg) to Wild Type and ASMKO Mice

Species	Lot of Olipudase Alfa	Dose (mg/kg) IV Bolus	$t_{1/2}$ β (hours)	CL (mL/hr/kg)	AUC (µg*hr/mL)	Study No.
C57BL/6 mice	SM008	3	3.05 ± 0.17	19.80 ± 2.22	155.00 ± 16.25	03-142Pnp
C57BL/6 mice	SM018	3	2.58 ± 0.14	24.60 ± 4.20	123.20 ± 18.44	03-142Pnp
C57BL/6 mice	SM034	3	2.56 ± 0.45	21.60 ± 2.82	140.64 ± 17.78	03-142Pnp
C57BL/6 mice	SM049	3	2.20 ± 0.41	24.00 ± 4.26	129.13 ± 24.39	03-142Pnp
C57BL/6 mice	SM049	3	2.27 ± 0.55	15.00 ± 2.16	171.60 ± 27.03	04-0841Pnp
C57BL/6 mice	SM066	3	1.93 ± 0.24	32.40 ± 5.10	84.38 ± 16.35	04-0841Pnp
C57BL/6 mice	SM078	3	1.90 ± 0.63	25.20 ± 5.64	108.10 ± 23.70	04-0841Pnp
ASMKO mice	10544-070	1	3.83 ± 0.83	21.00 ± 2.40	47.96 ± 5.43	02-0266Pnp
ASMKO mice	SM078	3	4.95 ± 1.23	24.60 ± 6.00	126.20 ± 25.55	12-03252
ASMKO mice	SM049	10	4.41 ± 0.83	17.16 ± 3.60	602.71 ± 120.28	06-0134Pnp
ASMKO mice	SM078	10	4.12 ± 1.15	22.80 ± 3.00	446.75 ± 62.40	06-0134Pnp

Abbreviations: ASMKO: acid-sphingomyelinase gene knockout; AUC: area under the concentration versus time curve extrapolated to infinity; CL: clearance; $t_{1/2}$ β: terminal half-life

Source: Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 14.

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Table 113. Exposure Parameter Values Associated With 30 mg/kg Olipudase Alfa Doses in Rats, Dogs, Monkeys, [CD1] Mice, and Rabbits (Mean ± SD)

Species	Sex	NOAEL dose (mg/kg)	Route	C_{max} (µg/mL)		AUC (µg*hr/mL)		Study No.
				Dose 1	Dose 7/13[a]	Dose 1	Dose 7/13[a]	
SD Rat	Male	30 QOW	IV Bolus	568.17 ± 110.49	810.04 ± 99.62	679.32 ± 147.88	1689.73 ± 285.73	03-0604Pnp
SD Rat	Female	30 QOW	IV Bolus	540.63 ± 141.30	521.89 ± 137.58	643.35 ± 91.29	1121.97 ± 175.06	03-0604Pnp
Beagle dog	Male	30	IV Bolus	427.75 ± 86.27	NA	2495.79± 806.04	NA	03-0623Pnp
Beagle dog	Female	30	IV Bolus	479.92 ± 53.32	NA	1664.59 ± 414.02	NA	03-0623Pnp
Cynomolgus monkey	Male	30 QOW	IV Infusion[b]	721.89 ± 114.39	707.09 ± 153.05	3834.81 ± 513.45	2434.22 ± 837.04	07007
Cynomolgus monkey	Female	30 QOW	IV Infusion[b]	690.64 ± 70.08	728.83 ± 148.04	3589.51 ± 255.27	2344.14 ± 837.70	07007
CD-1 Mouse	Female	30 QD from GD 6 to 15	IV Bolus	NA	409	NA	916[d]	TER0694
NZW Rabbit	Female	30 QD from GD 6 to 19	IV Infusion[c]	NA	TBD	NA	TBD	TER0698

Abbreviations: ASMKO: acid-sphingomyelinase gene knockout; AUC: area under the concentration versus time curve extrapolated to infinity; C_{max} : maximum concentration; NA: not applicable; NOAEL: no observable adverse effect level; QD: every day; QOW: every other week

a Values for ASMKO and CD-1 mice as well as NZW rabbits are at dose 7, while values for rats and cynomolgus monkeys are at dose 13.

b 30-minute infusion

c 10-minute infusion

d $AUC_{0\text{-}24}$

Source: Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 15.

Species values for elimination half-life, clearance, mean residence time, and volume of distribution after administration of a single olipudase alfa dose are reproduced in Table 114.

Table 114. Cross-Species Comparison of Terminal Half-Life, Clearance, Mean Residence Time, and Volume of Distribution

Parameter	C57BL/6 Mouse*	ASMKO Mouse**	Rat[3*]		Dog[4*]		Monkey[5*]
			Males	Females	Males	Females	
Dose (mg/kg)	3	3		30		30	30
$T_{1/2}\beta$(h)	2.6	4.9	1.1	2.7	4.5	9.6	7.3
CL (ml/h/kg)	22.5	24.6	31.8	21.6	18.6	13.2	28.6
MRT (h)	3.3	N/A	1.7	3.9	5.9	12.9	N/A
Vd (ml/kg)	73.2	168.5	52.0	59.7	105	149	233

Source: Reviewer-generated.

* Data excerpted from Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 23.

** Data excerpted from Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 24.

[3*] Data excerpted from Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 26

[4*] Data excerpted from Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 27

[5*] Data excerpted from Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 27

Abbreviations: ASMKO, acid sphingomyelinase knockout; CL, clearance; MRT, mean residence time; N/A, not assessed; $T_{1/2}\beta$, terminal half-life; Vd, volume of distribution.

In ASMKO mice, the time course of olipudase alfa biodistribution to liver, spleen, and lung after administration of a single (5 mg/kg) dose is reproduced in Figure 51.

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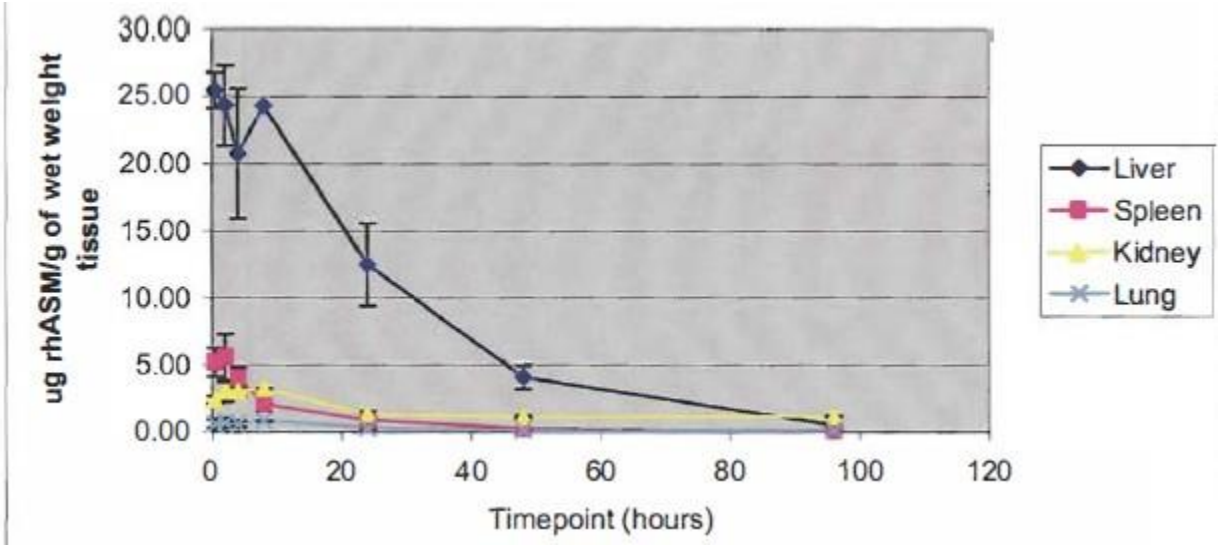
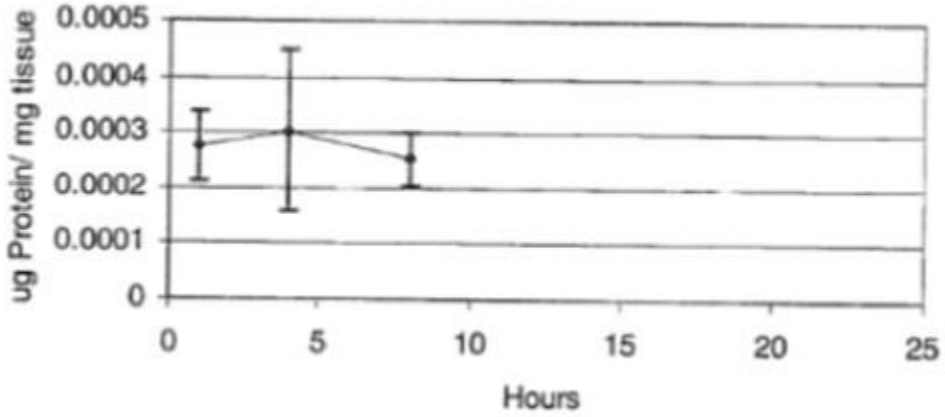
Figure 51. Distribution of Olipudase Alfa Following Administration of a Single (5 mg/kg) Dose to ASMKO Mice



Source: Genzyme study report 03-0380 Pnp, pg. 4.

Olipudase alfa was not detected in the brains of ASMKO mice, as depicted in Figure 52.

Figure 52. Brain Content of Olipudase Alfa Following Administration of a Single (5 mg/kg) Dose of Olipudase Alfa to ASMKO Mice



Source: Genzyme module 2.6.4, Nonclinical Pharmacokinetic Written Summary, pg 44.

No metabolism or excretion studies were conducted because olipudase alfa, as a large therapeutic protein, was expected to be eliminated by non-saturable proteolytic catabolism.

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13.1.4. Repeated-Dose Toxicity Studies

Table 115. Effect of Repeated Intravenous Administration of rhASM to ASMKO Mice [Over 13 Weeks] With a Four Week Recovery Period

Study Parameter	Study Information
Study no.:	04005
Study report location:	0001
Conducting laboratory and location:	Genzyme Corporation, Framingham MA
Date of study initiation:	April 19, 2004
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	rhASM, SM049 DP, 98%

Source: Review team.
Note: Tissue SPM levels reported in 04-0813 Pnp.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; Y, yes.

Key Study Findings

Administration of rhASM to ASMKO mice every other week [over 13 weeks] at dose levels of 0.3, 1, or 3 mg/kg was generally well-tolerated. Mild increases in serum cholesterol and ALT were reported. Target organ pathology was reversible and included minimal to mild adrenocortical ballooning degeneration and apoptosis of the zona fasciculata near the corticomedullary junction, as well as increased numbers of hepatocellular inflammatory foci. The original NOAEL was set at "≤3 mg/kg"; this was amended in 2020 to be 3 mg/kg, based on the opinion that pathology noted was not adverse, and did not persist at the end of recovery.

Reviewer's Comments: The Sponsor has represented this as a good laboratory practice (GLP) repeat-dose toxicology study. However, the study was not adequately powered. Particularly, it is not possible to determine from the small N sizes whether there is "confirmatory evidence" that would preclude the need for a second pivotal clinical trial (e.g., all animals survived until scheduled necropsy).

Table 116. 04005 Study Design and Methods

Dose (mg/kg)	N	Route of administration and Regimen	Endpoints and Sample Collections
End of Dosing Necropsy			
0 (Vehicle) 0.3 1.0 3.0	3/sex 5-6	Every other week x 7 doses	Clinical observations and body weights on dosing days. At necropsy, Clinical pathology, Urinalysis, Gross Pathology, Organ weights, Histopathology, blood for serum anti-rhASM*, SPM in liver, spleen, lung**

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Dose (mg/kg)	N	Route of administration and Regimen	Endpoints and Sample Collections
End of Recovery Necropsy			
0 (Vehicle)	3/sex	IV every other week x 7 doses	Clinical observations and body weights on dosing days. At necropsy, Clinical pathology, Urinalysis, Gross Pathology, Organ weights, Histopathology of all recommended organs/tissues, blood for serum anti-rhASM*, SPM in liver, spleen, lung**, liver rhASM content*
3.0	4 males, 2 females		
3.0	4 males, 2 females		

Source: Review team.
* ELISA
**Organic extraction using ASM enzymatic activity
Abbreviations: ELISA, enzyme-linked immunosorbent assay; IV, intravenous; N, total number of subjects; rhASM, recombinant human acid sphingomyelinase; SPM, sphingomyelin.

Results

Mortality

None.

Clinical Signs

Hypersensitivity in groups treated with 3 mg/kg.

Body Weight

No treatment-related effects.

Food Consumption

Not measured.

Ophthalmology

Not assessed.

ECG

Not assessed.

Hematology

No treatment-related effects.

Clinical Chemistry

Increased cholesterol unrelated to dose at end-of dosing necropsy (13 to 40%). Recovery values at 3 mg/kg were comparable to vehicle-treated values.

Organ Weights

Reductions in liver weight were unrelated to dose at the end of dosing necropsy (20 to 26%). Note that tissue levels of SPM in livers of untreated animals are approximately 100 mg/g in the

ASMKO mouse; it is unlikely that global reductions in SPM account for the magnitude of liver organ weight reduction.

Gross Pathology

Two animals (23 and 27) from end-of-dose necropsies were excluded from interpretation of macroscopic and microscopic findings, as these animals did not reveal changes typical of ASMKO mice. As noted in the IND review:

> The observed lesions in the treatment groups were similar to those in the control group (e.g. discoloration of spleen, lungs, and seminal vesicles), and…[may be] indicative of disease progression. Enlarged mandibular lymph node was observed only in the 3 mg/kg group (1/5 mice).

Microscopic Pathology

Adrenals and liver were target organs of rhASM. Mild adrenal cortical hemorrhagic congestion was present in all groups, although severity and incidence did not suggest that it was treatment-related. Minimal to mild ballooning degeneration and apoptosis of the zona fasciculata near the corticomedullary junction were reported at the end-of-dose; these were dose-related in incidence and severity, and not present at the end of the 4-week recovery.

In the liver, increased numbers of inflammatory foci (inflammation of mature neutrophiles) were reported at 1 and 3 mg/kg; these were not present at the end of the 4-week recovery.

Other findings that may represent SPM accumulation: vacuolization of Purkinje neurons in the brain in all animals; enlarged and vacuolated epididymal tubular linings in vehicle and treated males; foamy macrophages in splenic pulp in all group 1 and group 2 animals, a finding associated with ASMKO mice; foamy macrophages in thymic cortex of all animals in all groups; and foamy macrophages in mesenteric and mandibular lymph node sinuses of all vehicle and recovery animals; and erythroid hypoplasia in vehicle and recovery animals. Notably, the severity of the observation of large foamy cells in the marrow spaces of sternum and femur were reduced, suggesting efficacy of rhASM in clearing SPM from the marrow.

Table 117. rhASM: 13-Week Multiple Dose Intravenous Injection Toxicity Study in ASMKO Mice With a 4-Week Recovery

Study Parameter	Study Information
Study no.:	06031
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	January 3, 2007
GLP compliance:	Stated (no record of inspections)
QA statement:	None (for entire study)*
Drug, lot #, and % purity:	rhASM, SM078, purity unspecified

Source: Review team.
* Dosing solutions
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase

Key Study Findings

Administration of rhASM to ASMKO mice every other week [over 13 weeks] at dose levels of 0.3, 1, or 3 mg/kg (N=10/sex/group) was not associated with excessive mortality or toxicity. Treatment-related clinical observations were associated with hypersensitivity and limited to 3

mg/kg. Body weights and total body weight gains (BWG) were comparable across experimental groups in both sexes. Treatment-related trends toward reductions in AST and ALT in males and females, as well as reductions in alkaline phosphatase (ALP) in treated males, likely reflect interruption of pathophysiological disease progression. Absolute liver weights were reduced at all doses (~-18 to 22%) in treated females, although not treated males. Gross pathology was limited to observations of red discoloration in the gastrointestinal (GI) tract in three premature decedents **(**females**)** treated with 3 mg/kg. Microscopically, vehicle and diphenhydramine-treated mice in Groups 1 and 2 exhibited cytoplasmic vacuolization and foamy macrophages in visceral organs and CNS tissues. Conversely, observations of reduced incidence/severity of cytoplasmic vacuolization and the numbers/sizes of foamy macrophages were made in mice from rhASM-treated groups in liver, kidney, bone marrow (sternum and femur), thymus, lymph node (mandibular and mesenteric), adrenal gland, small intestine, spleen, stomach, trachea, pancreas, cervix, ovary, uterus, and epididymis. Additionally, rhASM ≥1 mg/kg was associated with dose-related reductions in the incidence/severity of hepatic single cell degeneration; and dose-related reductions in the incidence/severity of mixed cell infiltrates (histiocytes, lymphocytes, neutrophils, and/or plasma cells).

CNS tissues were unaffected by treatment.

After four weeks of recovery, the resumption of SPM accumulation was noted in adrenal, liver, kidney, and bone marrow; remaining tissues were comparable to those in the end-of-dose necropsy.

The NOAEL of rhASM was set by amendment in 2019 as 3 mg/kg.

Reviewer's Comments: This study essentially repeats/expands upon study 04005, although two control groups (vehicle- and diphenhydramine hydrochloride (DPH)-treated ASMKO animals) were included; and group sizes were increased (N=10/sex/group). Liver and adrenals were identified as target organs of toxicity in study 04005, such that the IND reviewer concluded there was no NOAEL. Specifically, adrenal findings in the earlier study (minimal to mild ballooning degeneration and apoptosis of the zona fasciculata near the corticomedullary junction) were not replicated in the present study; however, x-zone "congestion" of minimal-mild severity was noted in females in the present study, as well as in both sexes in the previous study. In the liver, increased numbers of inflammatory foci (inflammation of mature neutrophiles) were previously reported at 1 and 3 mg/kg in the earlier study; these were not reported here. Rather, these and observations of "single-cell degeneration" are presented as treatment-associated "reductions in incidence and severity", with a specific observation in the current study that "no hepatoxicity was observed".

The present study is regarded as the more cogent: there were 10/sex/dose group available for both end-of-dose and end-of-recovery necropsies (in 04005, there were 2-3/sex dose group at either necropsy). Since survival was not adversely impacted, there were no treatment-associated clinical observations that were not related to hypersensitivity, and weights were comparable in all experimental groups, a NOAEL of 3 mg/kg/day is appropriate. While TK was not conducted, C_{max} data for 3 mg/kg from study 10-00262 is 46.6 µg/mL.

Table 118. Study 06031 Methods

Method	Description
Doses:	0 (vehicle), 0.3, 1.0, 3.0 mg/kg
Frequency of dosing:	Every other week, beginning Day 1, for 7 total doses
Route of administration:	Intravenous
Dose volume:	N/A
rhASM Formulation/Vehicle:	Reconstitution: sterile water for injection Vehicle: (b) (4) mM sodium phosphate (b) (4) sucrose, (b) (4) mM methionine (b) (4)
Diphenhydramine Formulation/Vehicle:	Reconstitution: unspecified Normal saline
Species/Strain:	Mouse/C57BL, from which ASMKO animals were generated (b) (4)
Number/Sex/Group:	10+10 (end of study and end of recovery cohorts)
Age:	8-13 weeks at study start
Weight:	13-35g at study start
Satellite groups:	No. Importantly, TK evaluations were not conducted in this study.
Unique study design:	See below,
Deviation from study protocol:	Many.

Source: Review team.
Abbreviations: ASMKO, acid sphingomyelinase knockout; (b) (4) rhASM, recombinant human acid sphingomyelinase; TK, toxicokinetic.

Table 119. Study 06031 Design

Group	No. of animals at 13 weeks (animal numbers)		No. of animals at 16 weeks (animal numbers)		Substance[b] (IP)	Substance (IV)	Dose Level (mg/kg)	Dose Concentration (mg/mL)[a]
	Male	Female	Male	Female				
1	10 (1-10)	10 (11-20)	10 (21-30)	10 (31-40)	Saline	Vehicle Article	0	0
2	10 (41-50)	10 (51-60)	10 (61-70)	10 (71-80)	DPH	Vehicle Article	0	0
3	10 (81-90)	10 (91-100)	10 (101-110)	10 (111-120)		rhASM	0.3	0.10
4	10 (121-130)	10 (131-140)	10 (141-150)	10 (151-160)			1.0	0.33
5	10 (161-170)	10 (171-180)	10 (181-190)	10 (191-200)			3.0	1.00

[a] The dose volume was 6.0 mL/kg for Doses 1 and 2. Beginning with 3rd dose (Week 5), due to the sensitivity of the A_{280} assay (concentration verification) the dose volume was lowered to 3.0 mL/kg to increase the dose concentration (Doses 3-7).

[b] 5 mg/kg DPH or 0.9% Saline was administered beginning with the second dose at a dose volume of 1 mL/kg. Due to signs of hypersensitivity following the third dose, on the first dosing day of the fourth dose animals received 10 mg/kg DPH or 0.9% Saline at a dose volume of 2 mL/kg. For all remaining doses animals received 20 mg/kg DPH or 0.9% Saline at a dose volume of 4 mL/kg.

Source: Genzyme, report 06031, pg 12.

Observations and Results

Mortality

From DARRTS, Archive, February 25, 2010:

> ***Mortality:*** *The incidence of deaths is shown in the tables below (taken from the study report).*

Table 120. Premature Decedents (Male)

Group:	Group 1	Group 2	Group 3	Group 4	Group 5
Dose:	0 mg/kg	0 mg/kg	0.3 mg/kg	1.0 kg/kg	3.0 mg/kg
Total Animals:	20	20	20	20	20
Number of Early Deaths:	1	1	0	1	3
Day of Death:	-7	-1	NA	88	15, 32, 32

Source: Genzyme, report 06031.

Table 121. Premature Decedents (Female)

Group:	Group 1	Group 2	Group 3	Group 4	Group 5
Dose:	0 mg/kg	0 mg/kg	0.3 mg/kg	1.0 kg/kg	3.0 mg/kg
Total Animals	20	20	20	20	20
Number of Early Deaths:	1	1	1	0	1
Day of Death:	15	1	65	NA	79

Source: Genzyme, report 06031.

The death of a Group 4 male was attributed to atrial thrombosis/rupture, which the authors claim to be a spontaneous condition in mice. In two Group 5 males, the cause of death appeared to be a severe hypersensitivity reaction. Hydronephrosis was observed in the Group 2 female that died on day -1. The cause of death in the remaining mice was undetermined, but may have been related to dehydration, given that some mice had difficulties in drinking from the water bottles. The observed mortality incidence is not considered to be related to rhASM toxicity, given the small number deaths, the absence of dose-dependent mortality, the absence of gross or microscopic lesions, and the involvement of hypersensitivity reactions or dehydration in premature deaths.

Clinical Signs

Treatment-related clinical signs were limited to signs of hypersensitivity (lethargy, rapid respiration) among animals treated with 3 mg/kg.

Body Weights

The growth of ASMKO mice is known to be stunted, relative to WT C57BL littermates (see Figure 53).

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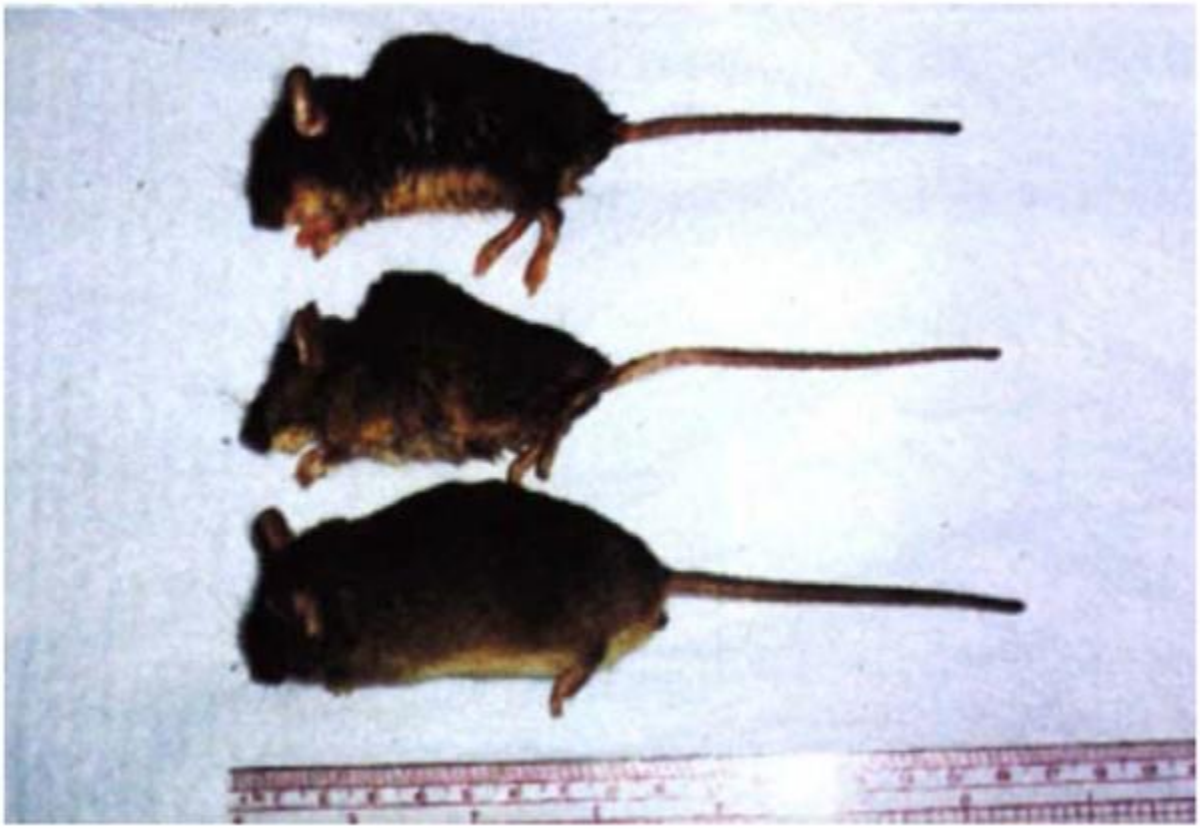
Figure 53. Phenotypes of ASMKO and C57BL/6 Mice

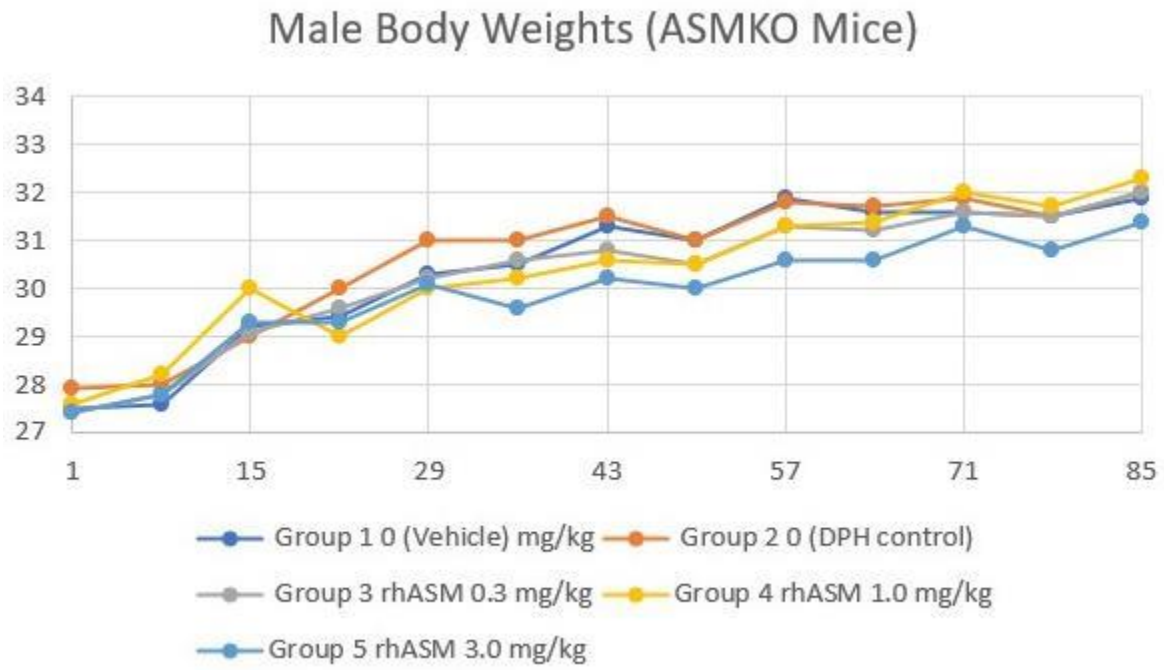


Source: (Horinouchi et al. 1995).
Note: Phenotype of the ASM knockout mouse. Of importance, the dramatic size difference and "hunched" appearance of the affected animals (top) compared to a control littermate (bottom) at four months of age.
Abbreviations: ASMKO, acid sphingomyelinase knockout.

Body weights in male and female mice (study days 1 to 85) are reproduced below, in Figure 54 and Figure 55 (males); and in Figure 56 and Figure 57 (females). Body weight gains (BWGs) were comparable across experimental groups in both sexes. Males ranged from 14.7 to 17% over the course of study days 1-85 and were unrelated to rhASM dose. Females ranged from 16.2 to 20.7% over the course of study days 1 to 85 and were likewise unrelated to rhASM dose.

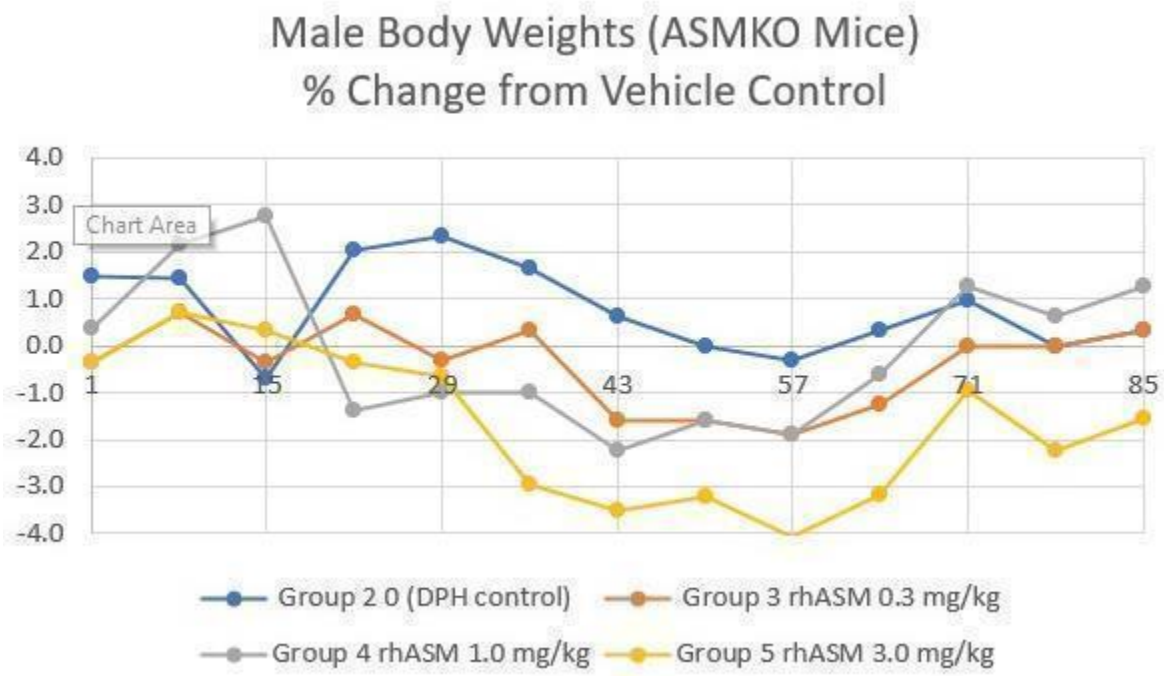
Reviewer's Comments: The IND review of this study (DARRTS, Archive, February 25, 2010) notes that male BWGs were 58% lower than those in DPH-treated controls (Study days 1-92). However, animals were fasted prior to necropsy on study day 92, which brings into question actual BWG values – for this reason, study days 1-85 are considered more relevant. When study days 1-85 are used to calculate BWG, the actual values for DPH-controls and rhASM-treated males (3 mg/kg) are 4.4 and 4.0 g, respectively. This difference (400 mcg in a 31-32 g mouse) is not presently adjudged to be meaningful. It is an important distinction, because the previous review of this study set the NOAEL in males at 1 mg/kg due to these differences in BWG.

Figure 54. Male Body Weights



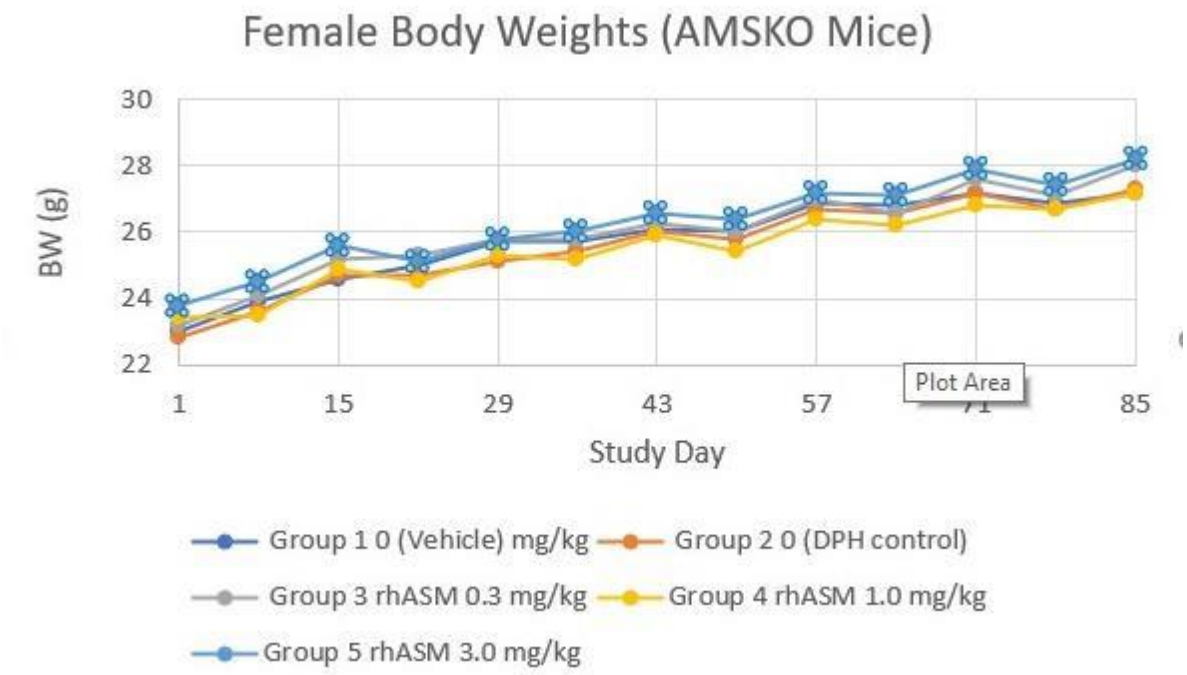
Source: Review team.

Figure 55. Male Body Weights (% Change From Vehicle Control)



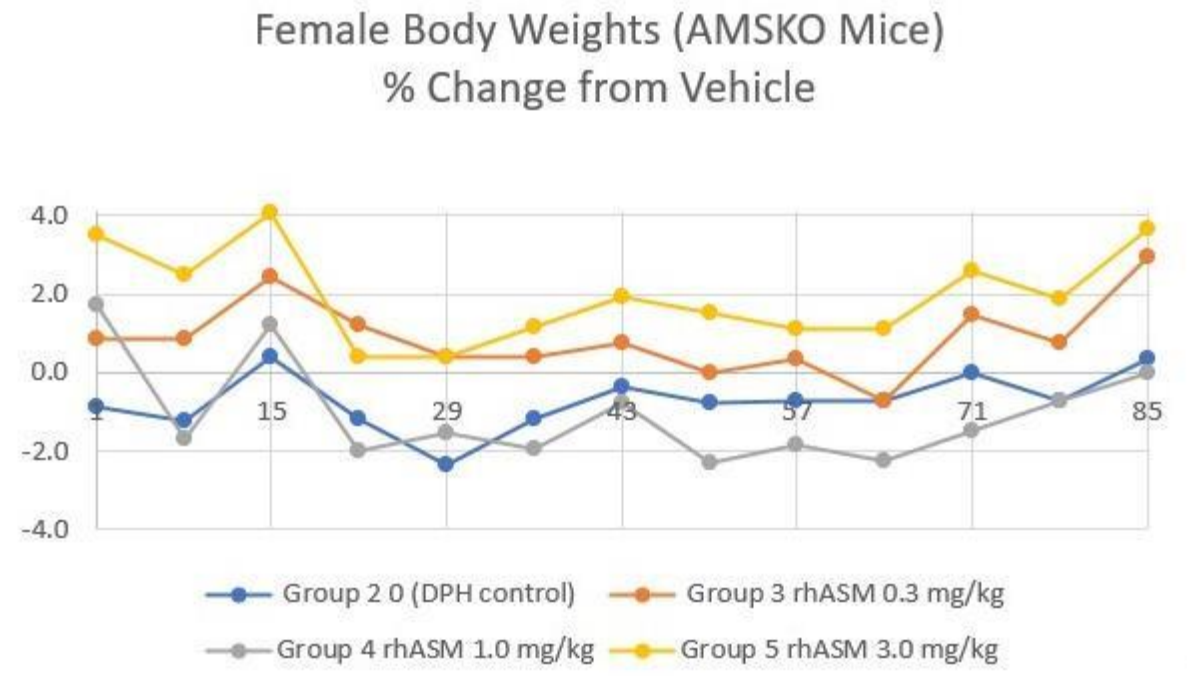
Source: Review team.

Figure 56. Female Body Weights



Source: Review team.

Figure 57. Female Body Weights (% Change From Vehicle Control)



Source: Review team.

Feed Consumption

Animals were group-housed. There were no apparent treatment-related effects on food consumption.

Ophthalmoscopy

There were no treatment-related effects.

ECG

Not conducted.

Clinical pathology

Treatment-related trends toward reductions in AST and ALT in males and females, as well as reductions in ALP in treated males, are attributed to interruption of pathophysiological disease progression. (These did not result in enhanced overall survival, relative to groups that received vehicle or diphenhydramine alone.) Remaining alterations to serum chemistry parameters were isolated, and unrelated to dose.

Urinalysis

Not conducted.

Gross Pathology

Gross pathology presently attributed to treatment was limited to findings in premature decedents; findings were largely limited to observations of red discoloration in the GI tract in females treated with 3 mg/kg.

Organ Weights

A limited number of organs were weighed at necropsy: liver, spleen, kidney, lung, heart, brain, and testis/ovary. Among treated males, there were no statistically-significant treatment-related findings. Among treated females, absolute liver weights were reduced at all doses (~-18 to 22%), attributed to reduced SPM content in liver. Remaining observations in females were unrelated to dose.

Histopathology

Adequate Battery: Y

Peer Review: N

Histological Findings:

Microscopically, vehicle and diphenhydramine-treated mice in Groups 1 and 2 exhibited cytoplasmic vacuolization and foamy macrophages in visceral organs and CNS tissues, consistent with the ASMKO mouse phenotype. Conversely, observations of reduced incidence/severity of cytoplasmic vacuolization and the numbers/sizes of foamy macrophages were made in mice from rhASM-treated groups. Affected tissues and organs included liver, kidney, bone marrow (sternum and femur), thymus, lymph node (mandibular and mesenteric), adrenal gland, small intestine, spleen, stomach, trachea, pancreas, cervix, ovary, uterus, and epididymis.

Organ-specific findings were limited to liver. rhASM doses ≥1 mg/kg were associated with dose-related decreases in the incidence/severity of single cell degeneration; and in the

incidence/severity of mixed cell infiltrates (histiocytes, lymphocytes, neutrophils, and/or plasma cells).

CNS tissues were unaffected by treatment.

After four weeks of recovery, the resumption of SPM accumulation was noted in adrenal, liver, kidney, and bone marrow; remaining tissues were comparable to those in the end-of-dose necropsy.

Toxicokinetics:

Not conducted.

Dosing Solution Analysis:

Group 3 dosing solutions failed analysis repeatedly, which the Applicant attributed to the assay's insensitivity at low concentrations of protein. Dosing solutions in Groups 4 and 5 were consistently within target concentrations at all timepoints tested.

Table 122. rhASM: 13-Week Repeat Dose Intravenous Injection Toxicity Study Following a Debulking Phase in ASMKO Mice

Study Parameter	Study Information
Study no.:	10-00262
Study report location:	001
Conducting laboratory and location:	Genzyme, Framingham MA
Date of study initiation:	March 15, 2010
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	rhASM, SM078, purity not specified

Source: Review team.
Note: Tissue SPM levels reported in 04-0813 Pnp.
Abbreviations: ASMKO, acid sphingomyelinase knockout; GLP, good laboratory practice; MA, Massachusetts; N, no; QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

There were no contemporaneous control groups in this study; instead, the reviewer is directed to findings reported for control animals in study 06031 (conducted 4 years earlier). Data generated for animals treated with 10 and 30 mg/kg were compared to those generated for animals treated with 3 mg/kg. Of note, this is the first toxicity study in ASMKO mice to assess serum rhASM concentrations.

rhASM was first administered intravenously to ASMKO mice at doses of 3 mg/kg every other day for 4 doses. After this "debulking" phase, doses of 3, 10, and 30 mg/kg were administered intravenously to 3 groups of ASMKO mice (n=4/sex, 8/sex, 8/sex, respectively) every other week for a total of 7 doses (the first day of the higher dose administration is designated study day 1). In addition to standard repeated-dose toxicity study parameters and endpoints, serum rhASM concentrations, plasma ceramide levels, acute phase proteins and a rodent multi-analyte profile (MAP) were assessed on days 1, 51, and 93.

Six early deaths were reported (five males and one female); these were unrelated to dose. Four of these deaths were attributed to cardiovascular compromise and hypotension secondary to procedure-related stress. Clinical observations were limited to lethargy, which was attributed to hypersensitivity. Group mean body weights of males treated with 10 and 30 mg/kg were lower during the second half of the study (-6to 10%, not dose-dependent) than values of males treated

with 3 mg/kg. Values for group mean body weights of females treated with 10 and 30 mg/kg were lower at the start of treatment (-6% and -9%, respectively). This reduction was mitigated by the end of the study among females treated with 10 mg/kg; however, the disparity persisted among animals treated with 30 mg/kg.

Serum rhASM concentrations were highly variable across dose groups and days tested. Concentrations were lower on day 93 than on day 1; this is attributed to anti-drug antibody (ADA) formation.

Plasma ceramide levels for all groups were elevated, relative to pre-dose levels, on study day 51; these persisted on study day 93. However, the magnitudes of these concentrations were unrelated to dose. There was a statistically significant decrease in serum amyloid P in Group 3 on study day 9 and 93 compared to pre-dose. There were statistically significant increases in serum amyloid A levels noted in Groups 2 and 3 on study day 51 and in Groups 1, 2, and 3 on study day 93 compared to pre-dose levels.

Most mice from all rhASM treatment groups had mild to moderate leukocytosis, generally characterized as lymphocytosis, neutrophilia, mild monocytosis, and eosinophilia. Mild thrombocytosis was observed in several mice from all three treatment groups; these changes may indicate chronic inflammation. Following rhASM treatment there were no statistically significant treatment- or dose-dependent changes in the average values for any of the clinical chemistry parameters when comparing Groups 2 and 3 to Group 1.

In treated males, dose-related reductions in both absolute and relative group mean lung weights were observed (-22.5% and -31%, respectively, at 10 and 30 mg/kg, relative to group 3 absolute values); absolute and relative lung weights were reduced in females at 30 mg/kg (-22.5%). Group mean absolute (although not relative) kidney weights were reduced by 12% and 19% among males and females, respectively, treated with 30 mg/kg. Absolute (although not relative) brain weights in females were reduced by -6% and -9%, respectively, at 10 and 30 mg/kg.

rhASM administration resulted in a dose-dependent clearance of renal, splenic, and hepatic SPM loads in ASMKO mice. Conversely, rhASM did not result in significant reduction in SPM load in the lungs of ASMKO mice treated with 10 or 30 mg/kg of rhASM, when compared to 3 mg/kg.

Interpretation of microscopic pathology data was difficult, due to the lack of contemporaneous control groups. Low numbers of treated males survived until scheduled necropsy. Organs and tissues with histopathologic findings included adrenals, aorta, bone marrow, epididymides, eyes, kidneys, lung, mesenteric lymph nodes, ovaries, pancreas, pituitary, preputial gland, testes, thymus, thyroid, and uterus; frequently, these were of minimal or mild severity. Unsurprisingly, CNS tissues were unaffected by treatment, as olipudase alfa does not penetrate the blood-brain barrier.

Reviewer's Comments: There was no effort by the pathologist in the current study to make direct comparisons with the pathology findings from study 06031. Specifically, in the current study, several organ systems have observations of cytoplasmic vacuolization that are dose-related in incidence; how these compare to the control observations from a study conducted 4 years earlier is best considered by a single pathologist.

Table 123. Study 10-00262 Dosing Regimen

Group	N/sex	Initial Regimen	Treatment Dose*
1	4	3 mg/kg	3 mg/kg from D 9 q o week x 7 doses
2	8	D1,3,5,7	10 mg/kg from D 9 q o week x 7 doses
3	8		30 mg/kg from D 9 q o week x 7 doses

Source: Reviewer-generated.
* DPH administered to all mice prior to each dose
Abbreviations: D, day; q o week, every other week.

Blood samples were collected prior to study start in order to characterize pre-dose PK and ceramide levels (subset 1, first half of animals in each sex/dose); and acute phase protein levels - i.e., serum amyloid-A and serum amyloid-P - with bilirubin, ALT, and rodent MAPs (subset 2, second half of animals in each sex/dose). The analytes included in the MAP are reproduced below, in Table 124.

After dose administration on D9, D51, and D93, these collections were repeated. Subset 1 incorporated a sample collection at t =5', to assess rhASM concentration; ceramide was assessed at 4 hours. Subset 2 collections included rodent MAP at 4 hours, and acute phase protein/liver function at 24 hours.

Table 124. Endpoints Assessed in the Rodent Multi-Analyte Profile

Analytes to be Tested		
Apolipoprotein A1	Interleukin-2	MIP-3 beta
C-Reactive Protein	Interleukin-3	MMP-9
CD40	Interleukin-4	MCP-1
CD40 Ligand	Interleukin-5	MCP-3
Endothelin-1	Interleukin-6	MCP-5
Eotaxin	Interleukin-7	Myeloperoxidase
Epidermal Growth Factor	Interleukin-10	Myoglobin
Factor VII	Interleukin-11	Oncostatin M
Fibrinogen	Interleukin-12p70	RANTES
FGF-basic	Interleukin-17	Serum Amyloid P
FGF-9	KC/GRO alpha	SGOT
GCP-2	Leukemia Inhibitory Factor	Stem Cell Factor
GM-CSF	Lymphotactin	Thrombopoietin
GST-alpha	M-CSF	TIMP 1
Haptoglobin	MDC	Tissue Factor
Immunoglobulin A	MIP-1 alpha	Tumor Necrosis Factor-alpha
Inducible Protein-10	MIP-1 beta	VCAM-1
Interferon-gamma	MIP-1 gamma	VEGF
Interleukin-1 alpha	MIP-2	von Willebrand Factor
Interleukin-1 beta		

Source: Genzyme report 10-00262, pg. 22.
Abbreviations: CD, cluster of differentiation; FGF, f broblast growth factor; GCP, granulocyte chemotactic protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRO, human growth-regulated oncogene; GST, glutathione S-transferase; KC, keratinocyte chemoattractant; MCP, murine monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; SGOT, serum glutamic-oxaloacetic transaminase; TIMP, tissue inhibitors of matrix metalloproteinases; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

Observations and Results

Mortality

Six early deaths were reported (five males and one female). Four of these deaths were attributed to cardiovascular compromise and hypotension secondary to procedure-related stress.

Table 125. Premature Mortality in 13-Week Study

Sex	Dose	Animal #	# of Doses	Comment
Male	3	1	7	D93, after DPM but before rhASM. Assessment: Procedure-related stress, followed by cardiovascular compromise and hypotension. Histopathology: cardiac dilation.
	10	12	4	D51, ~20 min after dosing. Assessment: Procedure-related stress, followed by cardiovascular compromise and hypotension.
		15	7	D 93. Euthanized for bleeding preputial abscess.
	30	30	6	D79. Assessment: Procedure-related stress, followed by cardiovascular compromise and hypotension.
		31	5	D 68. 3 days post-dose. Assessment: Procedure-related stress, followed by cardiovascular compromise and protracted hypotension. Histopathology: degeneration of adrenal cortex, known to be associated with hypotension.
Female	3	7	3	D 43. Euthanized due to complications from abdominal cavity cyst.

Source: Reviewer generated.

Clinical Observations

These were not summarized. The report indicated that treatment-related observations "consisted primarily of lethargy, indicative of a hypersensitivity response following repeat administration of rhASM. Observations of lethargy were apparent in the majority of mice beginning with the 3rd dose of the treatment phase for Group 2 and 3 but were seen in one to two mice in Groups 2 and 3 beginning with the 1st and 2nd treatment phase doses, respectively. Group 1 lethargy was sporadic but first appeared after the 2nd dose of the treatment phase."

Body Weight

Group mean body weights of males treated with 10 and 30 mg/kg were lower during the second half of the study (-6 to 10%, not dose-dependent) than values of males treated with 3 mg/kg. There was speculation that this was related to SPM clearance, although rhASM treatment could equally have been expected to lead to overall improvement in the growth and stature of animals. Values for group mean body weights of females treated with 10 and 30 mg/kg were lower at the start of treatment (-6% and -9%, respectively). This reduction was mitigated by the end of the study among females treated with 10 mg/kg; however, the disparity persisted among animals treated with 30 mg/kg.

Plasma Ceramide Levels

Plasma ceramide levels at the last time point examined (day 92) were less than levels previously seen following a single IV administration of 10 or 20 mg/kg rhASM (≥35,000 and 150,000 ng/mL, respectively), doses which were associated with severe toxicity (Studies 05-1008Pnp, 06-0129Pnp, 06-0778Pnp, and 07-1346). Nonetheless, these results show a significant elevation for all groups in plasma ceramide relative to pre-dose levels beginning on Study day 51, which

persisted on study day 93. Plasma ceramide levels across dose groups at the same timepoint did not differ. These data are depicted in Figure 58.

TK and ADA

Serum rhASM concentrations were highly variable across dose groups and days tested. Concentrations were lower on day 93 than on day 1; this is attributed to ADA formation. Results are reproduced in Table 126.

Table 126. Group Mean Serum rhASM Concentrations During 13 Weeks of Every Other Week Dosing

Dosage Group	Test Article Dosage (mg/kg/day)	Study Day/Timepoint	Mean (µg/mL)	St. Dev.	%CV
1	NA: Pre-Study	SD -1/Pre-Study	BDL	NA	NA
2	NA: Pre-Study	SD -1/Pre-Study	BDL	NA	NA
3	NA: Pre-Study	SD -1/Pre-Study	BDL	NA	NA
1	3	SD 9/5 min	70.55	10.58	15.0
2	10	SD 9/5 min	311.8	99.01	31.8
3	30	SD 9/5 min	1313	504.3	38.4
1	3	SD 51/5 min	79.32	10.20	12.9
2	10	SD 51/5 min	270.9	100.3	37.0
3	30	SD 51/5 min	1000	477.2	47.7
1	3	SD 93/5 min	46.65	5.738	12.3
2	10	SD 93/5 min	211.0	94.10	44.6
3	30	SD 93/5 min	617.9	300.2	48.6

Source: Genzyme report 10-00262-Pnp, pg. 166.
Abbreviations: %CV, percent coefficient of variation; BDL, below detectable limits; NA, not applicable; rhASM, recombinant human acid sphingomyelinase; SD, Study Day; St. Dev., standard deviation.

Antibody analysis results for serum taken from ASMKO mice at the time of sacrifice demonstrated a pronounced increase in mean antibody titer in Groups 2 and 3 (10 and 30 mg/kg, respectively) when compared to Group 1 (3 mg/kg). Individual animals in Group 1 had antibody titers ranging from 3,200 to 22,592 with an average of 10,094. Group 2 animals had antibody titers ranging from <200 to 459,573 with an average of 120,317. Group 3 animals had antibody titers ranging from 11,842 to 406,458 with an average of 125,881. These results suggest that repeat dosing of rhASM evoked increased antibody titers, which were associated with attenuated serum rhASM concentrations over time at doses ≥10 mg/kg.

Liver Function Tests and Acute Phase Protein Concentrations

There were no statistically significant changes noted in any group compared to pre-study values for alanine aminotransferase (ALT) or total bilirubin. There was a statistically significant decrease in serum amyloid P in Group 3 on study days 9 and 93 compared to pre-dose, which might suggest reduced inflammatory responses. There were statistically significant increases in serum amyloid A levels noted in Groups 2 and 3 on SD 51 and in Groups 1, 2, and 3 on study day 93 compared to study day -1. Despite the increases, the levels reached were lower than those

seen at similar time points following previous administrations of single doses of 3 or 10 mg/kg rhASM.

Rodent MAP Analysis

The study report states:

> *Despite significant changes in several cytokines in this study, it is unlikely these changes are toxicologically significant as there were no corresponding changes noted in the clinical chemistry or hematology parameters evaluated and there was no histopathological toxicity associated with rhASM administration.*

Clinical Pathology

There were no statistically significant changes in the average values for any hematology parameters when comparing Groups 2 and 3 to Group 1 (Appendix 9.6). Most mice from all rhASM treatment groups (6/6 in Group 1, 11/14 in Group 2, and 11/14 in Group 3) had mild to moderate leukocytosis. Leukocytosis was generally characterized as lymphocytosis, neutrophilia, mild monocytosis and eosinophilia. Mild thrombocytosis was observed in several mice from all three treatment groups. These changes may indicate chronic inflammation. The report noted "Epinephrine response due to excitement at the time of blood collection may also contribute to leukocytosis."

Following rhASM treatment there were no statistically significant treatment- or dose-dependent changes in the average values for any of the clinical chemistry parameters when comparing Groups 2 and 3 to Group 1.

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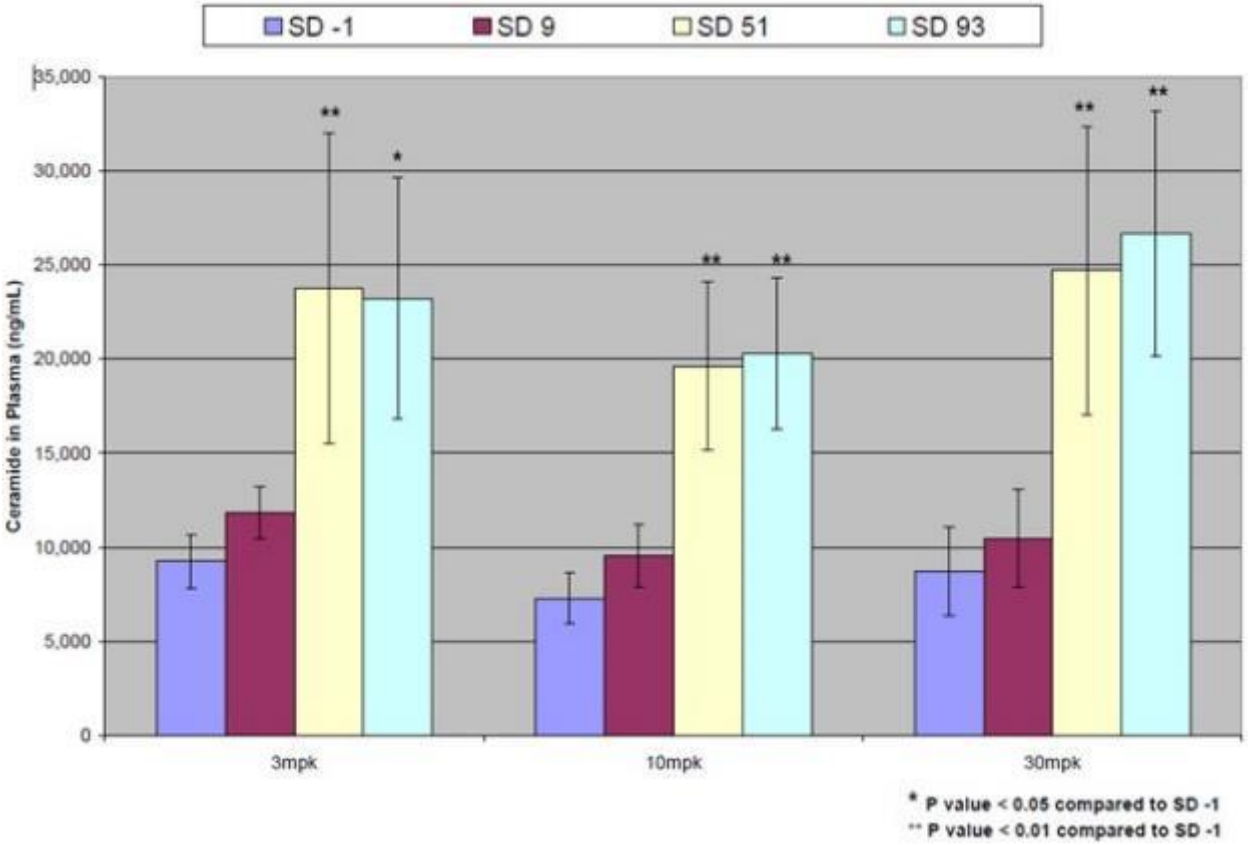
Figure 58. Plasma Ceramide in ASMKO Mice That Received rhASM (3, 10, or 30 mg/kg) Every Other Week for 13 Weeks



Source: Genzyme report 10-00262-Pnp, pg. 31.
* p-value<0.05 compared to SD -1
** p-value<0.01 compared to SD -1
Abbreviations: ASMKO, acid sphingomyelinase knockout; mpk, milligram per kilogram; SD, study day.

Organ Weights

In treated males, dose-related reductions in both absolute and relative group mean lung weights were observed (-22.5% and -31%, respectively, at 10 and 30 mg/kg, relative to group 3 absolute values). Group mean absolute (although not relative) kidney weights were reduced by 12% among animals treated with 30 mg/kg animals, when compared to those treated with 3 mg/kg. Reductions in absolute liver weights were observed, although these were not dose-related (-19% and -11% at 10 and 30 mg/kg, respectively).

Among treated females, reductions in both absolute and relative group mean lung weights were observed at 30 mg/kg (-22.5%, relative to group 3 absolute values; -11%, when absolute values were considered. Absolute (although not relative) brain weights were reduced by -6% and -9%, respectively, at 10 and 30 mg/kg, relative to group 3 values. Group mean absolute (although not relative) kidney weights were reduced by -19% among animals treated with 30 mg/kg animals, when compared to those treated with 3 mg/kg. Disparities between magnitudes of absolute and relative findings likely reflect the disparity in terminal body weights (TBW) between females in the 3 and 30 mg/kg dose groups.

All organ weight reductions were attributed to clearance of SPM, although this is unlikely: there were no reductions reported in spleen weights, which likewise were demonstrated to have

reduced SPM values in this and previous studies; conversely, in the present analysis, lung weights were reduced in the absence of demonstrated impact on SPM content.

SPM Load Analysis in Liver, Kidney, Spleen, and Lung

Repeated administrations of rhASM resulted in a dose-dependent clearance of renal SPM load in ASMKO mice, as well as a low SPM load in the spleen and liver of ASMKO mice. Conversely, rhASM did not result in significant reduction in SPM load in the lungs of ASMKO mice treated with 10 or 30 mg/kg of rhASM, when compared to 3 mg/kg.

Gross Pathology

There were no treatment-related observations.

Histopathology

Evaluation of microscopic pathology data was difficult, especially among treated males: only 3, 6, and 6 males survived until scheduled necropsy; and the reader is directed to compare these findings to those of controls in Study 06031, which was conducted 4 years prior. Many organs were affected; frequently, these were of minimal or mild severity. Unsurprisingly, CNS tissues were unaffected by treatment, as olipudase alfa does not penetrate the blood-brain barrier. Findings that may be related to treatment, or that may reflect improvement in the pathophysiology of the ASMKO mouse, are reproduced below in Table 127. Additionally, brain and spinal cord data are included for purposes of completeness.

Table 127. Histopathology Observations

	Males			Females		
Tissue Examined	**3 mg/kg (N=3)**	**10 mg/kg (N=6)**	**30 mg/kg (N=6)**	**3 mg/kg (N=3)**	**10 mg/kg (N=8)**	**30 mg/kg (N=8)**
Adrenal gland						
Hyperplasia subcapsular, minimal	0	0	2	3	5	7
Aorta						
Smooth muscle vacuolization, minimal	3	5	5	3	7	7
Bone, femur, or sternum						
Marrow, cellularity increased, moderate	3	6	6	3	8	8
Marrow, macrophages increased, minimal	2	3	0	1	0	0
Brain						
Vacuolization, neuronal, mild	3	6	6	3	8	8
Degeneration, Purkinje cell, moderate	3	6	6	3	8	8
Vacuolization, cerebellar stellate cells, minimal	3	6	6	3	8	8
Epididymides						
Vacuolization, tubular epithelium, minimal-moderate	3	6	6	-	-	-
Eyes with optic nerves						
Degeneration, bilateral, moderate-marked	0	2	0	2	3	3
Kidneys						
Mononuclear infiltrate, minimal	0	4	2	0	2	2
Vacuolization, tubular epithelium, min-mod	3	6	6	3	8	2
Lung						
Foamy macrophages, minimal-moderate	3	6	6	3	8	8
Vacuolization, epithelial, minimal	3	6	5	3	7	5
Lymph node, mesenteric						
Foamy macrophages, minimal-mild	3	5	4	3	7	8
Ovaries						
Foamy macrophages, minimal to moderate	-	-	-	3	8	8

	Males			Females		
Tissue Examined	**3 mg/kg (N=3)**	**10 mg/kg (N=6)**	**30 mg/kg (N=6)**	**3 mg/kg (N=3)**	**10 mg/kg (N=8)**	**30 mg/kg (N=8)**
Pancreas						
Vacuolization, acinar epithelium, minimal	3	5	6	3	5	3
Pituitary						
Vacuolization, pars nervosa, pituicytes	0	2	2	0	3	5
Preputial gland						
Inflammation, chronic, minimal-mild	1	0	2	-	-	-
Abscess	0	5	4	-	-	-
Seminal vesicles						
Vacuolization, epithelial, minimal	3	6	6	-	-	-
Spinal cord						
Vacuolization, neuronal, all sections, mild	3	6	6	3	8	8
Spleen						
Foamy macrophages, minimal	1	0	0	0	0	0
Testes						
Degeneration, tubular, minimal	2	6	3	-	-	-
Thymus						
Foamy macrophages, minimal-mild	2	6	6	3	7	5
Thyroid						
Vacuolization, epithelial, minimal	3	5	6	3	8	8
Uterus with cervix						
Vacuolization, epithelial, minimal-mild				3	8	8

Source: Reviewer generated.
Abbreviations: N, total number of subjects.

The following commentary is excerpted from the pathology report (Genzyme study report 10-00262-Pnp, pg. 213):

> *Microscopically, control mice (referenced from Genzyme study 06031) exhibited cytoplasmic vacuolization and/or foamy macrophages in a wide range of visceral organs as well as central nervous system tissues, consistent with the ASMKO phenotype. Relative to these controls, treated mice in the current study exhibited a test article related decrease in the incidence and/or severity of cytoplasmic vacuolization and the number/size of foamy macrophages in a variety of visceral tissues. Affected tissues were the same as those described previously (see Genzyme study 06031) and included liver, kidney, bone marrow, thymus, lymph nodes adrenal gland, small intestine, spleen, stomach, trachea, pancreas, cervix, ovary, uterus, and epididymis. Adding the debulking phase contributed to the decrease in incidence and/or severity of cytoplasmic vacuolization and the number/size of foamy macrophages. Central nervous system tissues were unaffected by treatment.*

Table 128. 26-Week Intravenous Injection Chronic Toxicity Study With Recombinant Human Acid Sphingomyelinase (rhASM) in Rats With a 4-Week Recovery Period

Study Parameter	Study Information
Study no.:	02027
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12/30/02
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SM034DP, 96.9%

Source: Review team.
Abbreviations: GLP, good laboratory practice; QA, quality assurance; (b) (4)

Key Study Findings

Olipudase alfa was administered intravenously to male and female SD rats once every 2 weeks for 26 weeks (14 total doses) at 3, 10, or 30 mg/kg; control groups included both saline and vehicle-treated cohorts. From the second to the eighth dose administration, DPH was given intravenously prior to olipudase alfa; however, it was determined that this produced convulsions, and the procedure was eliminated. Terminal necropsies were conducted at the end of dosing and following a 4-week recovery period.

Two males treated with 30 mg/kg died after blood sample collection; these deaths were not attributed to treatment. Clinical observations related to olipudase alfa administration were limited to signs associated with hypersensitivity. There were no adverse treatment-related findings on any in-life or terminal evaluations or procedures. The NOAEL was 30 mg/kg. $AUC_{(0\text{-}24)}$ values associated with this dose on day 183 were 1122 and 1690 µg*h/mL in females and males, respectively; C_{max} values were 522 and 810 µg/mL.

Table 129. Study 02027 Methods

Method	Description
Doses:	Olipudase alfa 0 (saline), 0(vehicle), 3, 10, and 30 mg/kg DPH 1.25-5 mg/kg (see Note below).
Frequency of dosing:	Once every 2 weeks
Route of administration:	IV injection
Dose volume:	8.11 mL/kg
Formulation/Vehicle:	Recombinant human acid sphingomyelinase (rhASM) placebo buffer
Species/Strain:	SD rats
Number/Sex/Group:	15/sex/group
Age:	7 weeks old
Weight:	196-239 g (male) and 155-189 g (female)
Satellite groups:	No
Unique study design:	None
Deviation from study protocol:	No impact on the overall interpretation of the study findings.

Source: Review team.
Note: Starting with the second dose (Day 15) and continuing through the eighth dose (Day 99), all rats were pretreated with an intravenous injection of diphenhydramine hydrochloride (DPH) to attenuate symptoms of a possible allergic reaction to rhASM. Adverse clinical observations attributed to DPH 5 mg/kg caused the dose to be reduced to 2.5 mg/kg at the seventh dose, then 1.25 mg/kg for the eighth dose. Thereafter, DPH dosing was eliminated.
DPH, diphenhydramine; IV, intravenous; SD, Sprague Dawley.

Table 130.Study 02027 Design

Group Toxicity Animals	No. of Animals Male	Female	Dose Level mg/kg/dose	Dose Concentration (mg/mL)[a]
1 (Control/Saline)[b]	5	5	0	0
2 (Control/Vehicle)[c]	15[d, e]	15[d, e]	0	0
3 (Low)	15[d, e]	15[d, e]	3	0.37
4 (Mid)	15[d, e]	15[d, e]	10	1.23
5 (High)	15[d, e]	15[d, e]	30	3.7

a Dose concentrations are based on actual values. The dose volume was 8.11 mL/kg.
b Animals received saline only.
c Animals received the control/vehicle article only.
d First 5 rats/sex/group were used for toxicokinetic blood collection.
e Animals designated for recovery sacrifice [last 5 surviving rats in Groups 2 and 3, Group 4 males, and Group 5 females; last 3 surviving Group 5 male rats; last 4 surviving Group 4 female rats)] underwent 4 weeks of recovery following at least 26 weeks of dose administration.

Source: Genzyme Study Report 02027, pg. 14.

Observations and Results

Mortality

There were five unscheduled deaths during the study. Neither of the female deaths are attributed to olipudase alfa administration. Although 3 deaths occurred in males treated with 30 mg/kg, relationship to treatment is uncertain (signs of hypersensitivity in 1, death following blood sample collection in 2). Information is reviewed in Table 131.

Table 131. Study 02027 Premature Decedents

Sex	Dose (mg/kg)	Animal	# Doses	Comment
Males	30	B58876	7	Day 85. Clinical signs of convulsions, irregular respiration, hypoactivity, paleness. Death occurred after pre-dose toxicokinetic sample collection and dose administration
		B58879	6	Day 71. Death occurred after dose administration. 1 day following blood sample collection.
		B58881	6	Day 81. No clinical observations. Found dead after clinical pathology sample collection.
Females	0 (vehicle)	B58898	2	Day 24. Found dead. Necropsy: pale kidneys, distended bladder with urine. Histopathology: lymphoid necrosis, renal infarction and inflammation, urethral dilation, necrosis, subacute inflammation
	10	B58935	3	Day 29. Clinical signs of labored, irregular respiration; sternal recumbency; cold to touch, disorientation, hypoactivity

Source: Reviewer generated.

Clinical Signs

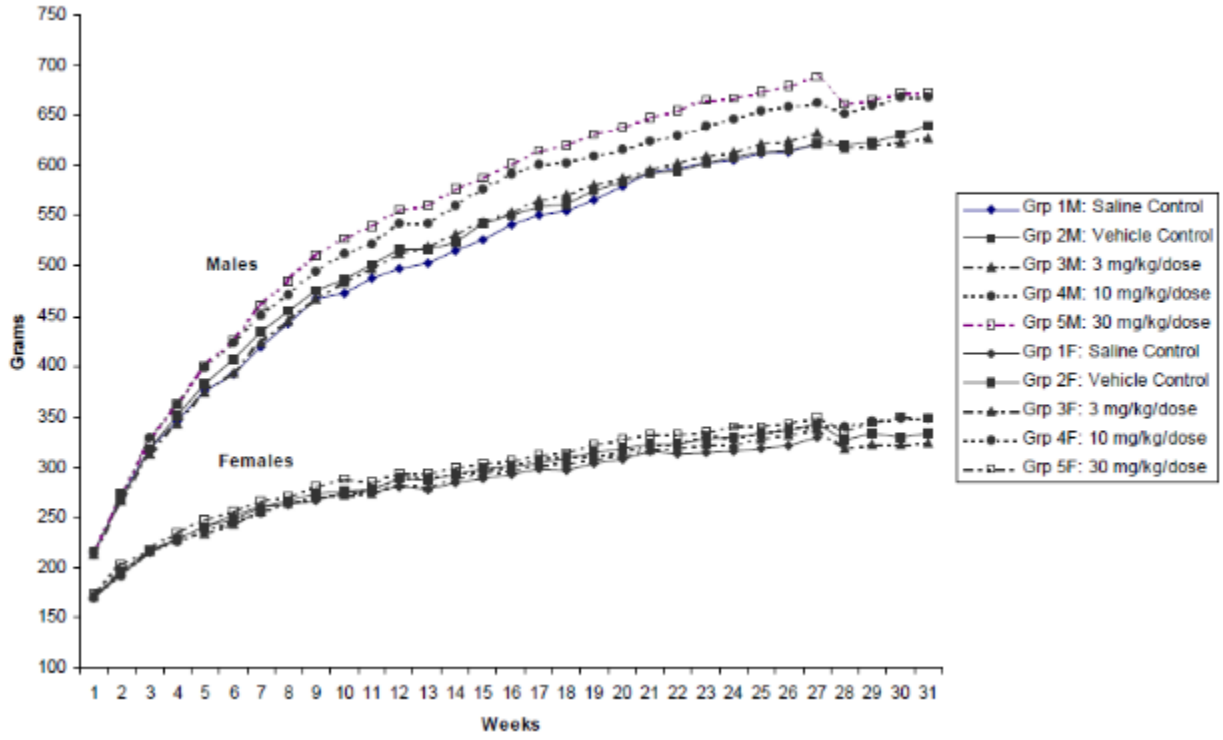
Hypoactivity was noted in 3 animals (Female B58935 on days 15 and 29, female B58931 on day 113, and male B58876 on day 85); these observations are attributed to hypersensitivity. Convulsions were noted in 1 vehicle female, 1 LD male, 3 MD males on days 85, 29 and 99, respectively. Starting with the ninth dose (day 113), DPH pretreatments were eliminated. No

further clinical signs convulsions were noted; as such, these were attributed to DPH administration.

Body Weights and Food Consumption

There were no meaningful adverse effects of olipudase alfa administration on body weights or food consumption in males or females.

Figure 59. Body Weights in Rats Treated With Olipudase Alfa Every Other Week for 26 Weeks



Source: Genzyme report 02027, pg. 23.
Abbreviations: F, female; Grp, group; M, male.

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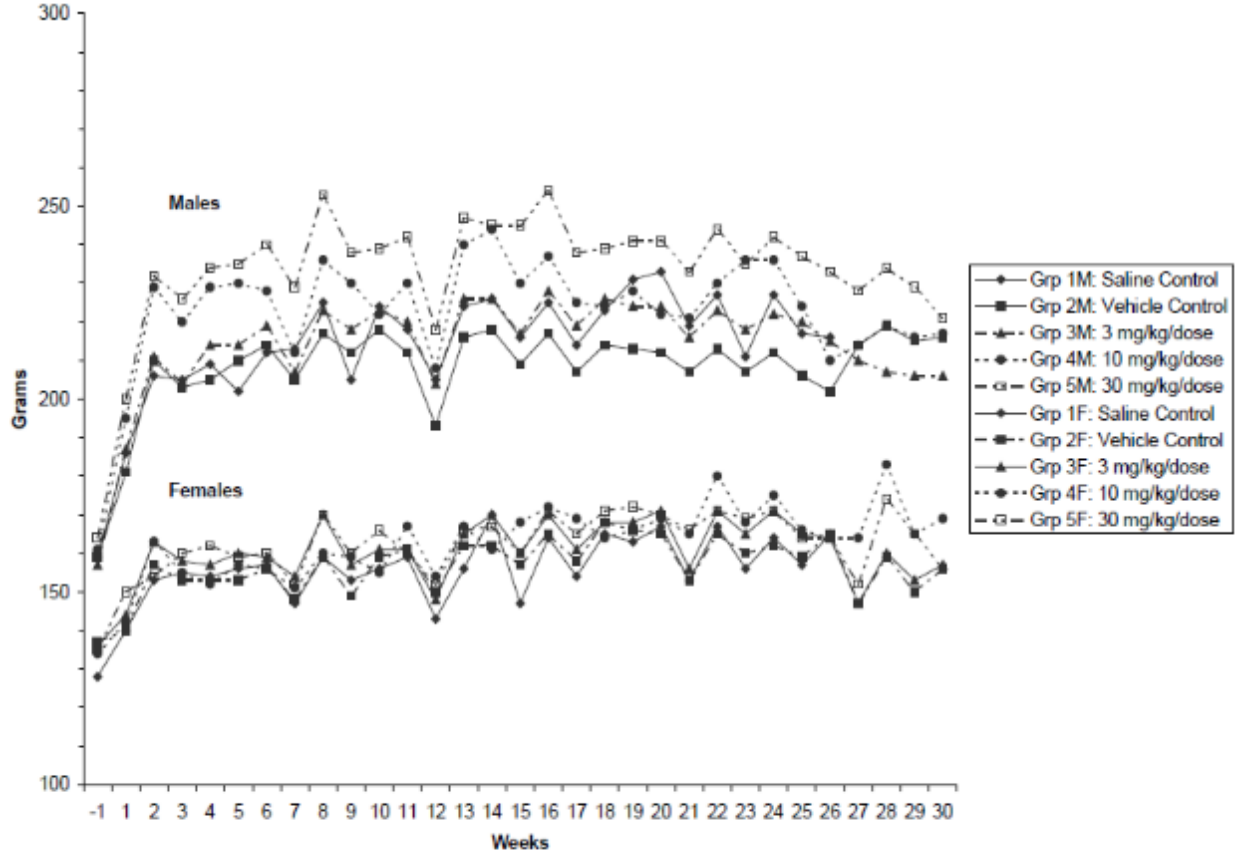
Figure 60. Food Consumption in Rats Treated With Olipudase Alfa Every Other Week for 26 Weeks



Source: Genzyme report 02027, pg. 24.
Abbreviations: F, female; Grp, group; M, male.

Ophthalmoscopy

There were no visible lesions in any animals.

ECG

Not conducted.

Hematology

Hematology parameters were comparable among all experimental groups.

Clinical Chemistry

Clinical chemistry parameters were comparable among all experimental groups.

Urinalysis

Urinalysis parameters were comparable among all experimental groups.

Gross Pathology

There were no treatment-related observations.

Organ Weights

Although not statistically significant, TBWs of 30 mg/kg males were ~12% greater than those in the vehicle control. Likewise in the 30 mg/kg group males, liver weights relative to brain weights were increased by 20%. This was not judged to be adverse, as there was no histopathologic correlate.

Histopathology

Adequate Battery: Yes

Peer Review: quality assurance statement indicates that there was a data review.

There were no treatment-related findings.

Special Evaluation

Anti-Drug Antibodies (ADA)

Serum samples were analyzed for the presence of antibodies to olipudase alfa on days 1, 85 and 183 of the study.

- On day 1, anti-olipudase alfa antibodies were not detected in any dose group.
- On day 85, anti-olipudase alfa antibodies were detected in 1/10 LD, 1/10 MD, and 2/10 HD animals.
- On day 183, anti-olipudase alfa antibodies were detected in 2/10 LD, 4/10 MD, and 1/10 HD animals.

Anti-olipudase alfa antibody responses were similar between male and female rats and did not correlate with hypersensitivity reactions or a decrease in exposure.

Liver Olipudase Alfa Concentrations

Liver sections were evaluated 24 hours and 28 days following administration of the final dose. olipudase alfa levels at 24 hours were increased in a dose-related profile in both males and females; by 28 days later, these were reduced, and comparable across treatment groups. Concentrations are reproduced below in Table 132. The reason for detection of rhASM in vehicle-treated animals was not addressed.

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Table 132. rhASM Liver Concentrations After Olipudase Alfa Administration Every Other Week for 26 Weeks

MALE	Liver rhASM levels 24 hours post final dose µg rhASM/g wet tissue mean +/- (SD)	Liver rhASM levels 28 days post final dose µg rhASM/g wet tissue mean +/- (SD)
Group 2 vehicle	0.21 (0.17)	NA
Group 3 3 mg/kg	0.57 (0.16)	0.27 (0.09)
Group 4 10 mg/kg	0.83 (0.35)	0.40 (0.16)
Group 5 30 mg/kg	2.31 (0.67)	0.38 (0.05)
FEMALE	Liver rhASM levels 24 hours post final dose µg rhASM/g wet tissue mean +/- SD	Liver rhASM levels 28 days post final dose µg rhASM/g wet tissue mean +/- SD
Group 2 vehicle	0.15 (0.09)	NA
Group 3 3 mg/kg	0.57 (0.26)	0.31 (0.05)
Group 4 10 mg/kg	0.89 (0.22)	0.44 (0.09)
Group 5 30 mg/kg	2.03 (0.74)	0.32 (0.04)

Source: Genzyme study report 03-0604 Pnp, pg. 31.
Abbreviations: N/A, not analyzed; rhASM, recombinant human acid sphingomyelinase; SD, standard deviation.

Toxicokinetics

The TK data were submitted in a different study report (Study No. 03-0604Pnp). Observations regarding the data were as follows:

- Olipudase alfa exposure in both the male and female rats increased in a less than dose proportional manner (3-30 mg/kg) where a 10-fold increase in dose results in only an approximately 7-fold increase in exposure.
- There were differences between males and females. Exposures were higher in male rats in the 10 and 30 mg/kg dose groups on days 1, 85 and 183; and in the 3 mg/kg group on day 183.
- All pre-dose serum samples from males and females on days 1, 85 and 183 were below the limit of detection for rhASM.

Data are reproduced below in Table 133, Table 134, and Table 135.

Table 133. Day 1 Toxicokinetic Parameters Following Repeat Administration of Olipudase Alfa to Male and Female Sprague-Dawley Rats (n=5/Sex/Group, Mean ± SD)

Parameter	3 mg/kg female	3 mg/kg male	10 mg/kg female	10 mg/kg male	30 mg/kg female	30 mg/kg male
C_{max} (µg/mL)[a]	75.15 ± 15.25	70.18 ± 21.21	122.74 ± 19.62	123.56 ± 36.80	540.63 ± 141.30	568.17 ± 110.49
$t_{1/2}$ β (hr)	0.63 ± 0.13	0.72 ± 0.24	0.63 ± 0.17	0.86 ± 0.27	0.76 ± 0.47	0.75 ± 0.67
AUC (µg*hr /mL)	130.39 ± 7.77	123.30 ± 6.12	184.88 ± 47.66	235.26 ± 66.78	643.35 ± 91.29	679.32 ± 147.88
AUC/dose (µg*hr/mL/mg/kg)	43.46 ± 2.59	41.10 ± 2.04	18.49 ± 4.77	23.53 ± 6.68	21.45 ± 3.04	22.64 ± 4.93

Abbreviations: C_{max}: maximum concentration; $t_{1/2\beta}$: terminal half-life; AUC: area under the concentration versus time curve extrapolated to infinity
a IV Bolus
Source: Genzyme report 02027.

Table 134. Day 85 Toxicokinetic Parameters Following Repeat Administration of Olipudase Alfa to Male and Female Sprague-Dawley Rats (n=5/Sex/Group, Mean ± SD)

Parameter	3 mg/kg female	3 mg/kg male	10 mg/kg female	10 mg/kg male	30 mg/kg female	30 mg/kg male
C_{max} (µg/mL)[a]	64.99 ± 6.34	91.81 ± 8.12	215.75 ± 27.73	226.83 ± 48.13	701.29 ± 33.92	880.90 ± 87.25
$t_{1/2}$ β (hr)	0.51 ± 0.12	0.60 ± 0.11	0.91 ± 0.56	1.43 ± 1.33	1.22 ± 0.63	1.49 ± 0.47
AUC (µg*hr /mL)	101.64 ± 10.27	160.29 ± 24.81	398.99 ± 119.87	541.47 ± 269.99	1255.71 ± 267.42	1871.77 ± 188.45
AUC/dose (µg*hr/mL/mg/kg)	33.88 ± 3.42	53.43 ± 8.27	39.90 ± 11.99	54.15 ± 27.00	41.86 ± 8.91	62.39 ± 6.28

Abbreviations: C_{max}: maximum concentration; $t_{1/2\beta}$: terminal half-life; AUC: area under the concentration versus time curve extrapolated to infinity
a IV Bolus
Source: Genzyme report 02027.

Table 135. Day 183 Toxicokinetic Parameters Following Repeat Administration of Olipudase Alfa to Male and Female Sprague-Dawley Rats (n=5/Sex/Group, Mean ± SD)

Parameter	3 mg/kg female	3 mg/kg male	10 mg/kg female	10 mg/kg male	30 mg/kg female	30 mg/kg male
C_{max} (µg/mL)[a]	96.29 ± 15.98	134.91 ± 11.17	19.75 ± 36.98	253.48 ± 54.56	521.89 ± 137.58	810.04 ± 99.62
$t_{1/2}$ β (hr)	1.45 ± 0.08	1.78 ± 0.25	1.50 ± 0.76	0.71 ± 0.31	1.48 ± 0.53	1.30 ± 0.12
AUC (µg*hr /mL)	143.84 ± 19.07	230.94 ± 24.50	386.93 ± 114.04	449.14 ± 151.65	1121.97 ± 175.06	1689.73 ± 285.73
AUC/dose (µg*hr/mL/mg/kg)	47.95 ± 6.36	76.98 ± 8.17	38.69 ± 11.40	44.91 ± 15.17	37.40 ± 5.84	56.32 ± 9.52

Abbreviations: C_{max}: maximum concentration; $t_{1/2\beta}$: terminal half-life; AUC: area under the concentration versus time curve extrapolated to infinity
a IV Bolus
Source: Genzyme report 02027.

Dosing Solution Analysis

Dose formulations at concentrations of 0.3 to 3.7 mg/mL used in the study were stable over a period of 22 hours at room temperature after preparation. The results from the analyses of dose formulation samples on the days 1, 43, 85, 127, and 183 were within ±16% of target concentration, confirming the accuracy of preparation.

Table 136. 26-Week Intravenous Infusion Chronic Toxicity and Toxicokinetic Study With Recombinant Human Acid Sphingomyelinase (rhASM) in Cynomolgus Monkeys With a 4-Week Recovery Period

Study Parameter	Study Information
Study no.:	07007
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/05/07
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SM066 (97.7% purity) and SM076 (97.9% purity)

Source: Review team.
Abbreviations: GLP, good laboratory practice; QA, quality assurance (b) (4)

Key Study Findings

IV administration of olipudase alfa to male and female monkeys once every 2 weeks for 26 weeks (13 total doses) at 3, 10, or 30 mg/kg was well tolerated. The NOAEL was 30 mg/kg, the highest dose tested.

Table 137. Study 07007 Methods

Method	Description
Doses:	0(vehicle), 3, 10, and 30 mg/kg/day
Frequency of dosing:	Once every 2 weeks
Route of administration:	IV injection
Dose volume:	7.7 mL/kg
Formulation/Vehicle:	Recombinant human acid sphingomyelinase (rhASM) placebo buffer, containing (b) (4) mM sodium phosphate (b) (4) % sucrose, (b) (4) mM (b) (4) methionine at pH 6.5
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	3M +2F (control), 4M +4F (LD, MD, and HD)
Age:	2.5 to 5 years old
Weight:	2.4 – 6.4 kg (male) and 1.9 - 3.0 kg (female)
Satellite groups:	Yes, recovery group (2M +2F for control, 3M +3F for LD and MD, and 3M +2F for HD).
Unique study design:	None
Deviation from study protocol:	No impact on the overall interpretation of the study findings.

Source: Review team.
Abbreviations: (b) (4) F, female; HD, high dose; IV, intravenous; LD, low dose; M, male; MD, middle dose.

Table 138. Study 07007 Design

Group No.	No. of Animals[b]		Test Article	Dose (mg/kg)	Dosing Regimen	Route of Administration
	Terminal M/F	Recovery Female				
1	3/4	2/2	Vehicle	0 mg/kg	Every other week for 26 weeks	IV
2	4/4	3/3	olipudase alfa	3 mg/kg		
3	4/4	3/3		10 mg/kg		
4	4/4	3/2		30 mg/kg		
5[a]	1/0	0/0	Vehicle	0 mg/kg	Every other week for 5 weeks	

Abbreviations: M: male; F: female; IV: Intravenous
a Animal I61776, a Group 1 male, was not dosed after Day 29 (third dose) due to an irreparable catheter dysfunction. The monkey was moved to Group 5, given a new animal number (I62480), and not dosed further, although it was on the same schedule for evaluation of all other parameters as the other animals in the group.
b Reflects the numbers of animals that survived to scheduled terminations
Source: Genzyme report 07007.

Observations and Results

Mortality

No effect. There were three unscheduled sacrifices on the study that were unrelated to treatment with the test article. A control female on day 110 (Week16), a control male on day 169 (Week 25), and a 30 mg/kg/day female on day 138 (Week 20) suffered accidental limb fractures and were euthanized for humane reasons.

Clinical Signs

No effect.

Body Weight

No effect.

Food Consumption

No effect.

Ophthalmoscopy

No effect.

ECG

Not conducted.

Hematology

No effect.

Clinical Chemistry

No effect.

Urinalysis

No effect.

Gross Pathology

No effect.

Organ Weights

No effect.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

No effect except microscopic findings at infusion and catheter sites.

These findings included intimal fibrosis, luminal fibrosis (fibrotic mass derived from organized thrombus surrounding the catheter located within the vessel lumen), intimal thickening, macrophage derived neoendothelium, granuloma, and granulomatous or suppurative inflammation. These findings were expected in studies where indwelling catheters were present and there was no effect of treatment on their incidence or severity.

Microscopic inflammatory, fibrotic, or vascular lesions were noted particularly in the kidney, lung, heart, and liver. These lesions were considered to result from the presence of the venous catheter and there was no effect of treatment on the incidence or severity of these lesions.

Special Evaluation

ADA

Results of antibody analysis suggested that the repeated administration of rhASM resulted in detectable levels of anti-rhASM antibodies.

Anti-olipudase alfa antibody levels were detectable in groups that received olipudase alfa by day 29 (after the 3rd dose). There was an overall trend in increasing anti-olipudase alfa antibody titers after repeated dosing, with maximal antibody titers observed between the seventh and thirteenth dose administrations. After the final dose administration (day 169), all of LD animals had detectable titers, 13 of 14 MD animals had detectable titers, and all of HD animals had detectable titers.

Vehicle animals had no detectable anti-olipudase alfa immune response throughout the duration of the study.

Toxicokinetics

Single dose toxicokinetics following the first rhASM infusion were not dose proportional, as the terminal elimination half-life increased, and clearance decreased with escalating dose levels.

The terminal elimination half-life following the first infusion ranged from 8.40 hours at 3.0 mg/kg to 13.4 hours at 30.0 mg/kg. Dose 1 rhASM exposure averaged 202 ug•hr/ml at 3.0 mg/kg, 988 ug•hr/ml at 10.0 mg/kg, and 3712 ug•hr/ml at 30.0 mg/kg.

Recombinant human ASM toxicokinetics following the sixth and thirteenth infusion were not consistent with those observed following the first infusion.

At each dose level rhASM exposure after Dose 6 and 13 was 30% to 50% lower than that observed following Dose 1. Changes in exposure with repeated rhASM infusions mediated increased clearance and decreases in the elimination half-life.

Nonlinear regression analysis indicated that decreases in rhASM exposures could be correlated to increased anti-rhASM titers.

Table 139. Day 1 TK Parameters Following the First Infusion of Olipudase Alfa in Cynomolgus Monkeys at 3, 10, or 30 mg/kg (n=6-7/Sex/Group, Mean ± SD)

Parameter	3 mg/kg female	3 mg/kg male	10 mg/kg[a] female	10 mg/kg[a] male	30 mg/kg female	30 mg/kg male
C_{max} (µg/mL)[b]	41.84 ±5.63	46.21 ± 7.10	254.66 ± 25.00	252.57 ± 26.47	690.64 ± 70.08	721.89 ± 114.39
$t_{1/2\beta}$ (hr)	8.16 ± 2.19	8.65 ± 2.19	11.20 ± 3.04	12.44 ± 2.80	14.19 ± 3.46	12.59 ± 2.15
AUC (µg*hr/mL)	186.84 ± 21.59	217.99 ± 45.34	936.15 ± 110.62	1039.15 ± 187.73	3589.51 ± 255.27	3834.81 ± 513.45
AUC/dose (µg*hr/mL/mg/kg)	62.28 ± 7.20	72.66 ± 15.11	93.62 ± 11.06	103.92 ± 18.77	119.65 ± 8.51	127.83 ± 17.12

Abbreviations: C_{max}: maximum concentration; $t_{1/2\beta}$: terminal half-life; AUC: area under the concentration versus time curve extrapolated to infinity

a n=6/sex

b IV Infusion, 30 minutes

Source: Genzyme report 07007.

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Table 140. Day 71 (Dose 6) TK Parameters Following Repeated Infusions of Olipudase Alfa in Cynomolgus Monkeys at 3, 10, or 30 mg/kg (n=7/Sex/Group, Mean ± SD)

Parameter	3 mg/kg female	3 mg/kg male	10 mg/kg female	10 mg/kg male	30 mg/kg female	30 mg/kg male
C_{max} (µg/mL)[a]	32.78 ± 8.62	38.94 ± 5.45	199.68 ± 62.87	194.54 ± 32.53	1214.74 ± 791.93	625.54 ± 97.59
$t_{1/2\beta}$ (hr)	6.76 ± 5.52	4.90 ± 3.29	8.06 ± 1.88	7.86 ± 3.28	4.93 ± 2.05	5.85 ± 1.28
AUC (µg*hr/mL)	113.93 ± 64.75	122.20 ± 64.05	701.29 ± 153.44	726.31 ± 248.77	2703.09 ± 308.02	2724.63 ± 394.36
AUC/dose (µg*hr/mL/mg/kg)	37.98 ± 21.58	40.73 ± 21.35	70.13 ± 15.34	72.63 ± 24.88	90.10 ± 10.27	90.82 ± 13.15

Abbreviations: C_{max}: maximum concentration; $t_{1/2\beta}$: terminal half-life; AUC: area under the concentration versus time curve extrapolated to infinity;
a IV Infusion, 30 minutes
Source: Genzyme report 07007.

Table 141. Day 169 (Dose 13) TK Parameters Following Repeated Infusions of Olipudase Alfa in Cynomolgus Monkeys at 3, 10, or 30 mg/kg (n=6-7/Sex/Group, Mean ± SD)

Parameter	3 mg/kg female	3 mg/kg male	10 mg/kg female	10 mg/kg male	30 mg/kg female[a]	30 mg/kg male
C_{max} (µg/mL)[b]	26.80 ± 11.69	33.29 ± 9.36	216.81 ± 70.73	200.63 ± 44.93	728.83 ± 148.04	707.09 ± 153.05
$t_{1/2\beta}$ (hr)	2.75 ± 2.40	3.68 ± 3.88	6.34 ± 4.99	10.09 ± 7.12	4.77 ± 1.64	7.86 ± 4.00
AUC (µg*hr/mL)	97.59 ± 81.36	98.81 ± 71.38	601.84 ± 283.70	741.21 ± 317.13	2344.14 ± 837.70	2434.22 ± 837.04
AUC/dose (µg*hr/mL/mg/kg)	32.53 ± 27.12	32.94 ± 23.79	60.18 ± 28.37	74.12 ± 31.71	78.14 ± 27.92	81.07 ± 27.90

Abbreviations: C_{max}: maximum concentration; $t_{1/2\beta}$: terminal half-life; AUC: area under the concentration versus time curve extrapolated to infinity;
a n=6 females
b IV Infusion, 30 minutes
Source: Genzyme report 07007.

Dosing Solution Analysis

Dose analysis results for the 1st, 6th and 13th dose concentration samples met the ±25% of expected value for all dose levels tested.

The real-time stability results collected in this study indicated that rhASM Drug Product (Lot SM066) diluted in rhASM buffer (b) (4) mM sodium phosphate, (b) (4)% sucrose, (b) (4) (b) (4) mM (b) (4) methionine at pH 6.5) and held in polypropylene tubes was stable at controlled room temperatures for up to 24 hours.

An evaluation of every other week pump accuracy measurements, which were based on weight of remaining test article and assumes a specific gravity of 1, showed individual dose administrations were within an acceptable range of ±20% for all or the majority of dosing days in all animals. All measurements were within this acceptable range for all animals on TK collection days with the exception of 2 animals on day 71: 3 mg/kg/dose Male I61783 (129.1%), and 30 mg/kg/dose Female I61827 (123.3%).

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Fertility and Early Embryonic Development

Table 142. GZ402665 (Olipudase Alfa): Intravenous Fertility and Early Embryonic Development to Implantation in Mice

Study Parameter	Study Information
Study no.:	FER0510
Study report location:	001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 10, 2017
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	rhASM, 7W0439, 97.2%

Source: Review team.
Abbreviations: GLP, good laboratory practice; (b) (4) QA, quality assurance; rhASM, recombinant human acid sphingomyelinase.

Key Study Findings

Male and female CD1 mice were treated with olipudase alfa (0/Saline, 0/DPH, 3, 10, or 30 mg/kg) every other day for 28 days (males) or 14 days (females) prior to cohabitation. Males and females were bred to corresponding experimental groups. Treatment of males continued until necropsy when sperm parameters were assessed. Male reproductive organ weights and histopathology were evaluated. Treatment of females continued through gestation day (GD) 7. Cesarean sections were conducted on GD 14. Cesarean section parameters and ovarian weights were evaluated.

There were 24 unscheduled decedents in this study (11 males and 13 females). Twenty-three of these deaths were related to treatment and attributed to hypersensitivity, although [same-day] post-dose clinical observations associated with hypersensitivity were only apparent in 7 of 23 animals. Conversely, 8 of 50 males and females in the 3 mg/kg dose group, 7 of 50 males and females in the 10 mg/kg dose group, and 1 of 50 animals (female) died without specific adverse clinical observations indicative of hypersensitivity that were temporally-related to the time of death. Notably, histopathologic evaluations were not conducted on any premature decedents, whether male or female, when deaths were attributed to hypersensitivity. Clinical observations associated with hypersensitivity included increased/decreased motor activity, ataxia, hyper-reactivity, tremors/whole body twitches, vocalization, and cold-to-touch. These were observed in some, although not most, premature decedents; as well as in animals that survived until scheduled necropsy, especially in the 30 mg/kg dose group.

There were no other treatment-related findings in this study. Considered together, there are no dose-related adverse findings independent of hypersensitivity. The parental NOAEL is 30 mg/kg. Data for AUC and C_{max} in females are taken from TER0694 (916 µg*h/mL and 409 µg/mL, respectively). Data for AUC and C_{max} in males are unavailable in this strain of mouse.

Table 143. Study FER0510 Methods

Method	Description
Doses:	0/Saline, 0/DPH, 3, 10, 30 mg/kg
Frequency of dosing:	Every other day
Dose volume:	7.7 or 8.1 mL/kg
Route of administration:	Intravenous (rhASM) Intraperitoneal (DPH)
Formulation/Vehicle:	(b) (4)mM sodium phosphate (b) (4)% sucrose, (b) (4)mM methionine, (b) (4) (pH =6.5)
Species/Strain:	Mouse / Crl: CD1(ICR)
Number/Sex/Group:	25
Satellite groups:	N
Study design:	See below (Table 144)
Deviation from study protocol:	Y (none impacting data interpretation or study integrity)

Source: Review team.
Abbreviations: DPH, diphenhydramine; (b) (4) N, no; rhASM, recombinant human acid sphingomyelinase; Y, yes.

Table 144. Study FER0510 Design (Mouse FEED Study)

Group No.	Test Material	Dose Level (mg/kg/dose)	Concentration (mg/mL)	Dose Volume[a] (mL/kg)	Route of Administration	No. of Animals (Assigned Mouse Numbers)	
						Males	Females
1	Control[b]/saline[c]	0	0	8.1/4 (M), 7.7/4 (F)	IV injection[d]/ IP injection[c]	25 (501-525)	25 (701-725)
2	Control[b]/DPH[e]	0/20	0/5	8.1/4 (M), 7.7/4 (F)	IV injection[d]/ IP injection[f]	25 (526-527, 25[g], 529-550)	25 (726-750)
3	Olipudase alfa/ DPH[e]	3.16/20	0.39/5	8.1/4 (M), 7.7/4 (F)	IV injection[d]/ IP injection[f]	25 (551-575)	25 (751-775)
4	Olipudase alfa/ DPH[e]	10/20	1.23/5	8.1/4 (M), 7.7/4 (F)	IV injection[d]/ IP injection[f]	25 (576-600)	25 (776-800)
5	Olipudase alfa/ DPH[e]	30/20	3.70/5	8.1/4 (M), 7.7/4 (F)	IV injection[d]/ IP injection[f]	25 (601-625)	25 (801-825)

M = Male; F = Female.
[a] See Appendix 1, Protocol, Amended Protocol, and Deviations.
[b] (b) (4)mM sodium phosphate, (b) (4)% sucrose, (b) (4)mM methionine, (b) (4) at a pH of 6.5
[c] Saline administration by intraperitoneal injection.
[d] Intravenous administration by bolus.
[e] Diphenhydramine Hydrochloride
[g] Intraperitoneal injection for DPH administration only (10 – 20 min prior to dose administration of control article or test article).
[g] Male 528 (Group 2) was found dead after tattooing, was excluded from study, and was replaced with male 25.
Source: Study report FER0510, pg. 28.
Abbreviations: DPH, diphenhydramine; FEED, Fertility and Early Embryonic Development ; IP, intraperitoneal; IV, intravenous; No., number.

Male mice were administered the test article or the control article formulations once every other day beginning 28 days before cohabitation, during cohabitation and continuing until euthanasia. Female mice were administered the test article or the control article formulations once every other day beginning 15 days before cohabitation, during cohabitation and continuing until (GD) 7. In Groups 2 through 5, beginning with the second dose, DPH was administered by IP injection 10-20 minutes prior to dosing the test article.

Males and females were bred to corresponding experimental groups. Fertility parameters were evaluated in both sexes, with estrous cyclicity also assessed in females. At male necropsy, sperm parameters were assessed; reproductive organ weights and histopathology were evaluated. Cesarean sections of females were conducted on GD 14, with cesarean section parameters and ovarian weights reported.

Observations and Results

Mortality

There were 24 unscheduled decedents in this study (11 males and 13 females). One female (818) was euthanized for inability to use the left forelimb; at necropsy, fractures of the radius and ulna were recorded. Remaining deaths were attributed to hypersensitivity, although [same-day] post-dose clinical observations associated with hypersensitivity were only apparent in 7 out of 22 animals. Specifically, 8 of 50 males and females in the 3 mg/kg dose group, 7 of 50 males and females in the 10 mg/kg dose group, and 1 of 50 animals (female) died without specific adverse clinical observations indicative of hypersensitivity that were temporally-related to the time of death. Notably, histopathologic evaluations were not conducted on any premature decedents, whether male or female, when deaths were attributed to hypersensitivity.

Mortality is outlined in Table 145.

Table 145. Unscheduled Mortality in the Mouse FEED Study

Sex	Dose	Animal	# of Doses	Time of Death, Postdose Clinical Observations (if any)
Male	3	555	12	Immediately after dosing. Ataxia
		558	9	57 min after dosing. Ataxia,
		563	17	67 min after dosing.
		564	7	41 min after dosing. Ataxia, decreased motor activity, absent righting reflex, labored breathing, gasping
		565	5	2h 49 min after dosing.
		566	11	35 min after dosing.
		569	6	73 min after dosing.
	10	580	7	34 min after dosing. Ataxia, decreased motor activity.
		587	8	<2h.
		595	5	96 min post dose.
		596	11	[Euthanized prior to dosing]. Tremors, body jerks.
Female	3	760	6	54 min after dosing. Decreased motor activity, ataxia, whole body twitches, cold to touch.
		761	7	80 min post dosing.
		763	5	[Euthanized day after dosing due to unspecified adverse clinical observations.]
		765	6	35 min after dosing. Decreased motor activity, whole body twitches, cold to touch, labored breathing
		768	8	35 min after dosing.
		772	1	35 min after dosing.
		775	5	79 min after dosing. Decreased motor activity.
	10	786	6	43 min after dosing.
		787	5	23 min after dosing.
		788	6	42 min after dosing.
		793	>7 (GD 1)	21 min after dosing.
	30	818	2	[Euthanized 89 min after dosing]. No use of left forelimb (necropsy confirmed fx of radius and ulna).
		823	5	83 min after dosing.

Source: Reviewer generated.
Abbreviations: FEED, Fertility and Early Embryonic Development ; fx, fracture; GD, gestation day.

Clinical Signs

Clinical observations associated with hypersensitivity included increased/decreased motor activity, ataxia, hyper-reactivity, tremors/whole body twitches, vocalization, and cold-to-touch.

These were observed in some, although not most, premature decedents; as well as in animals that survived until scheduled necropsy, especially in the 30 mg/kg dose group.

Body Weight

Group mean body weights of male mice did not differ meaningfully across experimental groups throughout the study. They ranged from 34.3 to 34.9 grams on the first day of dosing; from 34.7 to 36.5 grams at initiation of cohabitation; and from 36.3 to37.7 grams at the end of study.

Group mean body weights of female mice were also comparable across experimental groups, both prior to cohabitation and during gestation. They ranged from 27.4 to 27.8 grams on the first day of dosing; from 27.4 to 28.5 grams at initiation of cohabitation; from 26.7 to 27.4 grams on GD 0; and from 42.6 to 44.3 grams on GD 14.

Food Consumption

Mean food consumption was comparable in male and female mice across experimental groups. There were no treatment-related differences.

Toxicokinetics: Not assessed.

Dosing Solution Analysis

Solution concentrations, although not homogeneity nor stability, were tested. All means of sample replicates were within 10% of theoretical olipudase alfa concentrations in groups 3, 4, and 5. There was no evidence of olipudase alfa contamination in group 1 samples; group 2 samples were not tested, as per protocol.

Necropsy

There were no treatment-related observations.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Treated males were mated with treated females in this study, i.e., Group 1 males with Group 1 females, etc.

Treated Males

Male Fertility Parameters

The fertility index in males treated with 30 mg/kg was lower than either that in control groups 1 or 2, but within the lower range of historical control data (71.4%). It is noted that the historical control data cited are old (2009-2014), relative to the time of study conduct (2017). Study data are included in Table 146).

Reproductive organ weights: No olipudase alfa-related effects were noted on TBW or the absolute and relative weights of the male reproductive organs.

Sperm Assessment

Sperm motility and density were comparable across all experimental groups. Sperm motility ranged from 82.1% to 85.9%, and all values were within Testing Facility Historical Control (mean 86.2%; range 51.4% to 93.8%). Sperm density ranged from 1269.89 to 1587.39 across the

control and olipudase alfa dose groups; these values were lower than the historical control mean (1810.81), but within the lower range of historical control data.

Histopathology

Male reproductive organ histopathology was examined for groups 1,2 and 5. When there were no treatment-related findings in the 30 mg/kg olipudase alfa-treated males, organs from lower-dose males were not assessed.

Table 146. Summary of Mating and Fertility Parameters in Male Mice (Bred to Corresponding Experimental Groups of Female Mice)

GROUP TEST MATERIAL DOSE LEVEL (MG/KG/DAY)a		1 CONTROL/SALINE 0	2 CONTROL/DPH 0/20	3 OLIPUDASE ALFA/DPH 3.16/20	4 OLIPUDASE ALFA/DPH 10/20	5 OLIPUDASE ALFA/DPH 30/20
MICE IN COHABITATION	N	25	25	19b	21b	23c
DAYS IN COHABITATION d,e	MEAN±S.D.	2.2 ± 1.4 [24]	2.2 ± 1.4 [23]	2.5 ± 1.7	2.4 ± 1.9 [20]	2.0 ± 1.3
MICE THAT MATED e	N(%)	25(100.0)	25(100.0)	19(100.0)	19(90.5)	23(100.0)
FERTILITY INDEX f,g	N/N (%)	25/ 25 (100.0)	23/ 25 (92.0)	15/ 18h (83.3)	17/ 18i (94.4)	18/ 23 (78.3)
MICE WITH CONFIRMED MATING DATES	N	24	23	19	18	23
MATED WITH FEMALE j DAYS 1-7	N(%)	24(100.0)	23(100.0)	19(100.0)	18(100.0)	23(100.0)
MICE PREGNANT/MICE IN COHABITATION g	N/N (%)	25/ 25 (100.0)	23/ 25 (92.0)	15/ 18h (83.3)	17/ 20i (85.0)	18/ 23 (78.3)

a. Dose administration occurred once every other day on Day 1 of study through euthanasia.
b. Excludes values for mice that were found dead.
c. Excludes values for mice that were not assigned to cohabitation because there were no available female mice.
d. Restricted to mice with a confirmed mating date and mice that did not mate.
e. Includes only one mating for each male mouse.
f. Number of pregnancies/number of mice that mated.
g. Includes only one pregnancy for each mouse that impregnated more than one female mouse.
h. Excludes pairing for male 574 (cohort female 772); pregnancy status could not be determined due to early gestational age.
i. Excludes pairing for male 592 (cohort female 793); pregnancy status could not be determined due to early gestational age.

Source: Applicant Study Report FER0510, pg. 53.
Abbreviations: DPH, diphenhydramine; N, total number of subjects; SD, standard deviation.

Treated Females

Estrous Cyclicity, Mating and Fertility Parameters

Following treatment initiation, but prior to cohabitation, 0/25, 1/25, 2/20, 2/22, and 3/23 females were in persistent diestrus. Among olipudase alfa-treated females, however, all were pregnant after cohabitation but 1 female in the 30 mg/kg group. There were no treatment-related effects on mating or fertility. Study data are included in Table 147.

Table 147. Summary of Mating and Fertility Parameters in Female Mice (Bred to Corresponding Experimental Groups of Male Mice)

GROUP TEST MATERIAL DOSE LEVEL (MG/KG/DAY)a		1 CONTROL/SALINE 0	2 CONTROL/DPH 0/20	3 OLIPUDASE ALFA/DPH 3.16/20	4 OLIPUDASE ALFA/DPH 10/20	5 OLIPUDASE ALFA/DPH 30/20
FEMALES IN COHABITATION	N	25	25	19b	22b	23b
DAYS IN COHABITATION c	MEAN±S.D.	2.2 ± 1.4 [24]	2.2 ± 1.4 [23]	2.5 ± 1.7	2.5 ± 2.2 [21]	2.0 ± 1.3
FEMALES THAT MATED	N(%)	25(100.0)	25(100.0)	19(100.0)	22(100.0)	23(100.0)
FERTILITY INDEX d	N/N (%)	25/ 25 (100.0)	23/ 25 (92.0)	15/ 18e (83.3)	19/ 21f (90.5)	18/ 23 (78.3)
FEMALES WITH CONFIRMED MATING DATES	N	24	23	19	21	23
MATED BY FIRST MALE g DAYS 1-7	N(%)	24(100.0)	23(100.0)	19(100.0)	19(90.5)	23(100.0)
MATED BY SECOND MALE g	N(%)	0(0.0)	0(0.0)	0(0.0)	2(9.5)	0(0.0)
FEMALES PREGNANT/FEMALES IN COHABITATION	N/N (%)	25/ 25 (100.0)	23/ 25 (92.0)	15/ 18e (83.3)	19/ 21f (90.5)	18/ 23 (78.3)

[ ] = NUMBER OF VALUES AVERAGED
a. Dose administration occurred once every other day on Day 1 of study through Gestation Day 7.
b. Excludes values for mice that were found dead on euthanized due to adverse clinical observations.
c. Restricted to females with a confirmed mating date and females that did not mate.
d. Number of pregnancies/number of females that mated.
e. Excludes values for mouse 772; pregnancy status could not be determined due to early gestational age.
f. Excludes values for mouse 793; pregnancy status could not be determined due to early gestational age.
g. Restricted to females with a confirmed mating date.

Source: Applicant Study Report FER0510, pg. 66.
Abbreviations: DPH, diphenhydramine; N, total number of subjects; SD, standard deviation.

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Ovarian and uterine examinations of treated female mice bred to treated male mice. There were no treatment-related effects. Study data are included in Table 148.

Table 148. Summary of GD 14 Cesarean Section Parameters in Treated Female Mice (Bred to Corresponding Experimental Groups of Male Mice)

GROUP TEST MATERIAL DOSE LEVEL (MG/KG/DAY)a		1 CONTROL/SALINE 0	2 CONTROL/DPH 0/20	3 OLIPUDASE ALFA/DPH 3.16/20	4 OLIPUDASE ALFA/DPH 10/20	5 OLIPUDASE ALFA/DPH 30/20
MICE TESTED	N	25	25	18b,c	21b,d	23b
PREGNANT	N(%)	25(100.0)	23(92.0)	15(83.3)	19(90.5)	18(78.3)
MICE PREGNANT AND CAESAREAN-SECTIONED ON DAY 14 OF GESTATION	N	25	23	15	19	18
CORPORA LUTEA	MEAN±S.D.	14.1 ± 2.1	13.4 ± 3.1	14.4 ± 2.2	13.9 ± 1.8	14.9 ± 2.0
IMPLANTATIONS	MEAN±S.D.	13.0 ± 1.4	12.5 ± 3.0	13.0 ± 1.8	12.9 ± 1.7	13.2 ± 1.8
% PREIMPLANTATION LOSS	MEAN±S.D.	7.2 ± 7.4	7.6 ± 13.3	9.3 ± 7.0	6.7 ± 7.6	10.4 ± 14.2
VIABLE EMBRYOS	N MEAN±S.D.	295 11.8 ± 2.8	261 11.3 ± 2.9	184 12.3 ± 2.6	223 11.7 ± 2.6	222 12.3 ± 2.3
NONVIABLE EMBRYOS	N MEAN±S.D.	30 1.2 ± 2.6	26 1.1 ± 1.5	11 0.7 ± 1.3	23 1.2 ± 2.4	15 0.8 ± 0.9
% POSTIMPLANTATION LOSS	MEAN±S.D.	9.0 ± 20.1	10.0 ± 13.5	6.2 ± 11.0	9.0 ± 16.7	6.8 ± 7.4
MICE WITH ANY NONVIABLE EMBRYOS	N(%)	12(48.0)	14(60.9)	5(33.3)	8(42.1)	10(55.6)
MICE WITH ALL NONVIABLE EMBRYOS	N(%)	1(4.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
MICE WITH VIABLE EMBRYOS	N(%)	24(96.0)	23(100.0)	15(100.0)	19(100.0)	18(100.0)
PLACENTAE APPEARED NORMAL	N(%)	24(100.0)	23(100.0)	15(100.0)	19(100.0)	18(100.0)

% PREIMPLANTATION LOSS = [(NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS) / NUMBER OF CORPORA LUTEA] x 100
% POSTIMPLANTATION LOSS = [(NUMBER OF IMPLANTATIONS - NUMBER OF LIVE FETUSES) / NUMBER OF IMPLANTATIONS] x 100
a. Dose administration occurred once every other day on Day 1 of study through Gestation Day 7.
b. Excludes values for mice that were found dead or euthanized due to adverse clinical observations.
c. Excludes values for mouse 772; pregnancy status could not be determined due to early gestational age.
d. Excludes values for mouse 793; pregnancy status could not be determined due to early gestational age.

Source: Applicant Study Report FER0510, pg. 69.
Abbreviations: DPH, diphenhydramine; N, total number of subjects; SD, standard deviation.

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Organ Weights

Ovarian organ weights (absolute and relative) were comparable across experimental groups.

Histopathology

Not assessed.

13.2.2. Embryo-Fetal Development

Table 149. GZ402665 (Olipudase Alfa): Intravenous Embryo-Fetal Toxicity Study in Mice

Study Parameter	Study Information
Study no.:	TER0694
Study report location:	001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 24, 2016
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	rhASM, C6642, 96.1%

Source: Review team.
Abbreviations: GLP, good laboratory practice; (b) (4) QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; Y, yes.

Key Study Findings

Olipudase alfa was administered intravenously to pregnant CD1 mice over the period of organogenesis (GD 6-15), at doses of 3, 10, or 30 mg/kg/day. On GD 14, diphenhydramine was added to all olipudase alfa groups, in order to allay signs of hypersensitivity first observed at 3 mg/kg. There were two control groups (vehicle+saline, and vehicle+DPH). Maternal viability, clinical observations, body weights, food consumption, and toxicokinetics were assessed during the dosing interval. Cesarean sections were conducted on all surviving dams on GD 18. Fetuses were assessed for viability, as well as external, visceral, and skeletal malformations and variations.

There was extensive maternal and developmental mortality in the 3 mg/kg/day group. However, these findings were neither confirmed nor extended at higher doses, and so are not directly attributed to treatment. Treatment-related reduced activity was reported in all dose groups after the 9th (penultimate) dose (4,4 and 7 mice in the 3, 10 and 30 mg/kg dose groups, respectively); and ameliorated by DPH administration. There were no treatment related effects on maternal body weight or food consumption, nor macroscopic observations in any experimental group at necropsy. There were no dose-related findings on any parameter evaluated at maternal cesarean section, although the numbers of resorptions and the incidence of post-implantation loss were significantly greater than the control values in the conceptuses of dams treated with 3 mg/kg/day; there was a related reduction in the mean numbers of live fetuses per dam in this group. Fetal examinations did not reveal any treatment-related effects on overall fetal viability or body weights. However, at the highest 2 doses, there were 5 fetuses in 2 litters with exencephaly (2 and 3 fetuses at 10 and 30 mg/kg/day, respectively), with a single litter affected in each dose group. Exencephaly was not reported in either control group.

Olipudase alfa is a selective developmental toxicant. The maternal NOAEL was 30 mg/kg, which provides an exposure margin relative to that at the maximum recommended human dosage (MRHD) <1.5. The developmental NOAEL, based on findings of exencephaly at 10 and 30

mg/kg, is 3 mg/kg; the margin relative to the MRHD is 0.13 (approximately 1/7th the exposure at the MRHD).

Reviewer's Comments: While the findings at 3 mg/kg have been dismissed, they nonetheless have consequences for study data interpretation. Specifically, there were 14 evaluable litters among dams treated with 3 mg/kg. At the higher dose levels, there were 2 and 3 fetuses, respectively, in 10 and 30 mg/kg dose groups with exencephaly; single litters were affected at both mid- and high dose. The de facto developmental NOAEL is 3 mg/kg, although it is possible that 14 evaluable litters in this dose group were insufficient to determine a NOAEL for this finding. The relevance of this to human risk assessment is immaterial, however, as the margin at the assigned developmental NOAEL is significantly sub-therapeutic.

Table 150. Study TER0694 Methods

Method	Description
Doses:	0, 0/DPH. rhASM 3, 10, 30 mg/kg
Frequency of dosing:	Daily, GD 6-15
Dose volume:	rhASM 7.7 ml/kg DPH 4 ml/kg
Route of administration:	rhASM Intravenous DPH Intraperitoneal
Formulation/vehicle:	(b) (4) mM sodium phosphate, (b) (4) % sucrose, (b) (4) mM methionine, (b) (4) at a pH of 6.5
Species/strain:	Mouse, Crl:CD1(IGS)
Number/sex/group:	25
Satellite groups:	Y (toxicokinetic)
Study design:	See below
Deviation from study protocol:	Yes

Source: Review team.
Abbreviations: DPH, diphenhydramine; (b) (4) GD, gestation day; rhASM, recombinant human acid sphingomyelinase; Y, yes.

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Table 151. Study TER0694 Design

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Route of Administration	No. of Animals (Assigned Animal Numbers)	
						Main Study	TK/ADA Phase[d]
1	Control[a]/saline[b]	0	0	7.7/4	IV injection[c]/IP injection[b]	25 (2001-2005, 3001[g]; 2007-2025)	5 (2126-2130)
2	Control[a]/DPH[e]	0/20	0/5	7.7/4	IV injection[c]/IP injection[f]	25 (2026-2050)	5 (2131-2135)
3	Olipudase alfa/ DPH[e]	3	0.39	7.7/4	IV injection[c]/IP injection[f]	25 (2051-2075)	20 (2136-2155)
4	Olipudase alfa/ DPH[e]	10	1.30	7.7/4	IV injection[c]/IP injection[f]	25 (2076-2083, 3002[h]; 2085-2100)	20 (2156-2175)
5	Olipudase alfa/ DPH[e]	30	3.90	7.7/4	IV injection[c]/IP injection[f]	25 (2101-2125)	20 (2176-2195)

[a] (b) (4) mM sodium phosphate (b) (4) % sucrose, (b) (4) mM methionine (b) (4) at a pH of 6.5
[b] saline administered by Intraperitoneal injection.
[c] Intravenous administrated by bolus.
[d] Toxicokinetic (TK) and ADA animals were used for TK/ADA evaluation only.
[e] Diphenhydramine Hydrochloride
[f] Intraperitoneal injection for DPH administered (10 to 20 min prior to dose administration of control article or test article).
[g] Animal 2006 (Group 1) was found dead on GD 7 and was replaced by 3001.
[h] Animal 2084 (Group 4) was unscheduled euthanized on GD 7 due to early delivery and was replaced by 3002.

Source: Applicant study report, TER0694, pg 22.

The study report indicates that Diphenhydramine (DPH) administration was initiated on GD 14. Protocol amendment 7 (study report page 143) states that IP administration of DPH was to be occur only "if required. ". This was determined by examination of each dosed animal for hypersensitivity each day. In the event that signs of hypersensitivity were observed, that animal would be dosed with DPH 20 mg/kg; and all remaining mice not yet dosed would receive DPH 10-20 min prior to administration of control or test article. The text from the study report is as follows:

> *Initiation of dosing proceeded without the use of DPH or saline until 8 doses administration. When the sign of hypersensitivity was observed in Group 3 animals on GD 14 following the test article administration, DPH was immediately administrated to Groups 2 through 5. Group 1 animals were received saline. On GD 15, all mice received a prophylactic dose of DPH or saline approximately 10 to 20 minutes prior to each dose of test article or control article.*

Observations and Results

Mortality

Fourteen mice were found dead or euthanized. Available details for these animals are listed in Table 153. The reasons for the extensive mortality in Group 3 (nine Main Study and one TK satellite) are unclear, and the findings are not adequately addressed in the Study Report. Further, 8 of 10 of these females had no viable conceptuses; this was also not addressed. Both maternal and developmental mortality at 3 mg/kg were dismissed, as they were unrelated to dose. Nonetheless, these findings had consequences for study data interpretation. Specifically, there

were 14 evaluable litters among dams treated with 3 mg/kg. At the higher dose levels, there were 2 and 3 fetuses, respectively, in 10 and 30 mg/kg dose groups with exencephaly; single litters were affected at both mid- and high dose. It is unclear whether the 14 evaluable litters in the 3 mg/kg dose group were sufficient to determine a NOAEL for this finding.

Table 152. Observations of Unscheduled Decedents

Group	Dose (mg/kg/day)	Dam	GD	Comment
1	0	2060	7	Found dead.
		2128	12	Pregnant. [TK. Found dead after 2h sample collection]
2	0/20	-		
3	3	2072	12	Pregnant. Found dead during post-dose clinical observations. Red liquid discharge. No viable conceptuses.
		2075	12	Pregnant. Found dead during post-dose clinical observations. No viable conceptuses.
		2062	13	Pregnant. Found dead during post-dose clinical observations. No viable conceptuses.
		2071	13	Pregnant. Found dead during post-dose clinical observations. No viable conceptuses.
		2052	14	Not pregnant at necropsy. Lost weight (-4.4% between GD 7-14. Found dead during post-dose clinical observations.
		2058	14	Not pregnant at necropsy. Found dead during post-dose clinical observations.
		2066	14	Pregnant. Decreased activity. Found dead during post-dose clinical observations. No viable conceptuses.
		2069	14	Pregnant. Found dead during post-dose clinical observations. No viable conceptuses.
		2060	16	Pregnant. Reduced activity. Found dead during post-dose interval. No viable conceptuses.
		2144	12	Pregnant. [TK. Found dead after 2h sample collection]
4	10	2084	7	Euthanized after delivery of litter
		2087	18	Euthanized after delivery of litter
5	30	-		

Source: Reviewer generated.
Abbreviations: GD, gestation day; TK, toxicokinetic.

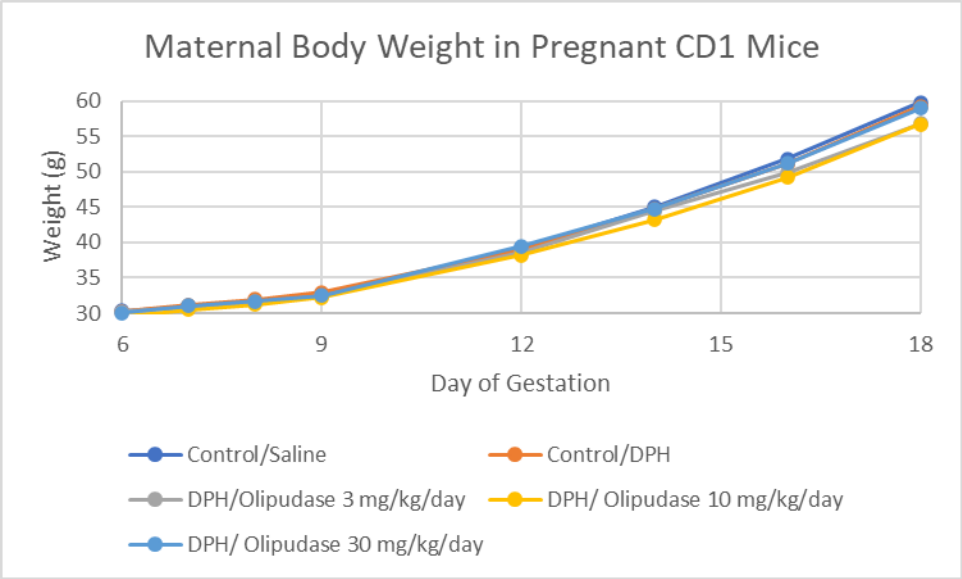
Clinical Signs

Treatment-related reduced activity was reported in all dose groups after the 9th (penultimate) dose (4,4 and 7 mice in the 3, 10 and 30 mg/kg dose groups, respectively. These were ameliorated by DPH administration. There were no comparable observations at any time in either control group. Remaining adverse clinical observations were associated with unscheduled deaths, as reviewed above.

Body Weight

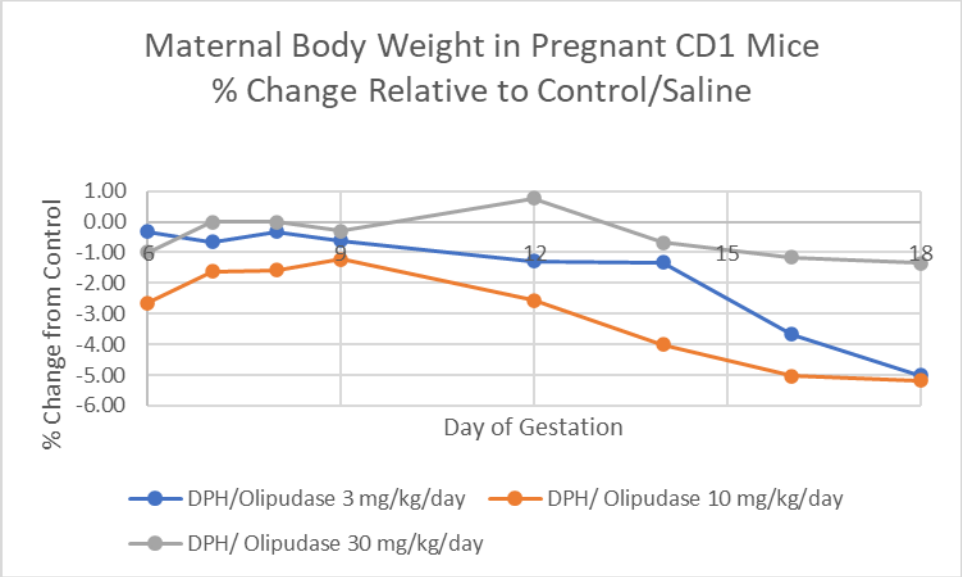
There were no treatment related effects on maternal body weight. Minor percent differences in body weight, relative to the Control/Saline group, were observed at the end of gestation in dams treated with 3 and 10 mg/kg/day, although not 30 mg/kg/day; as such, they are not attributed to olipudase alfa. See Figure 61 and Figure 62.

Figure 61. Maternal Body Weight in CD1 Mice



Source: Reviewer generated.
Abbreviations: CD, cluster of differentiation; DPH, diphenhydramine.

Figure 62. Maternal Body Weight in CD1 Mice Relative to Control



Source: Reviewer generated.
Abbreviations: CD, cluster of differentiation; DPH, diphenhydramine.

Food Consumption

There were no olipudase alfa-related effects on mean maternal food consumption at any dose. Mean maternal food consumption in the 3, 10, and 30 mg/kg/day dose groups was 96%, 96%, and 99% of the Group 1 controls for the interval of GD 6 to 18, respectively. There were no differences between the two control groups.

Toxicokinetics and ADA

Samples for TK evaluations were collected on GD 12 (after 7 of 10 doses). Maximum serum concentrations were observed at 0.033-0.166 hour (2-10 min, i.e., the first or second samples taken post IV injection). Increases in both olipudase alfa C_{max} and AUC_{0-24} were dose-

proportional. (Over the range of 3 to 30 mg/kg/day, C_{max} increased by 11.6 fold and AUC_{0-24} increased by 11.0 fold.)

Group mean TK parameters after dose administration on GD 12 are reproduced below in Table 153.

Table 153. Group Mean Toxicokinetic Parameters in CD1 Mice After Administration of 7 Doses of Olipudase Alfa (GD 12)

Sex	Dose (mg/kg/day)	t_{max} (h)	C_{max} (µg/mL)	AUC_{0-24} (µg.h/mL)
Female	3	0.166	35.2	83.1
	10	0.0333	176	278
	30	0.0333	409	916

Source: Applicant Study Report TER0694, pg 37.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; h, hour; t_{max}, time for maximum drug concentration.

Approximately 25% of GZ402665-treated TK animals (with ADA samples collected) were ADA positive. ADA did not appear to meaningfully impact C_{24} concentrations on GD 12, as reproduced in Table 154.

Table 154. Predose Olipudase Alfa Concentrations in ADA Positive and ADA Negative Pregnant Mice on GD 12

		Mean ± SD GZ402665 serum concentration C24hr (ug/mL) on GD 12		
Group	Dose (mg/kg/day)	in ADA negative-animals	in ADA positive animals	ADA positive/ADA negative %
3	3	0.345 ± 0.139	0.126 ± 0.153	36.5
4	10	1.18 ± 0.943	0.935 ± NC	79.3
5	30	2.25 ± 1.26	0.601 ± NC	26.7

Source: Applicant Study Report TER0694, pg 37.
Note: NC = not calculated because N=2.
Abbreviations: ADA, anti-drug antibody; GD, gestation day; SD, standard deviation.

Reviewer's Comments: Data from single-dose toxicokinetic studies in WT (C57BL/6) mice suggest that the elimination half-life is approximately 2 to 3 hr. Full strain-specific toxicokinetic parameters were not assessed for CD1 mice.

Dosing Solution Analysis

Formulation analyses ranged from 95.9% to 104.9% of expected concentrations.

Necropsy

There were no macroscopic observations in any experimental group.

Cesarean Section Data (Implantation Sites, Pre- and Postimplantation Loss, etc.)

There were no findings in cesarean section data that could be attributed to maternal olipudase alfa administration. Most parameters were comparable among all dose groups or did not differ significantly from Group 1 values (see Table 155). However, in group 3 there were statistically

significant increases in multiple endpoints assessing developmental mortality. In addition to 7/21 total litter losses in group 3, there were 3 dams in this treatment group with >30% post-implantation loss. Group mean early resorptions were increased (1.1 early resorption/litter compared with 0.4/litter in Group 1 controls, $p \leq 0.05$); as were late resorptions (1.4 late resorptions/litter compared with 0.4/litter in Group 1 controls); and total resorptions (2.4/litter compared with 0.8/litter in Group 1, $p < 0.01$). Collectively, postimplantation loss was increased (16.26% compared with 5.88% in Group 1 controls, $p \leq 0.05$). This was reflected in fewer live fetuses/litter (12.0/litter compared with 13.5/litter in Group 1 controls). Since these findings were neither confirmed nor extended at higher doses, they are not attributed to olipudase alfa administration.

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Table 155. Summary of Ovarian and Uterine Findings (Mean ± SD)

Ovarian and Uterine Findings	Dose (mg/kg) Olipudase				
	Saline/ Control (0)	DPH/ Control (0)	DPH/ Olipudase (3)	DPH/ Olipudase (10)	DPH/ Olipudase (30)
Dams bred	25	25	25	25	25
Dams pregnant	24	25	21	22	24
Dams with early delivery	0	0	0	1	0
Dams with 100% litter loss	1	0	7	0	1
Litters evaluated	23	25	14	21	23
Corpora Lutea	14.5±1.6	15.1±2.2	15.3±2.3	14.4±2.5	14.7±1.7
Implantations	14.4±1.6	14.6±2.0	14.4±1.7	13.7±2.6	14.0±1.5
Preimplantation loss (%)	0.58±1.95	2.66±4.13	4.93±7.27	5.08±8.91	3.88±7.66
Early Resorptions	0.4±0.9	1.1±1.0**	1.1±0.8*	0.7±0.9	0.9±2.4
Late Resorptions	0.4±0.9	0.4±0.7	1.4±1.6	0.3±0.6	0.3±0.70.8±1.3
Total Resorptions	0.8±1.3	1.5±1.2	2.4±2.2**	1.0±1.4	1.3±2.5
Dead Fetuses	0±0.2	0±0	0±0	0±0.2	0±0
Postimplantation loss (%)	5.88±9.28	10.28±8.51	16.14.45**	6.7±8.66	9.51±20.47
Live Fetuses	13.5±2.1	13.2±2.3	12.0±2.1	12.7±2.3	12.8±3.2
Gravid uterine weight	23.42±3.00	22.28±3.65	20.66±2.79	21.04±3.42	22.45±5.6
Carcass weight	N/A	N/A	N/A	N/A	N/A
Corrected weight change	N/A	N/A	N/A	N/A	N/A
Total weight change	N/A	N/A	N/A	N/A	N/A
Number of males/litter	6.8±2.6	6.9±2.6	5.9±2.4	5.9±2.6	5.8±2.1
Number of females/litter	6.8±2.2	6.2±2.3	6.1±1.8	6.8±2.6	7.0±2.6
Mean fetal weight (g)	1.334±0.100	1.314±0.073	1.294±0.064	1.314±0.082	1.352±0.062
Mean male weight (g)	1.364±0.107	1.344±0.088	1.328±0.080	1.338±0.102	1.369±0.078
Mean female weight (g)	1.306±0.109	1.284±0.078	1.262±0.068	1.300±.0.75	1.339±0.063

Source: Reviewer-generated.
Note: N/A = Not collected, summarized, or analyzed statistically
*p≤0.05
**p≤0.01
Abbreviations: DPH, diphenhydramine; SD, standard deviation.

Offspring (Malformations, Variations, etc.)

A summary of overall numbers of malformations, segregated by examination type, is reproduced in Table 156. Consideration of individual malformations generally demonstrated that there was no relationship to treatment.

Table 156. Count Data for External, Visceral and Skeletal Malformations

	Exam 1		Exam 2		Exam 3		Exam 4		Exam 5	
Malformations	**F**	**L**	**F**	**L**	**F**	**L**	**F**	**L**	**F**	**L**
External	326	24	329	25	168	14	266	21	307	23
w/ Malformation	0	0	1	1	4	4	3	2	3	1
Visceral	157	24	157	25	80	14	128	21	149	23
w/ Malformation	1	1	3	3	0	0	1	1	2	2
Skeletal	169	24	172	25	88	14	138	21	158	23
w/ Malformation	2	2	0	0	0	0	2	2	5	2

Source: Reviewer-generated.
Abbreviations: F, fetus; L, litter.

Exencephaly, however, was observed in both 10 and 30 mg/kg/day treatment groups. Litter and fetal incidences are reproduced below.

Table 157. Count Data for Exencephaly

Exencephaly	**Dose (mg/kg) Olipudase**				
	Saline/Control (0)	**DPH/Control (0)**	**DPH/ Olipudase (3)**	**DPH/ Olipudase (10)**	**DPH/ Olipudase (30)**
#Fetuses/litters examined	326/24	329/25	168/14	266/21	307/23
Affected fetuses/litters	0/0	0/0	0/0	2/1	3/1
% affected fetuses	0/0	0/0	0/0	0.75%	0.98%
% affected litters	0/0	0/0	0/0	4.8%	4.3%

Source: Reviewer-generated.
Abbreviations: DPH, diphenhydramine.

Historical control data were furnished for the period from June 2009-May 2014 (the present study was initiated in late 2016). During that period, 13 definitive studies were conducted, in which 4820 fetuses were examined from 372 litters; 3 fetuses (0.06%) from 3 litters (0.81%) were reported with exencephaly. It is unlikely that the observation of 5 fetuses in the present study, clustered in the 2 highest dose groups, is incidental.

Reviewer's Comments: The Study director did not assign this finding as treatment related, using the explanation that the observed litter incidences in the present study fall within the upper range of litter incidences in the historical control database. This is technically correct: any study that reports a single affected litter with an N of ~20 animals per treatment group naturally has an upper litter range of ~5% - this is the tyranny of small numbers. Another way to consider litter information is to envision that 3/13 studies in the database reported a single occurrence of exencephaly; i.e., ~1 in every 4 studies might be expected to report exencephaly. This is contrasted with the present data, whereby 5 fetuses – in the two highest dose groups – are reported in a single study. Considered together, this malformation is attributed to treatment.

Table 158. GZ402665 (Olipudase Alfa) An Intravenous Embryo-Fetal Development Study in Rabbits

Study Parameter	Study Information
Study no.:	TER0698
Study report location:	001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 10, 2019
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	rhASM, 131832-001, >98.4%

Source: Review team.
Abbreviations: GLP, good laboratory practice; (b) (4) QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; Y, yes.

Key Study Findings

Olipudase alfa was administered by IV infusion to pregnant rabbits daily during the period of organogenesis (GD 6-19). Rabbits were monitored during the dosing and post-dosing intervals for viability, abortion, clinical observations, body weight and food consumption. Blood samples were collected from satellite animals for TK analyses on GD 12. Cesarean sections were conducted on GD 29, and cesarean section parameters analyzed for potential effects of olipudase alfa administration. Fetuses were evaluated for effects on viability, weight, and morphology.

There were no treatment-related effects on maternal viability, abortion, body weight or food consumption. Clinical signs were limited to observations of hypoactivity, which are thought to be associated with hypersensitivity. Cesarean section parameters were comparable across experimental groups.

There were no olipudase alfa-associated effects on fetal viability, nor were there treatment-related external, visceral, or skeletal malformations or variations.

The maternal and developmental NOAELs were 30 mg/kg. The margin relative to the MRHD (calculated by AUC) is ~10.5.

Table 159. Study TER0698 Methods

Methods	Description
Doses:	0, 0/DPH. rhASM 3, 10, 30 mg/kg
Frequency of dosing:	Daily, GD 6-19
Dose volume:	rhASM 7.7 ml/kg
Route of administration:	Intravenous
Formulation/Vehicle:	(b) (4) mM sodium phosphate (b) (4) % sucrose, (b) (4) mM methionine, (b) (4) at a pH of 6.5
Species/Strain:	Rabbit, New Zealand White [Crl: KBL(NZW)]
Number/Sex/Group:	25
Satellite groups:	Y (toxicokinetic)
Study design:	See Table 160 below
Deviation from study protocol:	Yes

Source: Review team.
Abbreviations: DPH, diphenhydramine; (b) (4) GD, gestation day; rhASM, recombinant human acid sphingomyelinase; Y, yes.

Table 160. Study TER0698 Design

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Route of Administration	No. of Rabbits (Assigned Female Rabbit Numbers)	
						Main Study	Toxicokinetic Study
1	Control 1[a]	0	0	7.7	IV infusion	25 (8001- 8025)	3 (8201- 8203)
2	Control 2[a]	0	0	7.7	IV infusion	25 (8026- 8050)	3 (8204- 8206)
3	olipudase alfa	3	0.39	7.7	IV infusion	25 (8051- 8075)	3 (8207- 8209)
4	olipudase alfa	10	1.30	7.7	IV infusion	25(8076- 8100)	3 (8210- 8212)
5	olipudase alfa	30	4.00	7.5	IV infusion	25 (8101- 8125)	3 (8213- 8215)

[a] (b) (4) mM sodium phosphate (b) (4) % sucrose (b) (4) mM methionine. (b) (4) at a pH of 6.5.
Source: Applicant study report, TER0698, pg. 13.
Abbreviations: (b) (4) IV, intravenous; No., number.

One hundred twenty-five presumed pregnant New Zealand White [Crl:KBL(NZW)] female rabbits were randomly assigned to five main study dose groups (Groups 1 through 5, 25 rabbits per group). An additional, 15 female rabbits were randomly assigned to five dose groups (Groups 1 through 5), 3 rabbits per group for the purpose of TK blood sample collection. Formulations were administered by IV infusion (via marginal ear vein) for approximately 10 minutes to naturally bred females once daily from Gestation Day (GD) 6 through 19 (GD 6 through 19) at doses of 0, 3, 10, and 30 mg/kg/day. DPH at a dose of 10 mg/kg/day was available for use on study in the event that any hypersensitivity was observed in any rabbit; however, it was not required on study. Doses were adjusted daily on the basis of the most recently recorded body weight.

Observations and Results

Mortality and Abortion

There was no unscheduled mortality attributed to olipudase alfa administration. Does that aborted or delivered early were euthanized; aborted material and uterine contents were examined, insofar as possible. Data for abortions and early delivery are reproduced below (see Table 161).

Table 161. Summary of Abortions and Early Deliveries

Mode of Death	0 mg/kg/day (Control 1)	0 mg/kg/day (Control 2)	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Abortion	0	4	3	3	2
Early Delivery	0	0	0	1	0

Source: Applicant Study Report TER, pg. 34.

Abortions were observed in 0, 4, 3, 3, and 2 rabbits in the 0, 0, 3, 10, and 30 mg/kg/day dose groups between GD 19 and GD 26. A single female in the 10 mg/kg dose group prematurely delivered its litter on the day of scheduled euthanasia (GD 29) and was subsequently euthanized. The premature delivery and abortions were associated with markedly decreased food intake. As the incidences of these findings were unrelated to dose, and also occurred within a control group, the findings are not attributed to treatment with olipudase alfa.

All remaining rabbits assigned to the Main Study survived to scheduled euthanasia on GD 29.

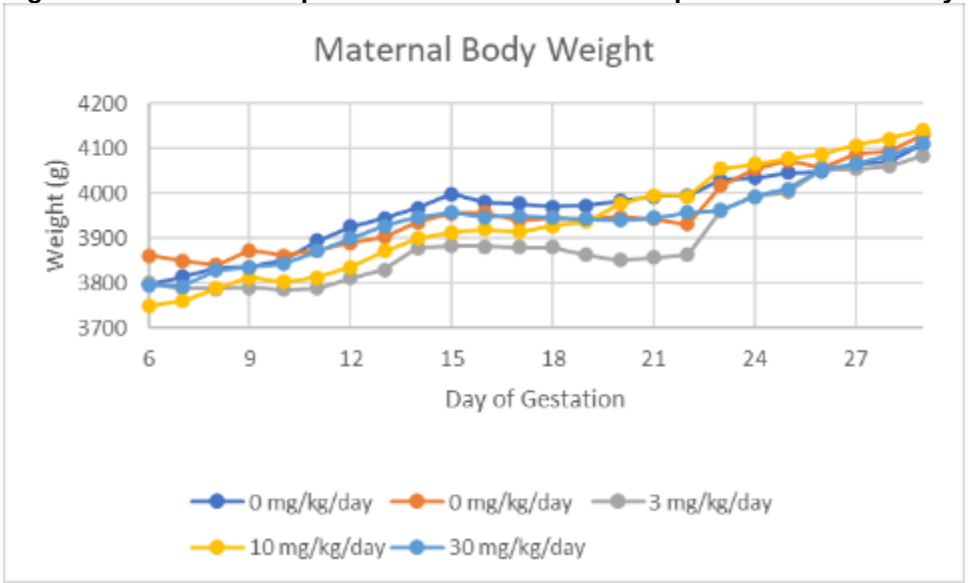
Clinical Signs

Clinical signs – beyond those associated with eventual abortion or early delivery – were limited to a dose-related increase in the incidence of ungroomed fur.

Body Weight

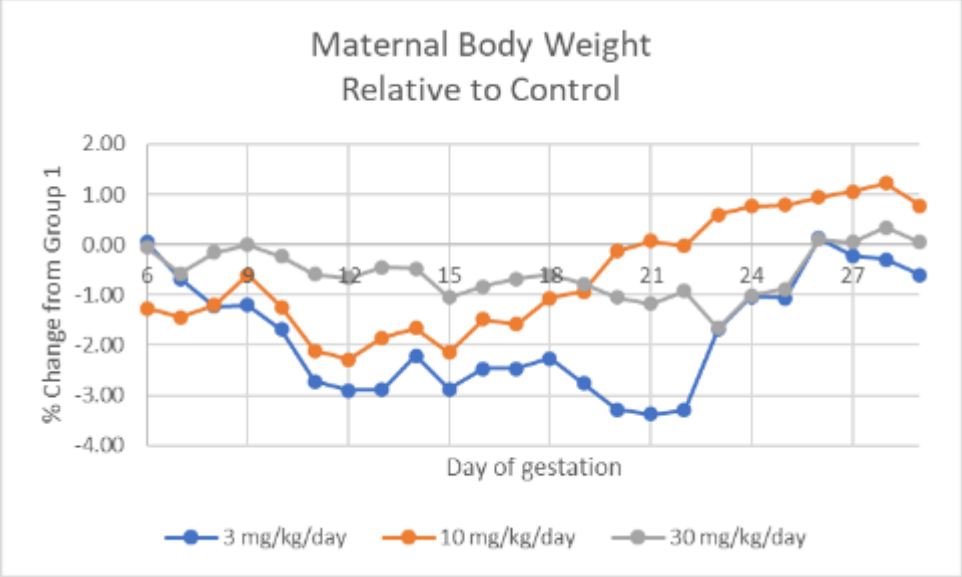
There were no biologically meaningful effects of olipudase alfa treatment on maternal body weights. Body weight, as well as percent difference from the Group 1 Control values, are depicted below in Figure 63 and Figure 64, respectively.

Figure 63. Effects of Olipudase Alfa Infusion on Group Mean Maternal Body Weight in Rabbits



Source: Reviewer-generated.

Figure 64. Effects of Olipudase Alfa Infusion on Group Mean Maternal Body Weight in Rabbits, Relative to Control

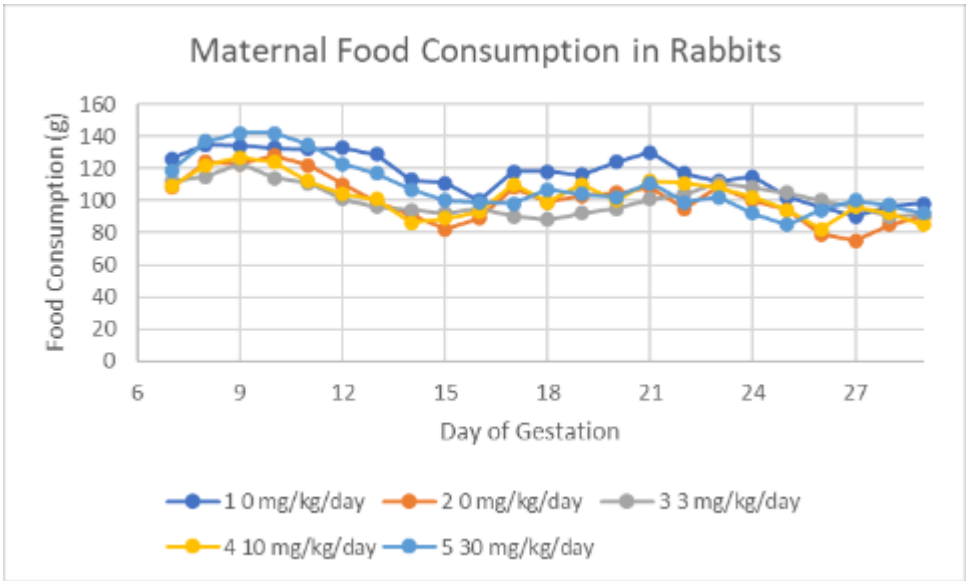


Source: Reviewer-generated.

Food Consumption

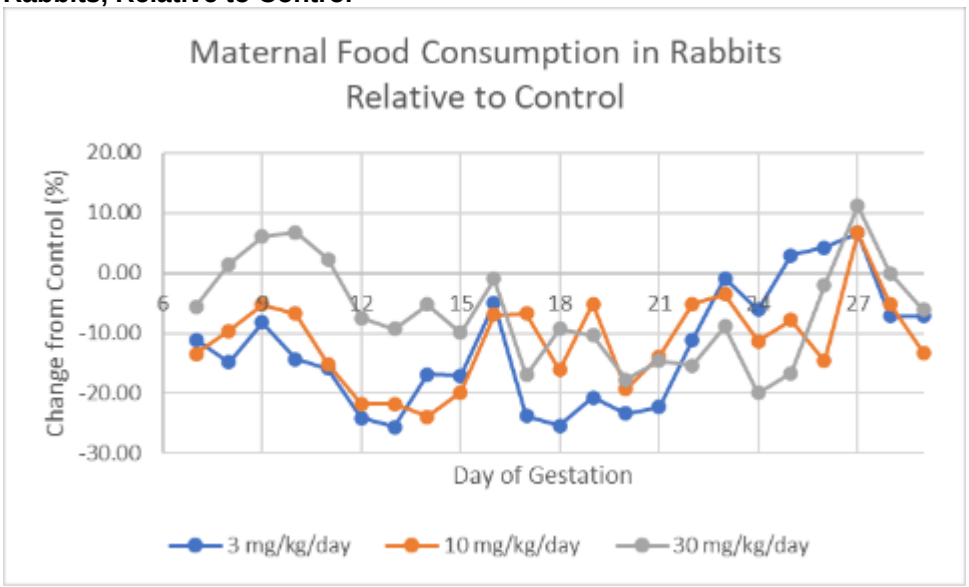
Group mean maternal food consumption was variable, although effects observed in olipudase alfa-treated does were unrelated to dose.

Figure 65. Effects of Olipudase Alfa Infusion on Group Mean Maternal Food Consumption in Rabbits



Source: Reviewer-generated.

Figure 66. Effects of Olipudase Alfa Infusion on Group Mean Maternal Food Consumption in Rabbits, Relative to Control



Source: Reviewer-generated.

Toxicokinetics and ADA

One rabbit each assigned to the TK satellite groups of 10 and 30 mg/kg was not pregnant; data for these animals were not included in TK analyses. Time of maximum concentration was observed at either 2 or 10 minutes after the end of infusion. Mean half-life ($T_{1/2}$) values were

6.36, 8.00, and 8.91 hr at 3, 10, and 30 mg/kg, respectively. Mean serum olipudase alfa exposure increased proportionally to dose increase from 3 to 30 mg/kg. Calculated TK parameters are reproduced in Table 162.

Table 162. Mean Serum Olipudase Alfa Exposure on GD 12 in Pregnant Female Rabbits

			C_{max} [µg/mL]				$AUC_{(0-24)}$ [hr*µg/mL]			
Analyte	GD	Dose (mg/kg)	Mean	% CV	SD	N	Mean	% CV	SD	N
GZ402665	12	3	114	8.39	9.56	3	598	17.1	102	3
		10	370	ID	ID	2	2000	ID	ID	2
		30	1180	ID	ID	2	6350	ID	ID	2

Source: Applicant study report TER0698, pg 970.
Note: ID = insufficient data to calculate % CV and SD when N=2
Note: Values are rounded to 3 significant figures.
Abbreviations: %CV, percent coefficient of variation; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; GD, gestation day; N, total number of subjects; SD, standard deviation.

There were no positive ADA responses on GD 6. On GD 12, none of the control pregnant females showed an ADA positive response. At 3 mg/kg/day, 3/3pregnant females had positive ADA results; titers ranged from 400 – 3200. At 10 mg/kg/day, 1/2 pregnant females had a positive ADA result, with titer reading of 100. At 30

mg/kg/day, 2/2 pregnant females showed positive ADA results on GD 12, with titer readings of 200 and 400, respectively. There were no obvious correlations between ADA results and GD 12 olipudase alfa exposures.

Necropsy

There were no macroscopic observations attributed to olipudase alfa treatment.

Cesarean Section

Cesarean section parameters were comparable across all experimental groups. These are reproduced in Table 163.

Table 163. Cesarean Section Parameters in Pregnant Rabbits

	Dose (mg/kg) Olipudase				
Cesarean Section Parameters	0 (Control/Saline) N=25	0 (Control/Saline) N=25	3 N=25	10 N=25	30 N=25
Does pregnant	21	23	24	25	25
Does aborted	0	4	3	3	2
Does with early delivery	0	0	0	1	0
Does with 100% litter loss	2	4	3	2	2
Litters evaluated	19	19	21	21	23
Corpora Lutea	11.7±2.0	12.3±2.7	11.0±2.2	11.3±1.8	11.7±2.6
Implantations	10.7±1.8	10.6±2.6	10.0±2.4	10.8±1.5	10.8±2.4
Preimplantation loss (%)	8.33±11.31	12.87±14.75	8.13±16.80	4.16±6.18	7.16±12.57
Early Resorptions	1.2±3.3	0.4±1.0	0.9±1.4	0.2±2.7	0.2±2.5
Late Resorptions	0.2±0.6	0.5±0.6	0.2±0.5	0.6±1.2	0.6±1.2
Total Resorptions	1.4±3.3	0.9±1.0	1.1±1.5	0.8±1.4	0.8±1.2
Dead Fetuses	0	0	0	0	0
Postimplantation loss (%)	12.63±29.64	8.54±9.89	11.30±14.97	8.22±16.21	7.25±9.93

	Dose (mg/kg) Olipudase				
Live Fetuses	9.2±3.4	9.7±2.7	8.9±2.7	10.0±2.3	10.0±2.4
Gravid uterine weight*	N/A	N/A	N/A	N/A	N/A
Carcass weight	N/A	N/A	N/A	N/A	N/A
Corrected weight change	N/A	N/A	N/A	N/A	N/A
Total weight change	N/A	N/A	N/A	N/A	N/A
Number of males/litter	4.8±2.4	4.8±2.6	4.4±2.5	4.0±2.3	5.2±2.0
Number of females/litter	4.4±2.1	4.9±1.6	4.1.7	6.0±1.9	4.8±2.2
Mean fetal weight (g)	39.36±3.07	38.83±4.54	38.42±5.55	37.79±4.36	39.45±3.75
Mean male weight (g)	40.35±3.88	39.84±5.42	38.99±6.02	38.49±4.59	39.44±3.76
Mean female weight (g)	38.32±3.49	38.17±5.01	38.12±6.22	37.41±4.36	39.36±4.08

Source: Reviewer-generated.
* Inadvertently omitted.
Abbreviations: N, total number of subjects; N/A, Not assessed.

Fetal Evaluations

There were no olipudase alfa-related external, visceral, or skeletal malformations or variations.

Placental Transfer of Olipudase Alfa in Mice

Table 164. Evaluation of Olipudase Alfa Transfer From Pregnant CD1 Mice to Fetuses

Study Parameter	Study Information
Study no.:	MSSM-8120
Study report location:	0037
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 1, 2020
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	Olipudase alfa, C1090479, unspecified

Source: Review team.
Abbreviations: CD, cluster of differentiation; N, no; (b) (4)

Key Study Findings. Olipudase alfa (3 mg/kg) or saline (2/group) was administered as a single dose on GD 15 to pregnant CD1 mice. Embryos were harvested at 6 or 24 h after Olipudase alfa administration, then bisected in the sagittal plane; each half was homogenized and subjected to analysis for enzymatic activity or Olipudase alfa concentration.

Enzymatic activity and olipudase alfa concentrations were comparable between saline and Olipudase alfa treatment groups at both timepoints.

Table 165. Study MSSM-8120 Design and Methods

Group	N (Dams)	N (Fetuses)	Test Article	Timepoint after Olipudase Administration (h)	Fetal Sample Collections
1	2	~30	0.9% NaCl	6	Each fetus was bisected in the sagittal plane, such that half was evaluated for enzymatic activity and half for olipudase alfa concentration
2	2		Olipudase alfa (3 mg/kg)	6	
3	2	~30	0.9% NaCl	24	
4	2		Olipudase alfa (3 mg/kg)	24	

Source: Reviewer-generated.

Abbreviations: N, number of mice.

Eight pregnant mice (8-12 weeks of age) received a single dose of Olipudase alfa (3 mg/kg) or saline, administered intravenously on GD 15. Embryos were harvested at 6 or 24 hours (2dams/dose group, N=~30 embryos per time point). Each embryo was divided through the sagittal plane, then each half homogenized and assigned to detection of enzymatic activity or olipudase alfa concentration. Olipudase alfa activity was determined using a fluorescent UPLC procedure. Olipudase alfa concentration was determined using an ELISA.

Additionally, maternal livers were harvested at the time of cesarean section to determine enzymatic activity and Olipudase alfa concentration, in order to demonstrate that injections were successful.

Results

Table 166. Embryonic Enzyme Activity and Tissue Concentration After Maternal Administration of a Single Dose of Olipudase Alfa on GD 15, at 6 and 24h Post-dose

Test article	Saline		Olipudase	
Timepoint (h)	6	24	6	24
Olipudase activity (pmol/h/mg protein)	11.88±1.61	9.96±1.25	10.08+0.74 (NS)	9.80±0.52 (NS)
Concentration of olipudase (ng/mg protein)	3.44±0.76	3.48±0.56	3.08±0.30 (NS)	3.35±0.35 (NS)

Source: Reviewer-generated.
Abbreviations: NS, not significant

13.2.3. Prenatal and Postnatal Development

Table 167. GZ402665 (Olipudase Alfa): An Intravenous Pre-/Postnatal Developmental Toxicity Study in Mice, Including a Postnatal Behavioral/Functional Evaluation

Study Parameter	Study Information
Study no.:	DPN0380
Study report location:	001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 18, 2017
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	rhASM, C6644, 97.2%

Source: Review team.
Abbreviations: GLP, good laboratory practice (b) (4) QA, quality assurance; rhASM, recombinant human acid sphingomyelinase; Y, yes.

Key Study Findings

Olipudase alfa was administered intravenously at doses of 3, 10, or 30 mg/kg every other day to pregnant CD1 mice from GD 6 through GD 18; then resumed after completion of parturition, from LD 1 to LD 19. Mice were pre-treated with intraperitoneal DPH 10-20 min prior to administration of olipudase alfa. There were two control groups (vehicle+saline, and vehicle+DPH). Maternal viability, clinical observations, body weights, and littering parameters were assessed. F1 generation males and females were evaluated for viability, clinical observations, body weights, food consumption, age of attainment of landmarks of sexual maturation, neurological development, and reproductive performance.

The numbers of pregnant animals with surviving pups available for complete postnatal evaluation (birth through reproductive performance) were 23, 23, 12, 21, and 22. As reported in the mouse embryo-fetal development (EFD) study, maternal and developmental mortality were over-represented in the 3 mg/kg/day dose group. All clinical observations were attributed to hypersensitivity. These included decreased motor activity, cold to touch, hunched posture, dehydration, pale extremities, and swollen body. Mean maternal body weights were comparable to those in the control groups in olipudase alfa 10 and 30 mg/kg dose groups. The value for the 3 mg/kg/dose group was significantly lower on GD 18 (-7%) than that for control Group 2; this was subsequently reflected in reduced numbers of liveborn offspring. There were no olipudase alfa-related necropsy observations, whether among premature decedents or dams that survived to postnatal day (PND) 21.

F1 survival was reduced in groups treated with 3 and 30 mg/kg olipudase alfa; these were likewise attributed to hypersensitivity, although a direct association could not be drawn at the lower dose. At 3 mg/kg, both the group mean values for liveborn pups (8.6 versus 11.2) and the lactation index (87.7 versus 98%) were reduced, relative to the relevant control values. A reduction in the lactation index among progeny of dams treated with 30 mg/kg was attributed to poor maternal care; pup deaths were temporally associated with maternal clinical observations associated with hypersensitivity, and generally preceded maternal mortality/euthanasia.

Remaining F1 assessments were comparable among experimental groups. There were no findings attributed to maternal olipudase alfa administration.

Reviewer's Comments: The mouse pre-and postnatal development (PPND) study confirmed and extended the findings reported in the EFD study. The reasons that 3 mg/kg, although not 10 or 30 mg/kg, evoked extensive toxicity in both studies are unclear:

It is possible, although not plausible, that hypersensitivity is somehow limited to the lower dose. It is possible that maternal and developmental toxicity, as evidenced by mortality, reflect a biphasic dose response relationship. That said, there are insufficient dose levels to test this.

Further, it is noted that exencephaly was not reported in the PPND; this is unsurprising, for 2 reasons:

It is well-known that malformed pups are cannibalized after parturition. (6 pups from 5 litters of dams treated with 30 mg/kg were reported as "missing, presumed cannibalized"; this is contrasted with reports of 2 pups in 2 litters and 3 pups in 3 litters in the 2 control groups). Treatment in the PPND was every other day, while treatment in the EFD was daily.

Considered together, there was no dose-related evidence of toxicity that was not consistent with hypersensitivity. As such, maternal and developmental NOAELs are set at 30 mg/kg.

Table 168.Study DPN0380 Methods

Method	Description
Doses:	0/Saline, 0/DPH 20 mg/kg, 3, 10, 30 mg/kg
Frequency of dosing:	GD 6 – LD 19/20, every other day
Dose volume:	8.1 mL/kg Vehicle/olipudase alfa 4 mL/kg DPH
Route of administration:	IV bolus
Formulation/Vehicle:	(b) (4) mM sodium phosphate (b) (4) % sucrose, (b) (4) mM methionine, (b) (4) @ pH =6.5
Species/Strain:	Mouse, Crl:CD1(IGS)
Number/Sex/Group:	25
Satellite groups:	N
Study design:	See below.
Deviation from study protocol:	[Immaterial to study integrity or data interpretation]

Source: Review team.
Abbreviations: DPH, diphenhydramine; (b) (4) GD, gestation day; IV, intravenous; LD, lactation day; N, no.

Table 169 Study DPN0380 Design

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Route of Administration	No. of Mice
1	Control[a]/saline[b]	0	0	8.1/4	IV injection[c]/ IP injection[b]	25
2	Control[a]/DPH[d,e]	0/20	0/5	8.1/4	IV injection[c]/ IP injection[e]	25
3	Olipudase alfa/ DPH[d,e]	3.16/20	0.39/5	8.1/4	IV injection[c]/ IP injection[e]	25
4	Olipudase alfa/ DPH[d,e]	10/20	1.23/5	8.1/4	IV injection[c]/ IP injection[e]	25
5	Olipudase alfa/ DPH[d,e]	30/20	3.70/5	8.1/4	IV injection[c]/ IP injection[e]	25

[a] (b) (4) mM sodium phosphate (b) (4) % sucrose, (b) (4) mM methionine (b) (4) at a pH of 6.5.
[b] Saline administration by intraperitoneal injection.
[c] Intravenous administration by bolus.
[d] Diphenhydramine Hydrochloride.
[e] Intraperitoneal injection for DPH administration only (10 to 20 min prior to dose administration of control article or test article).

Source: Study Report DPN0380, pg. 15.

Observations and Results (F0)

Pregnancy Status, Mortality, Abortion, and Animal Disposition

The numbers of pregnant animals with surviving pups available for complete postnatal evaluation (birth through reproductive performance) were 23, 23, 12, 21, and 22. Some females were never pregnant (1, 2, 2, 3, 0). As reported in the mouse EFD study, maternal and developmental mortality were over-represented in the 3 mg/kg/day dose group. Two dams were euthanized on GD 23 with 100% early resorptions. Five dams were found dead between GD 16 and LD 2; this was generally attributed to hypersensitivity. One dam aborted on GD 16 and was euthanized. Three dams were euthanized during the lactation period after all pups died. A listing of all premature decedents is reproduced below, in Table 170.

Table 170. Premature Decedents in the Mouse PPND Study

Group	Olipudase Alfa Dose (mg/kg)	Dam	GD/LD	Comment
1	0/Saline	7805	LD 14	Euthanized. Swollen hindlimb, hunched posture, swollen mammary glands.
3	3	7856	LD 20	Euthanized. No surviving pups.
		7862	GD 23	Euthanized. No viable conceptuses. (All early resorptions.)
		7863	LD 2	Found dead (reduced motor activity, cold to touch)
		7864	LD 1	Euthanized. No surviving pups.
		7866	GD 16	Found dead. No adverse clinical observations.
		7867	GD 23	Euthanized. No viable conceptuses. (All early resorptions.)
		7869	LD 1	Euthanized. No surviving pups.
		7870	LD 2	Found dead. No adverse clinical observations
		7871	GD 16	Euthanized after abortion.
		7872	GD 14	Found dead (reduced motor activity)
		7873	LD 2	Found dead.
4	10	7894	LD 1	Euthanized. No surviving pups.
5	30	7903	LD 16	Euthanized (reduced motor activity, dehydration, pale extremities, whole body swollen)
		7919	LD 5	Found dead (reduced motor activity, hunched posture)
		7925	LD 12	Euthanized. No surviving pups.

Source: Reviewer-generated.
Abbreviations: GD, gestation day; LD, lactation day; PPND, pre and postnatal.

Clinical Observations

Clinical observations attributed to hypersensitivity occurred in all olipudase alfa-treated groups during the gestation and lactation periods. These signs included increased or decreased motor activity, cold to touch, hunched posture, moderate dehydration (based on skin turgor), pale extremities, and swollen body.

Body Weight

Mean maternal body weights were comparable to those in the control groups in olipudase alfa 10 and 30 mg/kg dose groups. The value for the 3 mg/kg/dose group was significantly lower on GD 18 (-7%) than that for control Group 2; this is associated with a reduction in the group mean number of liveborn offspring (8.6 versus 11.2, respectively).

During the lactation period, the same dose group profiles were observed, although the magnitude of the reduction in the olipudase alfa 3 mg/kg group (-4.1%) was not biologically meaningful. These data are reproduced in Figure 67 and Figure 68.

Food consumption

Not assessed.

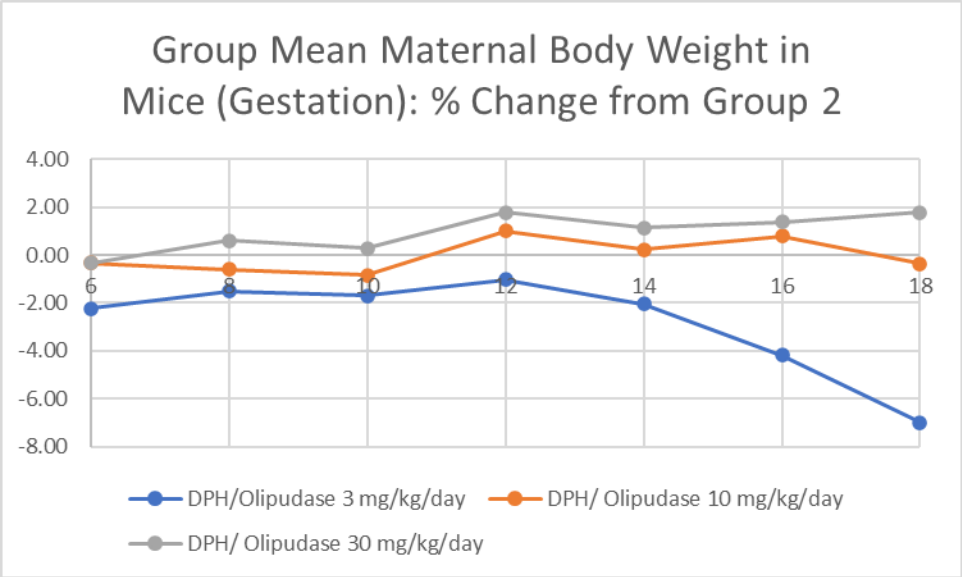
Toxicokinetics

Not assessed.

Necropsy

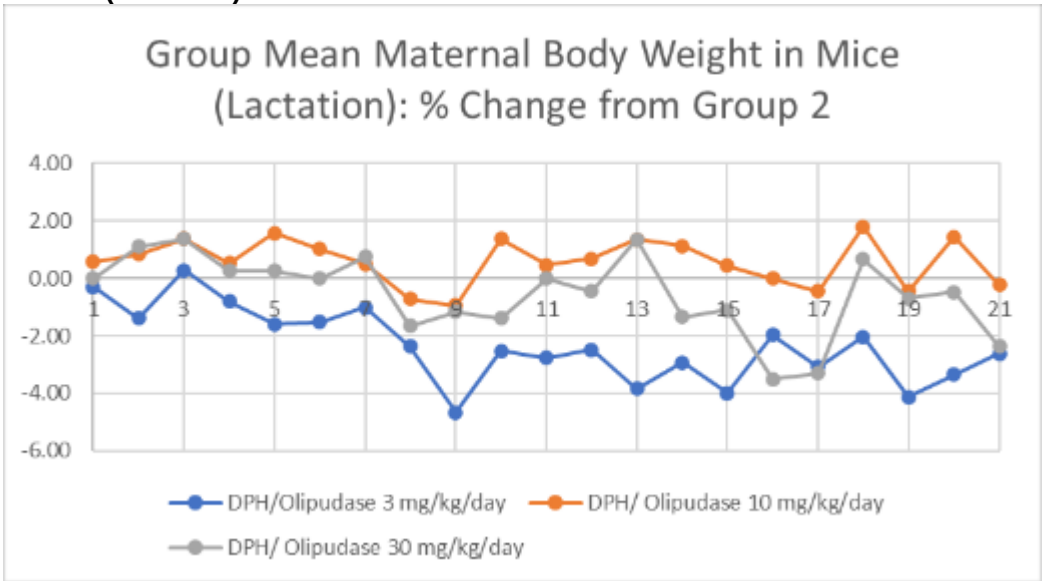
There were no olipudase alfa-related necropsy observations, whether among premature decedents or animals that survived to PND 21.

Figure 67. Effects of Olipudase Alfa Administration on Maternal Body Weight in Mice, Relative to Control (Gestation)



Source: Reviewer generated.
Abbreviations: DPH, diphenhydramine.

Figure 68. Effects of Olipudase Alfa Administration on Maternal Body Weight in Mice, Relative to Control (Lactation)



Source: Reviewer generated.
Abbreviations: DPH, diphenhydramine.

Dosing Solution Analysis

Results for the control article dosing solutions (Group 1) were all lower limit of quantification (0.10 mg/mL). Concentration results for test article formulations prepared at target concentrations of 0.39, 1.23, and 3.70 mg/mL olipudase alfa (Groups 3, 4 and 5, respectively) were all within 20% of the expected concentration.

Observations and Results (F1).

Survival

The study design did not incorporate culling of litters. Consequently, the numbers of pups per dam was highly variable in each experimental group.

Pup mortality was increased in groups 3 and 5. The lactation index in group 5 (number of viable pups on PND 21/number of viable pups on PND 4) was significantly reduced, relative to that in Group 2 (87.7% versus 98%, respectively). However, pup deaths were temporally associated with maternal clinical observations thought to reflect hypersensitivity; and generally preceded maternal mortality/euthanasia. This finding is not attributed to maternal treatment with olipudase alfa.

Pup mortality in group 3 reflected reductions in the mean number of liveborn pups (8.9±4.5, relative to 13.1+2.1 and 11.2±2.9 in groups 1 and 2, respectively); as well as a reduction in the lactation index (87.9%). Neither of these findings could be directly associated with maternal hypersensitivity.

Clinical Observations

There were no treatment-related clinical observations. Findings that were reported were not dose dependent; occurred in only 1-2 litters; or were observed in a limited number of pups in each group.

Body Weight

No statistically significant differences occurred among the groups for the overall postweaning, precohabitation, or gestation periods. Weights of males and females are reproduced in Figure 69 and Figure 70, respectively.

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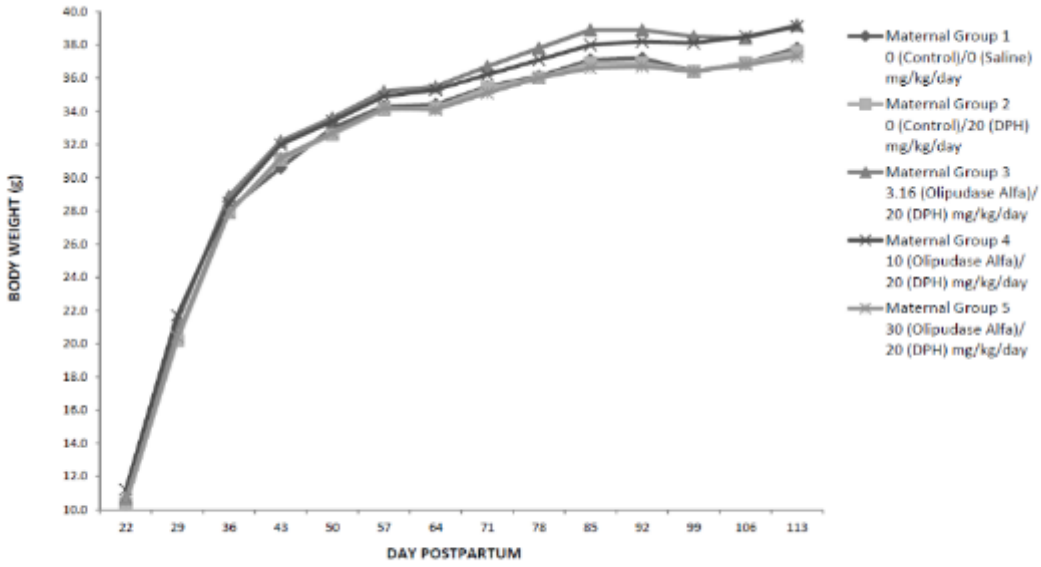
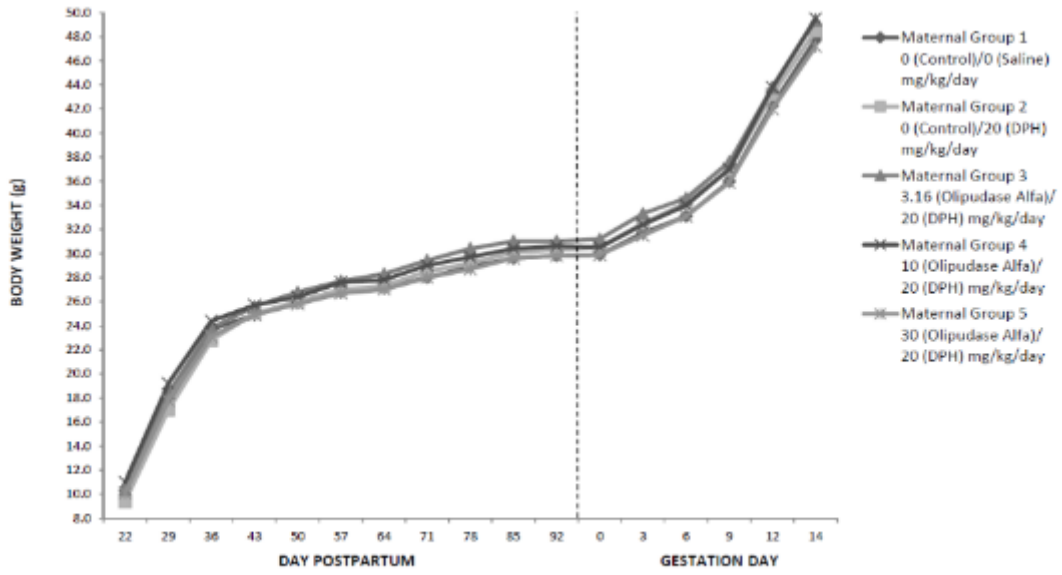
Figure 69. F1 Generation Male Mice



Source: Applicant report DPN0380, pg 50.
Abbreviations: DPH, diphenhydramine.

Figure 70. F1 Generation Female Mice



Source: Applicant report DPN0380, pg 51.
Abbreviations: DPH, diphenhydramine.

Food Consumption

Food consumption values for the F1 generation male and female mice in the postweaning, precohabitation, or gestation periods were unaffected by maternal dosages of olipudase alfa.

Physical Development

Attainment of sexual landmarks was comparable across experimental groups in both males and females. Data are reproduced in Table 171.

Table 171. Age of Attainment of Landmarks of Sexual Maturity in F1 Mice

MATERNAL GROUP		1	2	3	4	5
TEST MATERIAL		CONTROL/SALINE	CONTROL/DPH	OLIPUDASE ALFA/DPH	OLIPUDASE ALFA/DPH	OLIPUDASE ALFA/DPH
MATERNAL DOSE LEVEL (MG/KG/DAY)		0	0/20	3.16/20	10/20	30/20
MALE MICE	N	25	25	23a	25	25
PREPUTIAL SEPARATION b	MEAN±S.D.	27.8 ± 1.9	27.8 ± 1.7	28.3 ± 2.7	28.4 ± 1.5	27.9 ± 2.2
BODY WEIGHT AT SEPARATION (G)c	MEAN±S.D.	18.50 ± 3.26	18.61 ± 3.12	20.67 ± 1.93*	20.06 ± 2.70**	19.20 ± 2.57
FEMALE MICE	N	24d	25	23d	25	25
VAGINAL PATENCY e	MEAN±S.D.	26.9 ± 2.3	26.5 ± 3.5	27.4 ± 3.0	25.8 ± 2.0	26.3 ± 2.3
BODY WEIGHT AT VAGINAL PATENCY (G)f	MEAN±S.D.	15.49 ± 2.11	14.15 ± 2.91	16.05 ± 2.69	15.60 ± 2.74	14.06 ± 1.09

a. Excludes mice that were euthanized on Day 23 postpartum due to adverse clinical observations.
b. Average day postpartum that the prepuce was observed to be separated.
c. Average body weight on day prepuce was first observed to be separated.
d. Excludes values for mice of which the exact day of maturity could not be determined.
e. Average day postpartum that the vagina was observed to be patent.
f. Average body weight on day vagina was first observed to be patent.
* Significantly different from the Group 2 value ($p \leq 0.05$); analyses restricted to Groups 2 through 5.
** Significantly different from the Group 2 value ($p \leq 0.01$); analyses restricted to Groups 3 through 5.

Source: Applicant report DPN0380, pg 94.
Abbreviations: DPH, diphenhydramine; N, total number of subjects; SD, standard deviation.

Neurological Assessment

There were no treatment-related effects on acoustic startle, when F1 males and females were assessed for reactivity to auditory stimuli, or latency to same, on PND 65. There were no treatment-related differences in either ambulation or fine movement in either sex during motor activity testing when evaluated on PND 60. There were neither treatment-related differences, nor biologically important effects on learning, memory, or swimming performance in the Morris Water Maze in the on PND 66 and 90.

Reproduction

Mating and fertility parameters, necropsy observations, organ weights and their ratios to TBW, and cesarean-section and litter parameters were unaffected in F1 generation male and female mice by maternal olipudase alfa administration during pregnancy and lactation.

Excretion of Olipudase Alfa into the Milk of Lactating Mice

Table 172. Evaluation of Olipudase Alfa Transfer into the Milk of Lactating Mice

Study Parameter	Study Information
Study no.:	MSSM-1120
Study report location:	0037
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 1, 2020
GLP compliance:	N
QA statement:	N
Drug, lot #, and % purity:	Olipudase alfa, C1090479, unspecified

Source: Review team.
Abbreviations: N, no; (b) (4)

Key Study Findings

Olipudase alfa (3 mg/kg) or 0.9% NaCl was administered intravenously once on PND 7 to lactating CD1 mice. Oxytocin (0.1 mL of 2 international units (IU) solution) was administered on PND 9 (route of administration unspecified), and milk was collected within 1 minute. Milk from olipudase-treated dams contained approximately 477 ng/mL olipudase alfa.

Reviewer's Comments: The bioavailability of olipudase alfa in pups was not addressed. However, it is unlikely that the protein would be absorbed intact from the neonatal gastrointestinal tract.

Table 173. Study MSSM-1120 Methods

Method	Description
Doses:	0/Saline, 0/DPH 20 mg/kg, 3, 10, 30 mg/kg
Frequency of dosing:	Once
Dose volume:	Unspecified
Route of administration:	Intravenous
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	Mouse, CD
Number/Sex/Group:	5
Satellite groups:	N
Study design:	See below.
Deviation from study protocol:	Unspecified

Source: Review team.
Abbreviations: CD, cluster of differentiation; DPH, diphenhydramine; N, no.

Table 174. Study Design and Methods

Group	Mouse Strain	Number of Animals	Test Article	Dosing Regimen/Route of Administration	Sample Collection
1	CD1	5	Saline	Single dose/IV	Two days post-dose, mothers were administered oxytocin and milk was collected within 1 minute.
2		5	Olipudase alfa (3 mg/kg)		

Source: Sanofi study report MSSM-1120.

Five lactating female mice (8-12 weeks of age) were used per group. Pregnancy was determined by daily visual examination of plugs. After the female mice delivered their pups, males were removed from the cage. On PND 7, dams received a single tail vein injection of Olipudase alfa (3 mg/kg) or saline. On PND 9, dams received an injection of oxytocin (0.1 ml of 2 IU stock), and milk was collected within 1 min. All samples were frozen and stored at -20°C for further analysis. Olipudase alfa activity was determined using a fluorescent UPLC procedure. Olipudase alfa concentration was determined using an ELISA.

Results.

Table 175 Olipudase in Milk of Mouse Dams: Enzymatic Activity and Concentration 48h After Administration

Test Article	Saline	Olipudase
Olipudase activity (pmol/h/mL)	5.6±1.07	10.83±2.90*
Concentration of olipudase (ng/mL)	20.62±10.96	477.48±129.47**

Source: Reviewer-generated
*p=0.0054
**p=0.0001

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Not Applicable.

14.2. In Vivo Studies

14.2.1. ASCEND Study

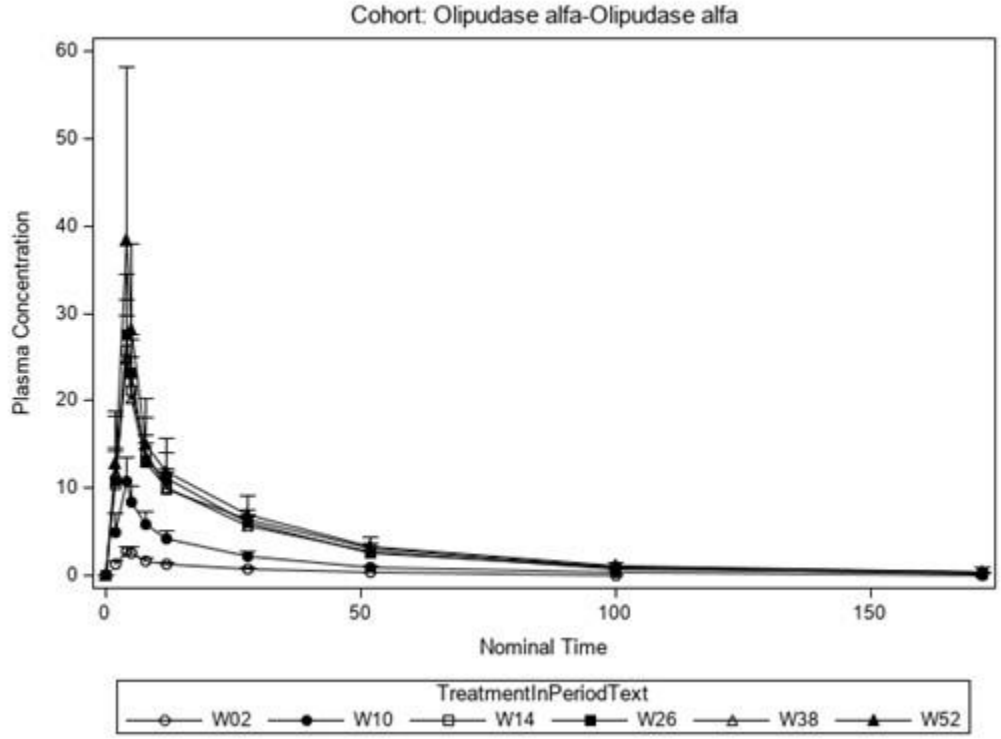
See Section 6.2.1 for details of the study design of ASCEND.

14.2.1.1. Pharmacokinetics

Following IV infusion of olipudase alfa, plasma concentrations of olipudase alfa peaked approximately at the end of infusion (Figure 71 and Figure 72). Following IV infusion of 3.0 mg/kg, mean $t_{1/2}z$ values ranged from 32 to 38 hours. Table 176 provides a summary of the PK parameters of $AUC_{0\text{-}inf}$ and C_{max} following multiple dose administrations of olipudase alfa by different manufacturing processes. PK variability for individual subject's AUC_{inf} is shown in Figure 73 and the results indicated similar variability at different dosages.

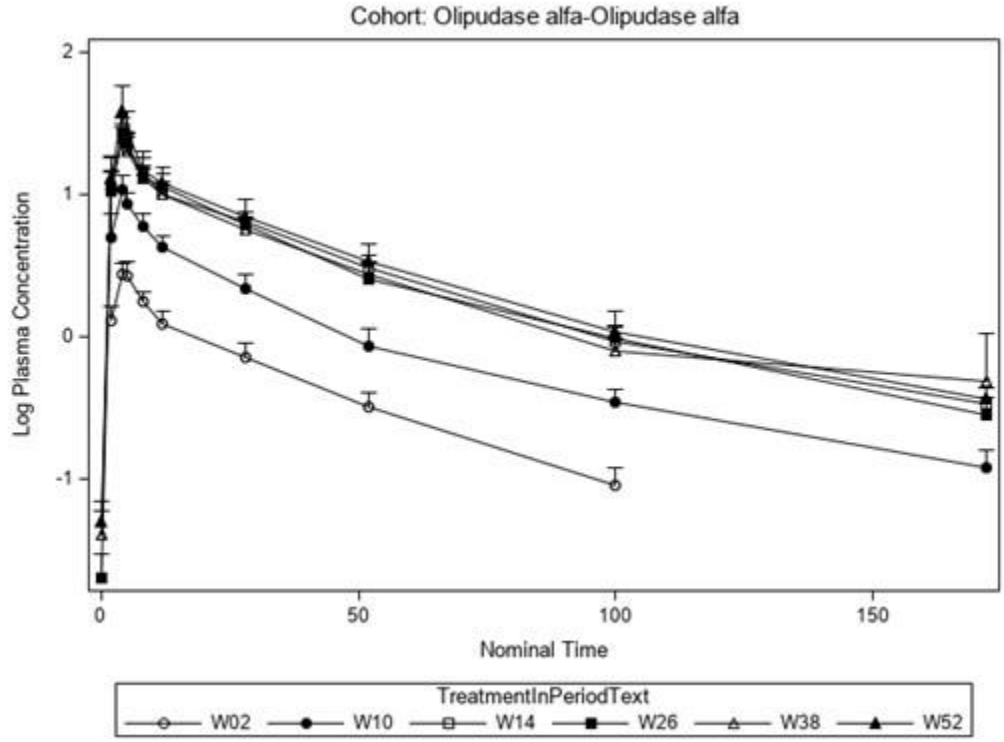
Subjects with ASMD showed a dose-proportional increase in olipudase alfa exposure across the doses ranging from 0.3 to 3.0 mg/kg during the dose escalation phase. Over the 10-fold dosage range of 0.3 to 3.0 mg/kg, the mean C_{max} and $AUC_{0\text{-}inf}$ increased by 9.7- and 10.2-fold, respectively (Table 176). Due to insufficient PK profiles, PK parameters at 0.1 mg/kg could not be adequately estimated by the NCA method.

Figure 71. Mean Plasma Concentration-Time Profiles of Olipudase Alfa at Week 2 (0.3 mg/kg), Week 10 (1.0 mg/kg), Week 14 (2.0 mg/kg), and Week 26-52 (3 mg/kg) in Linear Scale



Source: Reviewer's plot using the Applicant's submitted dataset (pc.xpt, pp.xpt).

Figure 72. Mean Plasma Concentration-Time Profiles of Olipudase Alfa at Week 2 (0.3 mg/kg), Week 10 (1.0 mg/kg), Week 14 (2.0 mg/kg), and Week 26-52 (3 mg/kg) in Semi-Logarithmic Scale



Source: Reviewer's plot using the Applicant's submitted dataset (pc.xpt, pp.xpt).

Table 176. Plasma Pharmacokinetic Parameters of Olipudase Alfa Following Multiple Doses of Olipudase Alfa in ASCEND

ARM	Visit	Process	Number of Subjects (N)	AUC_{tau} Mean (h*ug/mL)	AUC_{tau} SD	C_{max} Mean (ug/mL)	C_{max} SD	CL Mean (mL/h/kg)	CL SD	$T_{1/2}z$ Mean (h)	$T_{1/2}z$ SD
OA-OA	WEEK 2	C (b) (4)	13	60.6	11.3	3.0	0.7	5.1	0.9	25.2	2.4
OA-OA	WEEK 10	C	12	232.2	50.6	11.0	2.6	4.5	0.9	34.1	2.6
OA-OA	WEEK 14	C	11	587.0	102.6	28.3	6.1	5.1	0.9	35.0	2.1
OA-OA	WEEK 26	C	13	606.1	70.9	31.8	8.2	4.9	0.8	38.6	7.9
OA-OA	WEEK 38	C	16	672.9	122.3	32.4	6.0	4.6	0.8	37.9	3.5
OA-OA	WEEK 52	C	18	639.5	195.5	35.3	18.5	4.7	1.0	36.9	6.5
OA-OA	WEEK 54	C	16	648.3	209.9	31.9	10.4	4.6	1.2	36.7	8.3
OA-OA	WEEK 68	C	18	739.7	153.3	35.2	13.9	4.2	0.7	35.2	5.8
OA-OA	WEEK 80	C	1	571.3	.	25.7	.	5.3	.	37.3	.
OA-OA	WEEK 80	C	15	748.6	119.7	42.6	17.9	4.1	0.7	37.3	6.5
OA-OA	WEEK 132	C	3	851.3	170.4	62.3	40.7	3.6	0.7	30.6	3.6
OA-OA	WEEK 132	C	9	729.6	139.0	34.9	7.7	4.2	0.8	37.1	4.3
OA-OA	WEEK 184	C	2	969.4	.	42.1	6.6	3.1	.	37.8	.
OA-OA	WEEK 184	C	1	.	.	33.4	.	.	.	.	.
PL-OA	WEEK 54	C	15	18.8	4.6	0.9	0.3	5.6	1.5	19.7	3.2
PL-OA	WEEK 68	C	14	555.6	223.4	26.9	8.8	5.0	1.6	28.7	7.9
PL-OA	WEEK 80	C	15	544.5	178.7	27.8	8.0	5.3	1.3	32.7	7.4
PL-OA	WEEK 132	C	4	340.8	196.1	28.1	16.3	4.6	0.5	26.7	7.5
PL-OA	WEEK 132	C	8	633.5	154.5	29.2	10.0	5.0	1.5	33.3	3.5
PL-OA	WEEK 184	C	2	694.2	.	30.4	.	4.3	.	31.3	0.8
PL-OA	WEEK 184	C	2	481.9	1.0	23.7	0.0	5.2	1.5	24.3	2.0
PL-OA	WEEK 236	C	1	.	.	40.5	.	.	.	.	.

Source: Reviewer's summary table using the Applicant's submitted dataset.
Abbreviations: AUC, area under the concentration-time curve, CL, clearance; C_{max}, maximum plasma concentration; $T_{1/2}z$, drug elimination during the terminal phase; SD, standard deviation.
The PK parameters are summarized by weeks relative to initiation administration of olipudase alfa. OA-OA = olipudase alfa→olipudase alfa group; PL-OA = placebo→olipudase alfa group.

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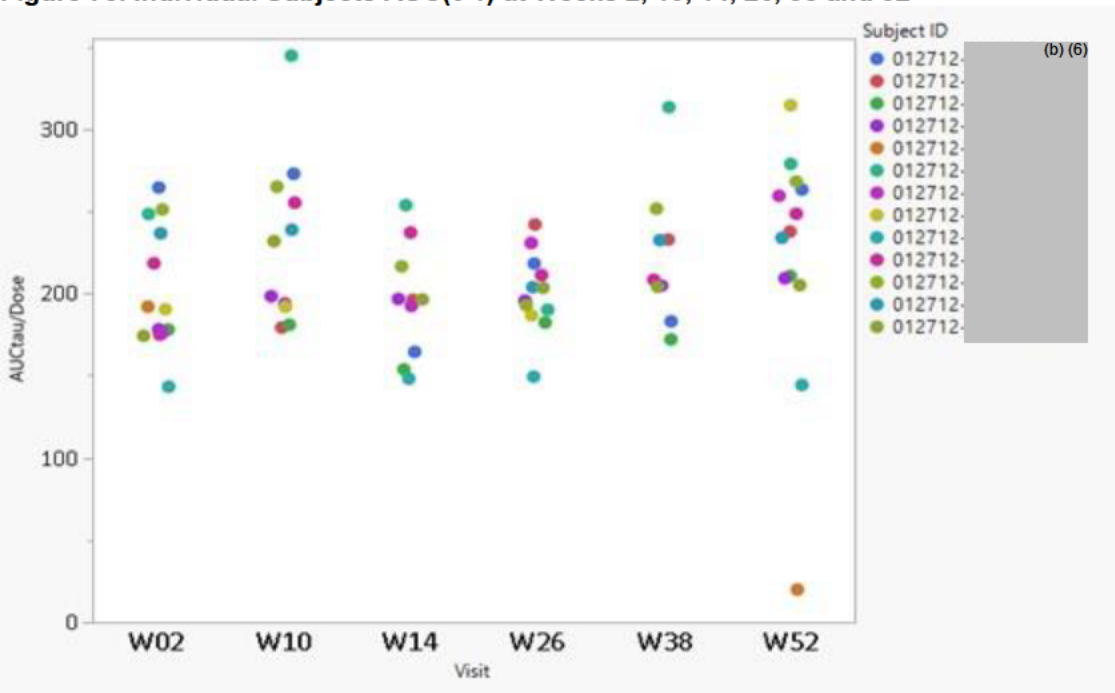
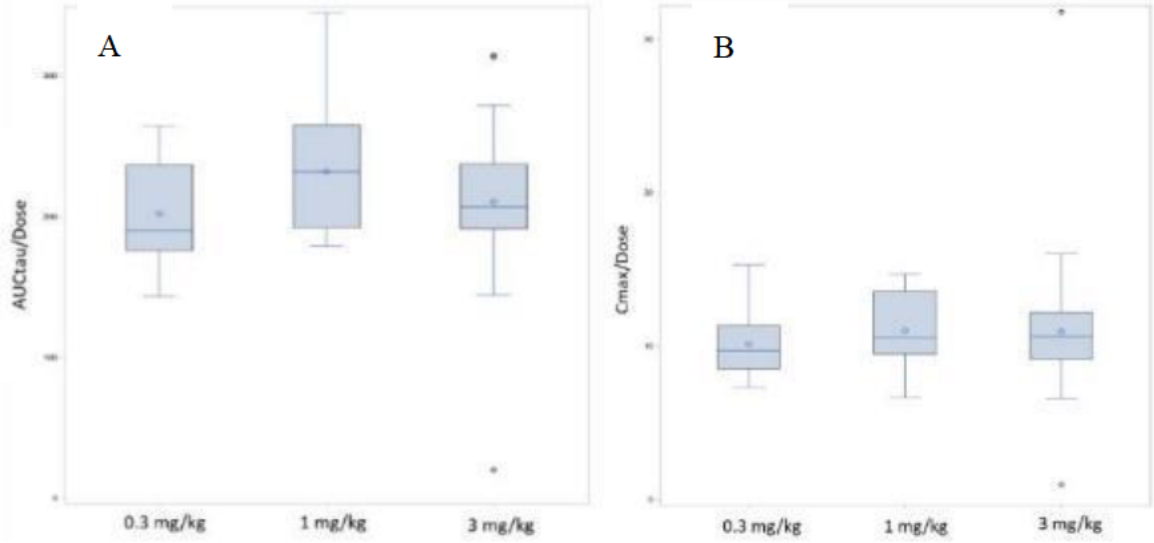
Figure 73. Individual Subjects AUC(0-τ) at Weeks 2, 10, 14, 26, 38 and 52



Source: Reviewer's plot using the Applicant's submitted dataset (pc.xpt, pp.xpt).

Figure 74. Dose Proportionality Evaluation of Olipudase Alfa by (A) Dose Normalized Mean $AUC_{0\text{-}tau}$ and (B) Dose Normalized C_{max} Following IV Infusion of 0.3, 1.0 and 3.0 mg/kg in Adult Subjects with ASMD (ASCEND)



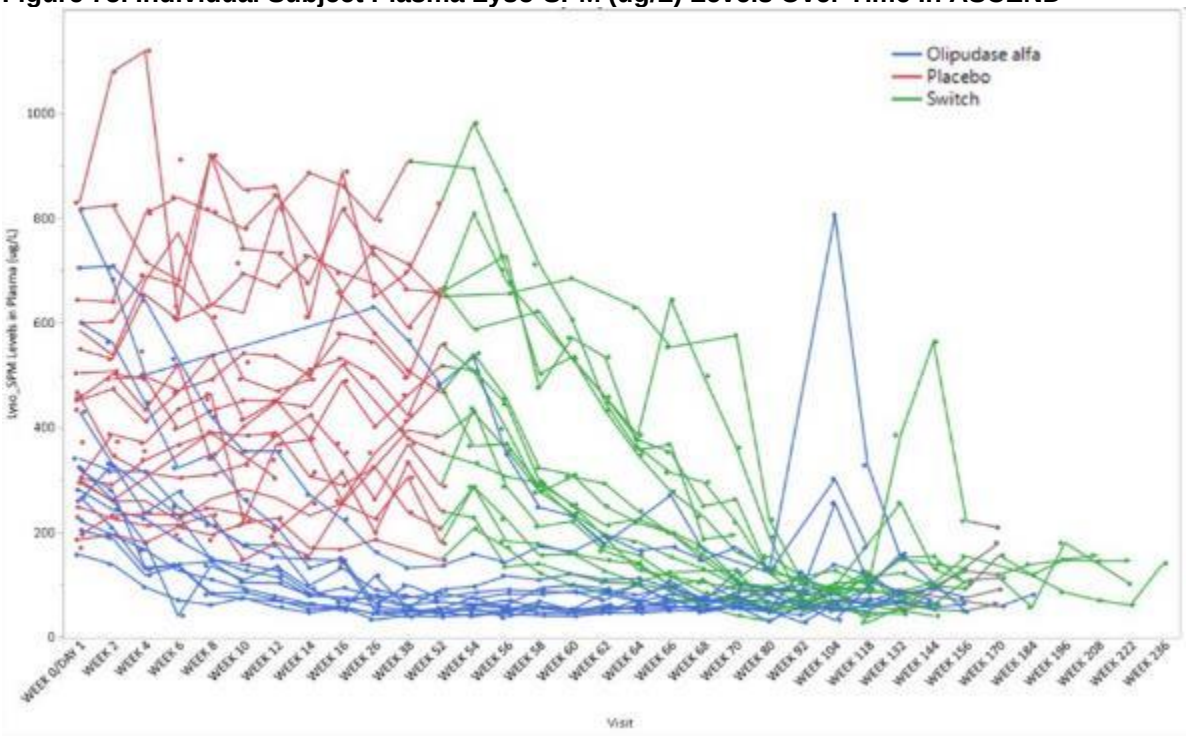
Source: Reviewer's plot using the Applicant's submitted dataset

14.2.1.2. Pharmacodynamics

Individual pre-infusion plasma lyso-SPM and ceramide levels in subjects with ASMD in ASCEND are shown in Figure 75 and Figure 76, respectively. Pre-infusion plasma lyso-SPM and ceramide levels decreased following treatment with olipudase alfa. The plasma lyso-SPM

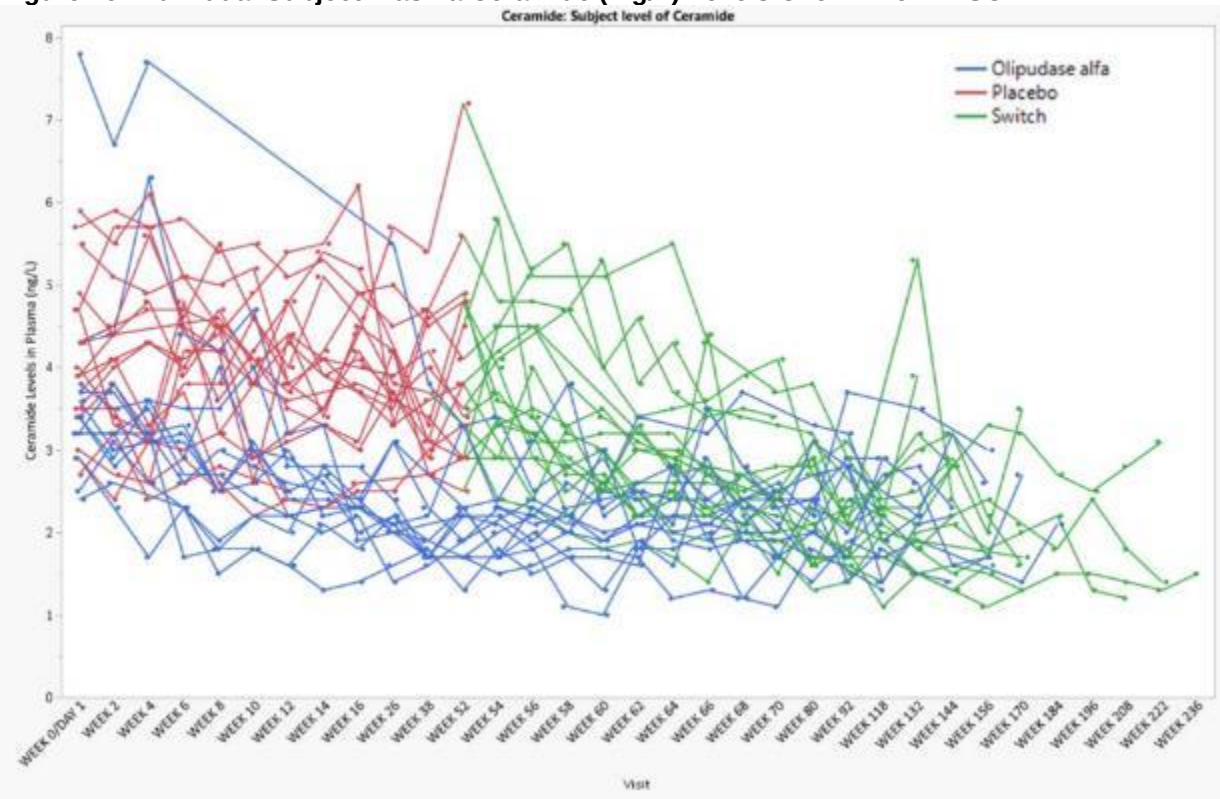
and ceramide levels by manufacturing processes are shown in Figure 77 and Figure 78, respectively.

Figure 75. Individual Subject Plasma Lyso-SPM (ug/L) Levels Over Time In ASCEND



Source: Reviewer's plot using the Applicant's submitted datasets.

Figure 76. Individual Subject Plasma Ceramide (mg/L) Levels Over Time In ASCEND



Source: Reviewer's generated plot using the Applicant's submitted datasets.

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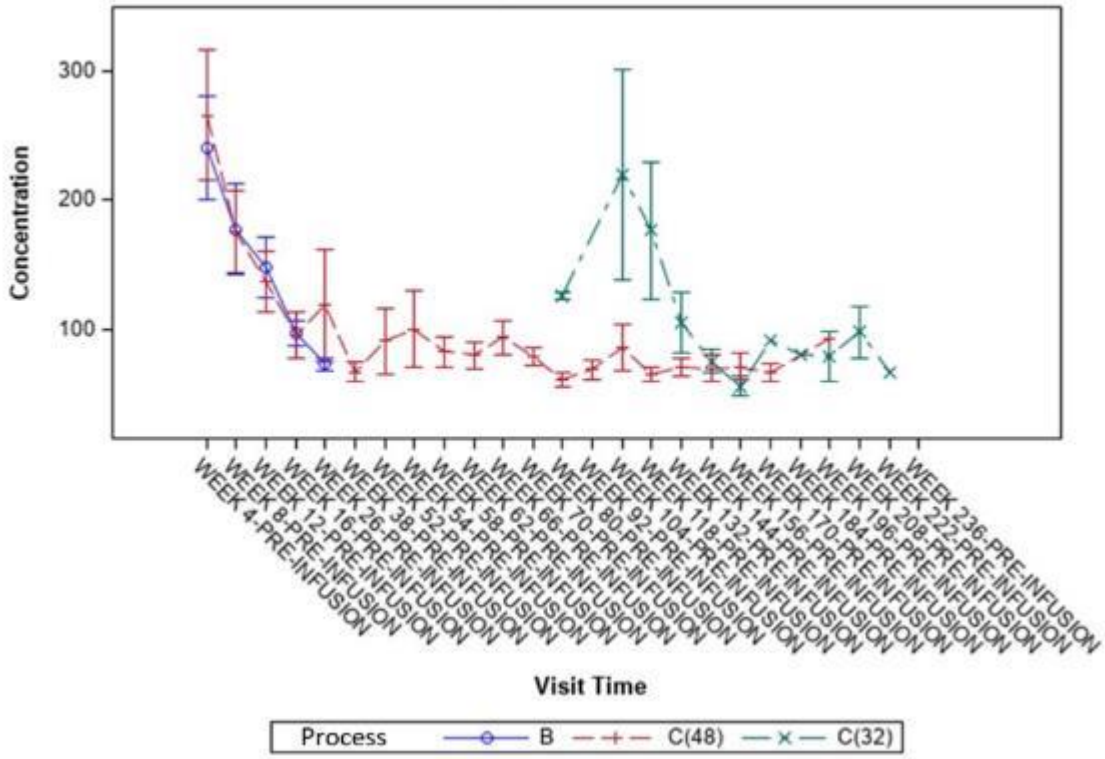
Figure 77: Pre-Infusion Mean ± SD Plasma Lyso-SPM Concentrations (ug/L) by Manufacturing Processes in Subjects With ASMD (ASCEND)



Source: Reviewer's analyses based on the Applicant's submitted datasets.

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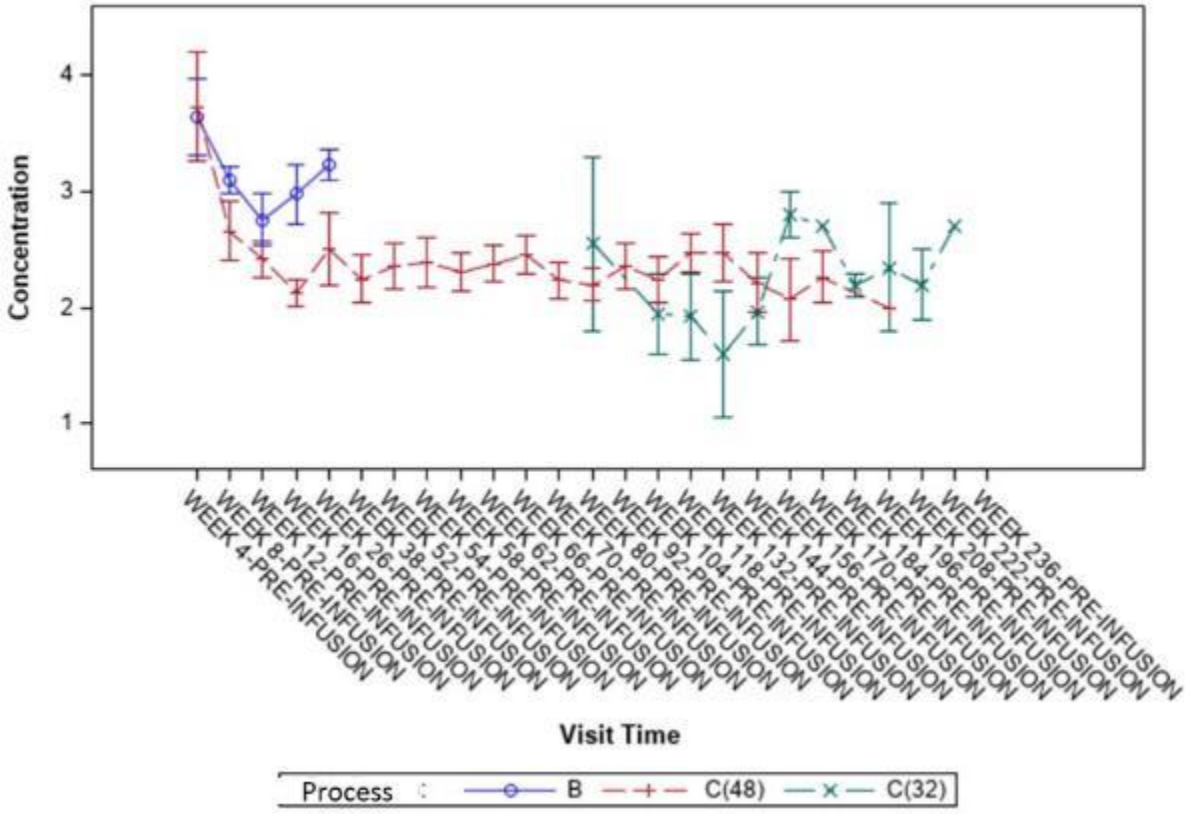
Figure 78: Pre-Infusion Mean ± SD Plasma Ceramide Concentration (mg/L) by Manufacturing Processes in Subjects With ASMD (ASCEND)



Source: Reviewer's generated plot using the Applicant's submitted datasets.

14.2.2. ASCEND PED Study

14.2.2.1. Pharmacokinetics

The PK parameters of olipudase alfa in ASCEND-PED are summarized in Table 177. The mean $t_{1/2z}$ values ranged from 15.9 to 24.6 hours. The PK parameters by pediatric age groups, adolescent (12 to <18 years, 4 subjects), child (2 to <12 years, 15 subjects), and infant (<2 years, 1 subject), are summarized in Table 178. A comparison of PK parameters between process B and process B at Week 52 is provided in Table 179.

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Table 177. Plasma Pharmacokinetic Parameters of Olipudase Alfa Following Multiple Doses of Olipudase Alfa in Pediatric Subjects (ASCEND-PED)

Visit	Number of Subjects (N)	AUC_{tau} Mean (h*ug/mL)	AUC_{tau} SD	C_{max} Mean (ug/mL)	C_{max} SD	CL Mean (mL/h/kg)	CL SD	$T_{1/2}z$ Mean (h)	$T_{1/2}z$ SD
WEEK 4	8	41.937	28.147	4.175	2.4093	4.24255	2.92286	15.8758	9.96735
WEEK 12	7	171.017	30.566	10.6114	1.337	6.03558	1.23311	21.8171	1.85941
WEEK 16	2	511.468	135.874	28.9	10.6066	6.08001	1.61519	22.5223	2.61881
WEEK 18	1	509.793	.	23.2	.	5.88474	.	23.1193	.
WEEK 20	2	437.831	62.487	22.1	1.5556	6.92246	0.98797	22.3431	2.09844
WEEK 22	1	538.955	.	30.4	.	5.56633	.	24.5627	.
WEEK 28	1	67.54	.	3.77	.	4.44182	.	19.304	.
WEEK 38	1	0	.	0.775	.	0.0001	.	0.0001	.
WEEK 50	1	324.38	.	15	.	9.24841	.	21.9543	.
WEEK 52	8	490.611	114.742	24.575	8.1307	6.42566	1.54793	23.4156	1.0629

Source: Reviewer's summary table based on the Applicant's submitted datasets.
Note: Only Process C data were used.
Abbreviations: AUC, area under the concentration-time curve, CL, clearance; C_{max}, maximum plasma concentration; $T_{1/2}z$, drug elimination during the terminal phase; SD, standard deviation.

Table 178. Plasma Pharmacokinetic Parameters of Olipudase Alfa Following Multiple Doses of Olipudase Alfa in Pediatric Cohorts (ASCEND-PED)

Visit	Cohort	Number of Subjects (N)	AUC_{inf} Mean (h*ug/mL)	AUC_{inf} SD	C_{max} Mean (ug/mL)	C_{max} SD	CL Mean (mL/h/kg)	CL SD	$T_{1/2}z$ Mean (h)	$T_{1/2}z$ SD
WEEK 4	Child	7	47.9	24.3	4.5	2.4	4.8	2.6	18.1	8.2
WEEK 4	Infant	1	0.0	.	2.1	.	0.0	.	0.0	.
WEEK 16	Child	2	511.6	135.9	28.9	10.6	6.1	1.6	22.5	2.6
WEEK 18	Child	1	509.9	.	23.2	.	5.9	.	23.1	.
WEEK 20	Child	2	438.0	62.5	22.1	1.6	6.9	1.0	22.3	2.1
WEEK 22	Child	1	539.1	.	30.4	.	5.6	.	24.6	.
WEEK 28	Infant	1	67.5	.	3.8	.	4.4	.	19.3	.
WEEK 38	Infant	1	0.0	.	0.8	.	0.0	.	0.0	.
WEEK 50	Infant	1	324.5	.	15.0	.	9.2	.	22.0	.
WEEK 52	Child	7	511.5	106.6	25.9	7.8	6.1	1.4	23.6	0.9
WEEK 52	Infant	1	345.7	.	15.5	.	8.7	.	21.9	.

Source: Reviewer's summary table based on the Applicant's submitted datasets.
Abbreviations: AUC, area under the concentration-time curve, CL, clearance; C_{max}, maximum plasma concentration; $T_{1/2}z$, drug elimination during the terminal phase; SD, standard deviation.

Table 179. Comparison of Olipudase Alfa PK Parameters Between Process B and Process C(b) (4) at 3 mg/kg Q2W in Pediatric Subjects (ASCEND-PED)

Process	Number of Subjects (N)	AUC_{inf} Mean (h*ug/mL)	AUC_{inf} SD	C_{max} Mean (ug/mL)	C_{max} SD
B	11	469.0	53.7	22.2	3.0
C(b) (4)	8	490.7	114.8	24.6	8.1

Source: Reviewer-generated table based on the Applicant's datasets.

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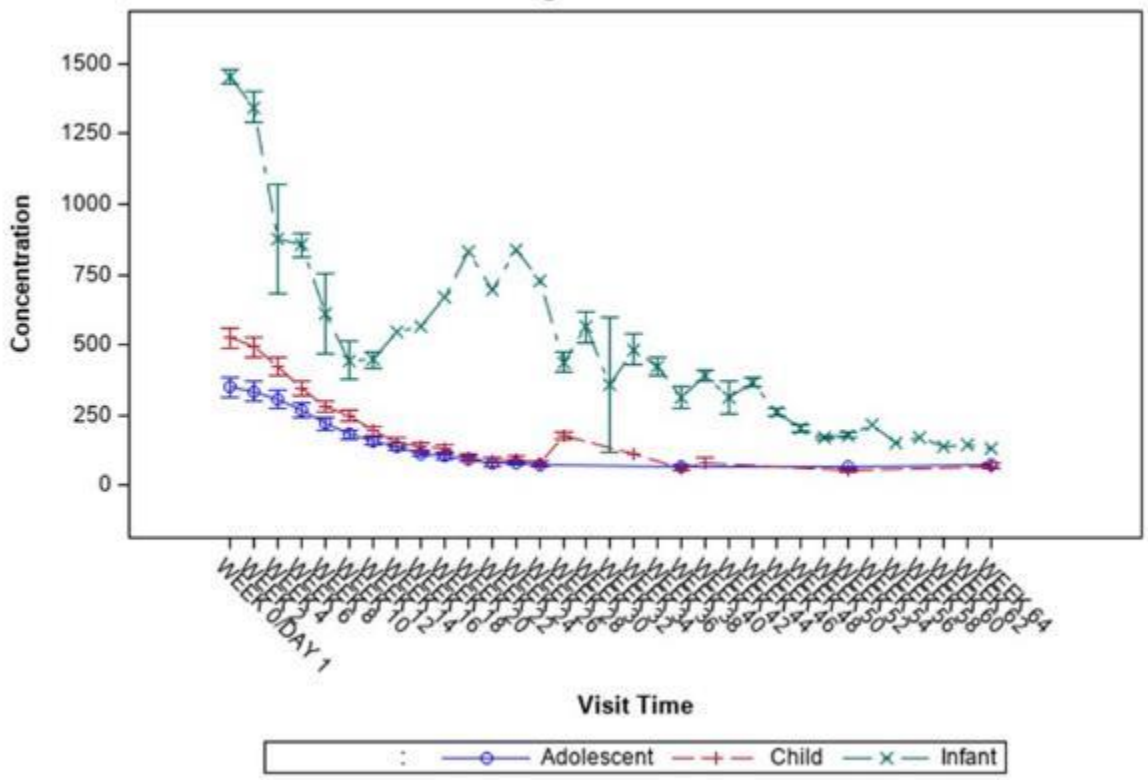
14.2.2.2. Pharmacodynamics

The pre-infusion plasma Lyso-SPM and ceramide levels in pediatric subjects with ASMD by age groups are shown in Figure 79 and Figure 80, respectively. A comparison of plasma Lyso-SPM between process B and process C is provided in Figure 81.

Figure 79: Mean Plasma Lyso-SPM Levels in Pediatric Subjects With ASMD (ASCEND-PED)



Source: Reviewer's analyses based on the Applicant's submitted datasets.

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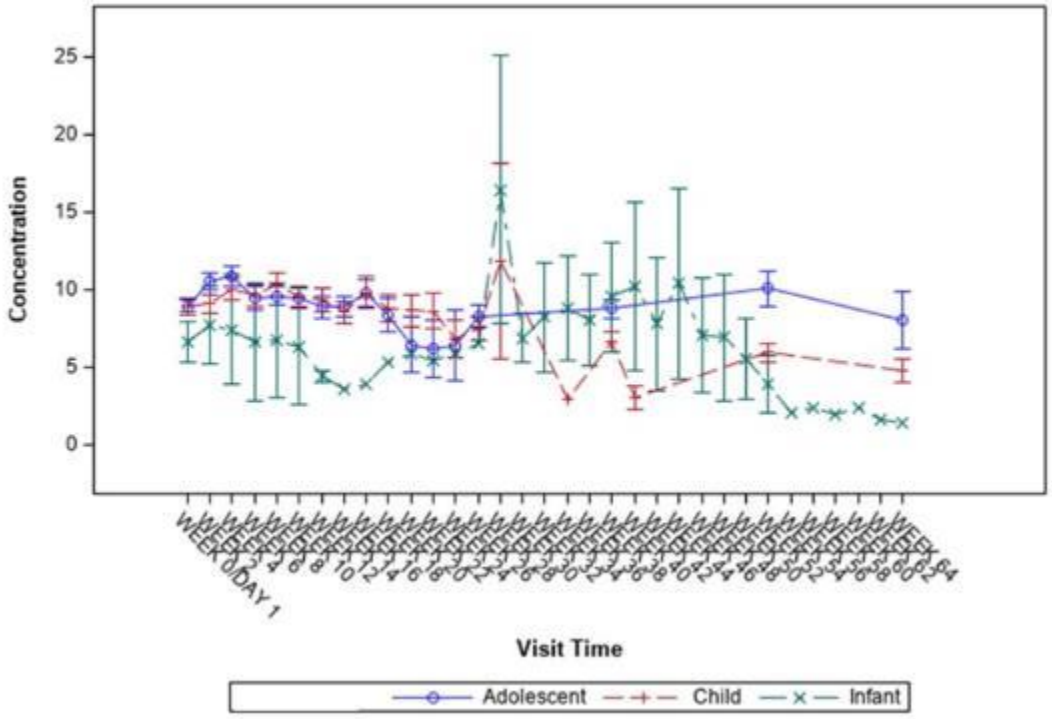
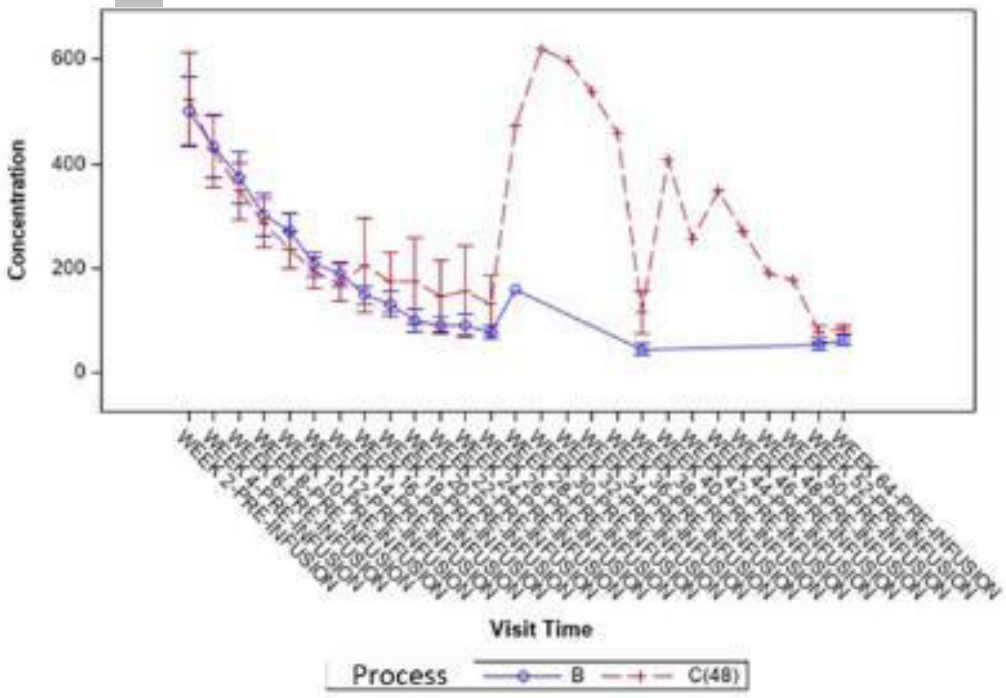
Figure 80: Mean Plasma Ceramide Levels Over the Time in Pediatric Subjects With ASMD (ASCEND-PED)



Source: Reviewer's analyses based on the Applicant's submitted datasets.

Figure 81: Comparison of Plasma Lyso-SPM Levels Between Manufacturing Process B and Process C(b) (4) in ASCEND-PED.

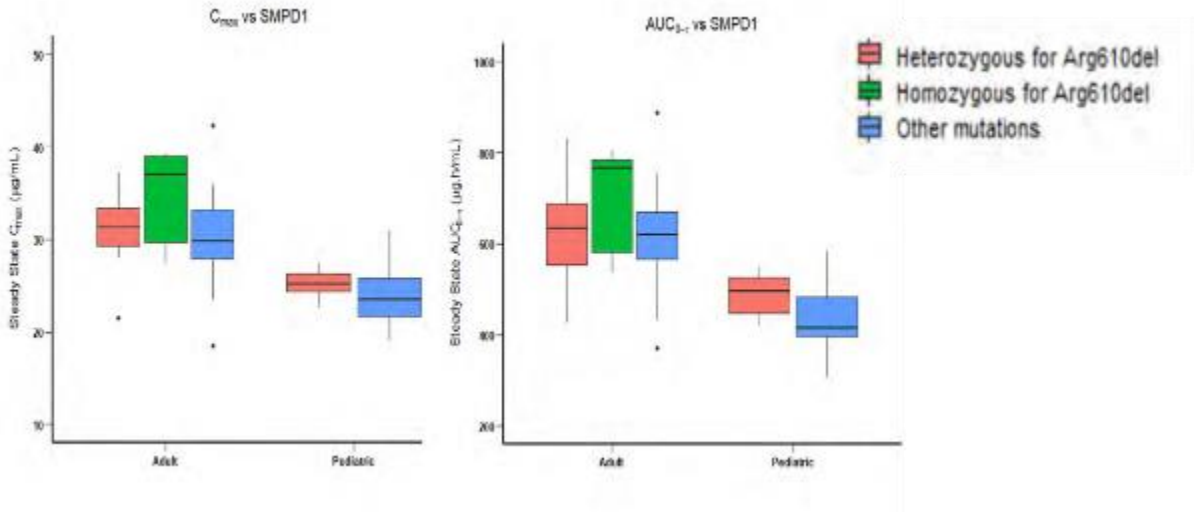


Source: Reviewer's analyses based on the Applicant's submitted datasets.

14.3. Baseline SMPD1 Pathogenic Variants

To assess the impact of SMPD1 genotype on PK, popPK model derived olipudase alfa C_{max} and AUC0-τ values at 3.0 mg/kg were compared by SMPD1 genotype subgroups (homozygous for Arg610del, heterozygous for Arg610del, and other variants). Among the 38 adult subjects from DFI13412 and DFI12712 (ASCEND), 5 (13%) were homozygous for Arg610del, 12 (32%) were heterozygous for Arg610del, and 21 (55%) were with other variants. Among the 20 pediatric subjects from DFI13803 (ASCEND-Peds), 6 subjects (30%) were heterozygous for Arg610del, 14 (70%) were with other variants, and no subjects were homozygous for Arg610del. As shown in Figure 82, Cmax and AUC0-τ overlapped in adult and pediatric subjects across the SMPD1 genotype subgroups.

Figure 82. Olipudase Alfa Exposure Following 3.0 mg/kg IV Q2W in Adult and Pediatric Subjects With ASMD by Different SMPD1 Genotypes



Source: Section 3.3.1.9 of Summary of Clinical Pharmacology report.

14.4. Immunogenicity Summary

Immunogenicity of the olipudase alfa was evaluated in four clinical trials which included 60 subjects with ASMD (40 adult and 20 pediatric subjects). Of these, 38 subjects were exposed to Manufacturing process C and were included in the ADA evaluable population which was used for immunogenicity analyses.

14.4.1. Immunogenicity Incidences

Blood samples for immunogenicity assessment were collected in all clinical trials. The immunogenicity assessment followed a tiered approach (i.e., ADA screening, confirmatory assay, ADA titer, and NAb characterization in ADA-positive samples). NAb to olipudase alfa was assessed by determination of inhibition of enzyme catalytic activity or inhibition of cellular uptake. The incidence of ADA response in patients with ASMD are presented in Table 180. Overall, 36.8% of subjects with ASMD (30% of adults and 62.5% of pediatric subjects) developed treatment-induced ADA while receiving olipudase alfa. Pediatric subjects had

relatively higher ADA titers than adults. One adult and one pediatric ADA positive subject were characterized as positive for NAb that inhibit enzyme catalytic activity. No ADA positive subject was characterized as NAb that inhibit cellular uptake of olipudase alfa.

Table 180. Incidence of Antidrug Antibodies in Subjects With ASMD (Process C)

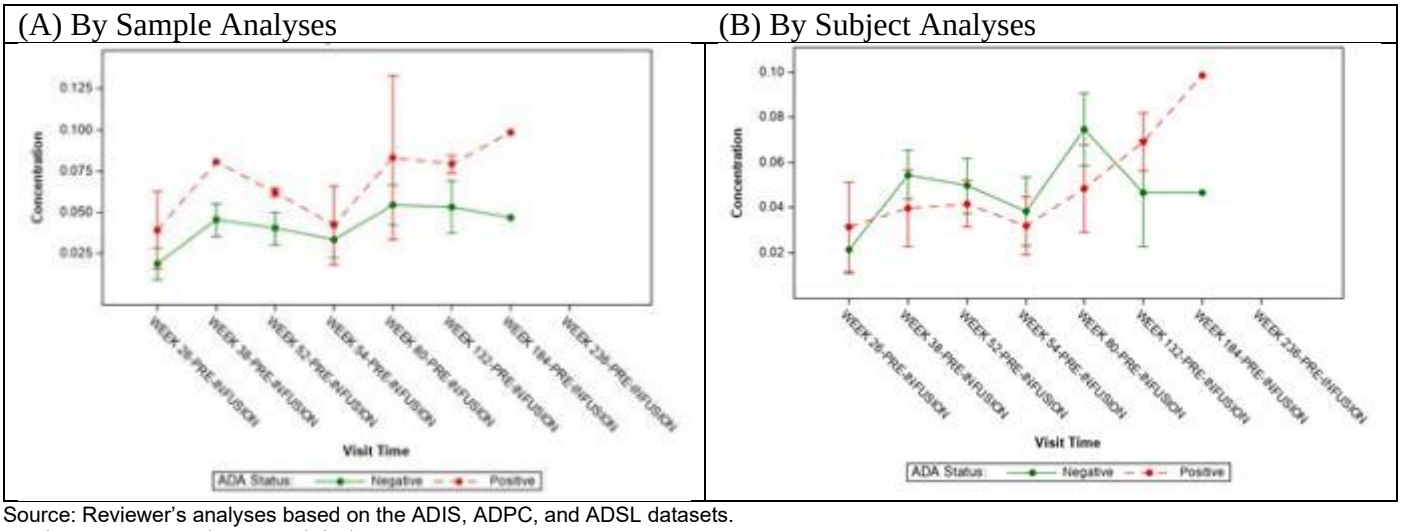
Antidrug Antibody Responses	Adult DFI12712	Pediatric DFI13412	Overall Population
N	30	8	38
Anti-drug antibodies			
ADA Positive	12	6	18
ADA at baseline	3	1	4
Treatment induced ADA	9	5	14
Peak ADA Titer	400	1600	1600
Neutralizing antibodies			
Inhibition catalytic activity	1	1	2
Cellular uptake	0	0	0

Source: Independent analyses by the review team.
ADA, antidrug antibody; ASMD, acid sphingomyelinase deficiency; N, number of subjects.

14.4.2. Impact of Immunogenicity on PK

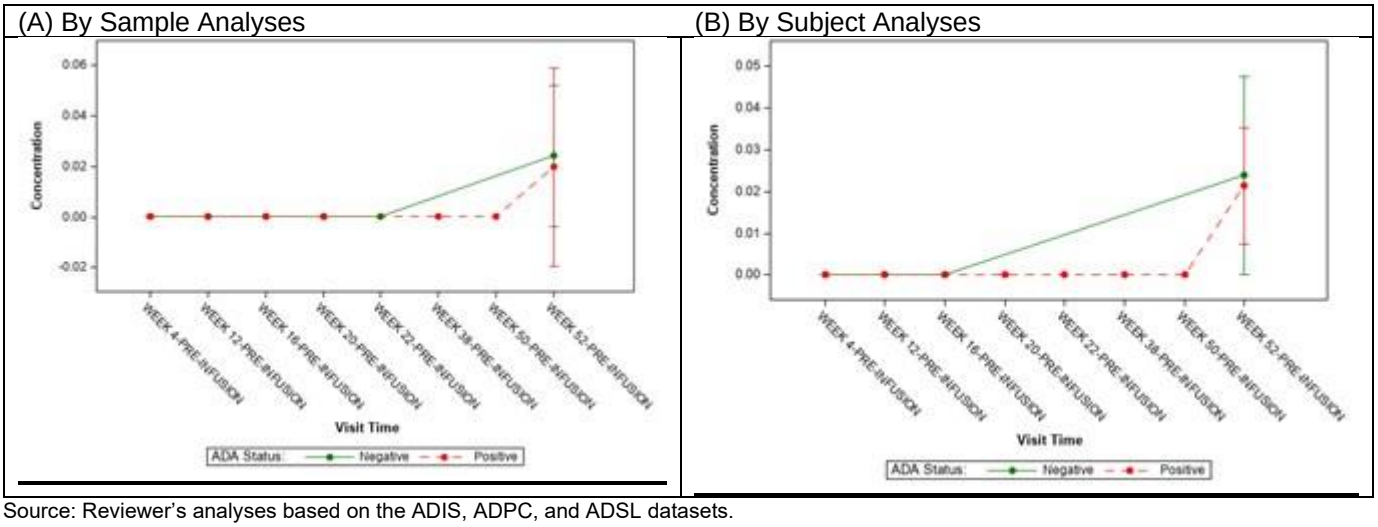
The impact of immunogenicity on PK was evaluated by subject ADA status (i.e., ADA positive versus ADA negative subjects) and by sample ADA status. There was no apparent trend in change of PK concentration by ADA status in adults (Figure 83) or in pediatrics (Figure 84). Of note, a popPK modeling approach was used to evaluate whether ADA affected olipudase alfa PK in adult and pediatric patients. The popPK analysis did not identify ADA as a significant covariate influencing olipudase alfa PK. Furthermore, ADA titer did not have any trend on olipudase alfa exposures.

Figure 83. Impact of Immunogenicity on PK (A) by Sample and (B) by Subject ADA Status in Adults



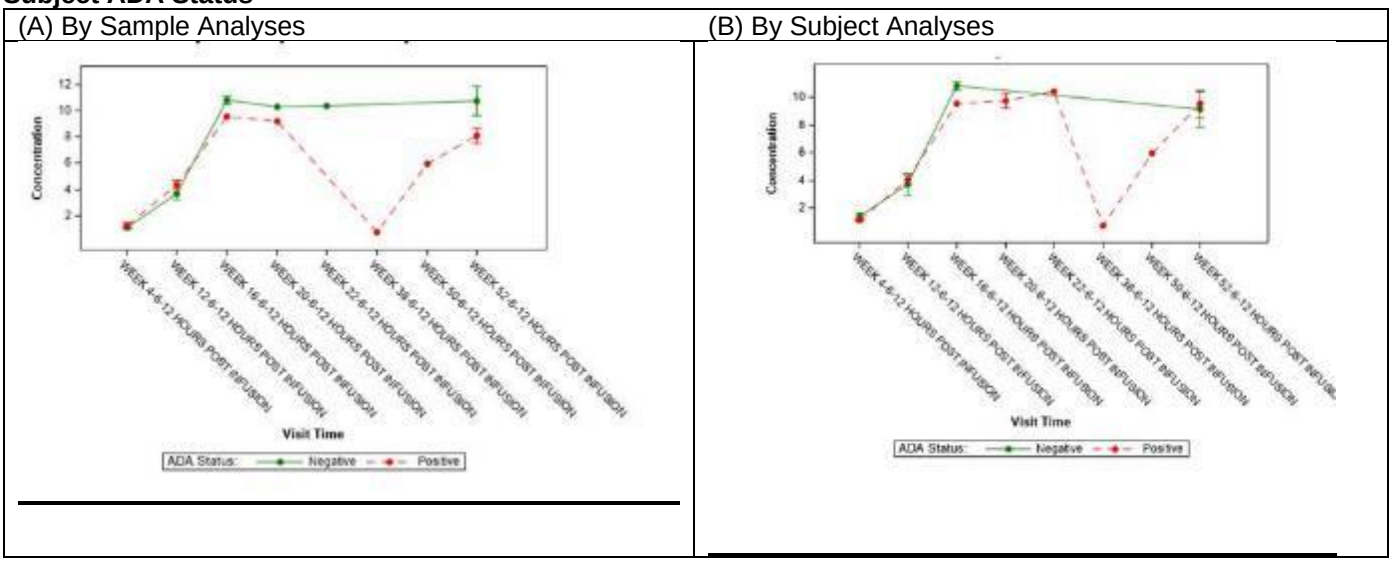
Source: Reviewer's analyses based on the ADIS, ADPC, and ADSL datasets.
Y axis- PK concentration at pre-infusion.
Abbreviations: ADA, anti-drug antibody

Figure 84. Impact of Immunogenicity on PK (Pre-Infusion) (A) by Sample and (B) by Subject ADA Status in Pediatrics



Source: Reviewer's analyses based on the ADIS, ADPC, and ADSL datasets.
Y axis- PK concentration at pre-infusion.
Abbreviations: ADA, anti-drug antibody

Figure 85. Impact of Immunogenicity on PK (6-12 hour Post-Infusion) (A) by Sample and (B) by Subject ADA Status



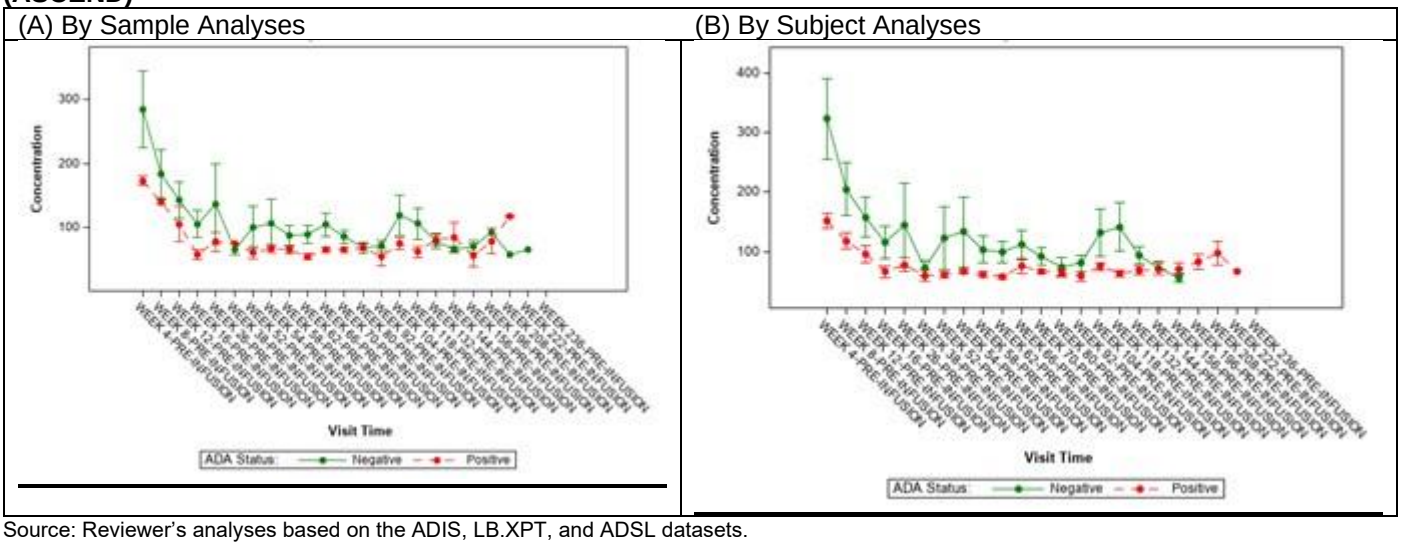
Source: Reviewer's analyses based on the ADIS, ADPC, and ADSL datasets.
Y axis- PK concentration at 6-12 post-infusion.
Abbreviations: ADA, anti-drug antibody

14.4.3. Impact of Immunogenicity on Pharmacodynamics

The plasma lyso-SPM and ceramide levels in adult subjects in ASCEND by ADA status are shown in Figure 86 and Figure 87, respectively. Overall, the reduction in plasma lyso-SPM and ceramide levels showed similar trend between ADA+ subjects and ADA- subjects. At Week 52, the mean (SD) plasma lyso-SPM level in ADA+ subjects (N=9) was 61.7 (16.7) ug/L, compared to 123.9 (148.2) ug/L in ADA- subjects (N=8). At Week 52, the mean (SD) ceramide level was 2.5 (0.8) mg/L in ADA+ subjects, compared to 2.2 (0.8) mg/L in ADA- subjects.

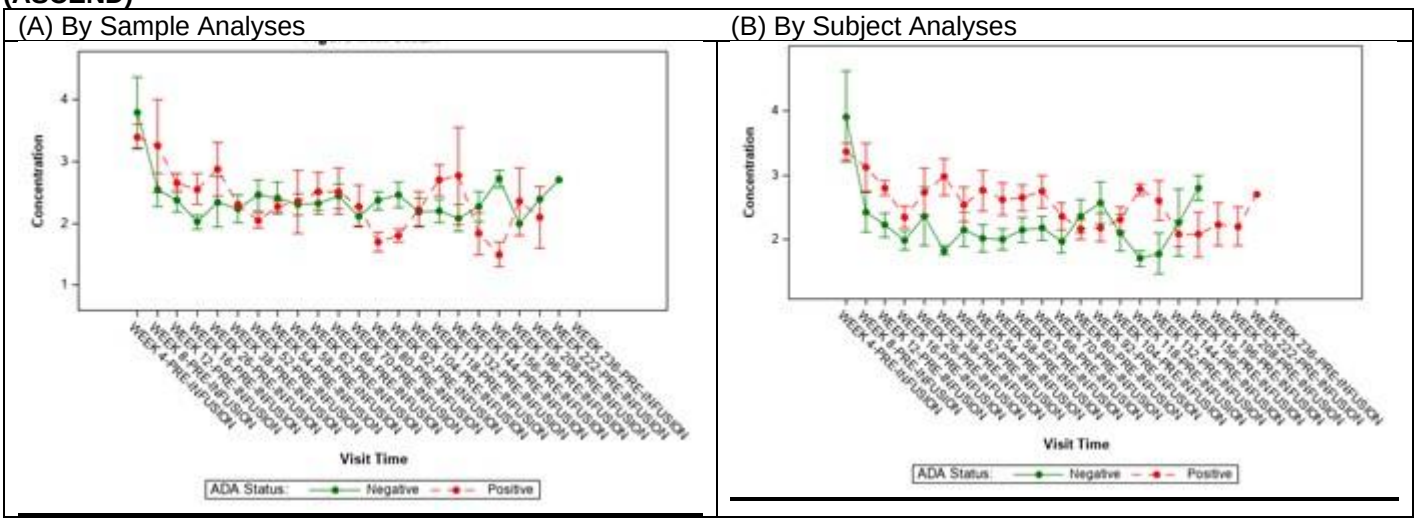
The plasma lyso-SPM and ceramide levels in pediatric subjects by ADA status are shown in Figure 88 and Figure 89, respectively. The plasma lyso-SPM and ceramide levels showed similar trend of reduction between ADA- subjects (n=2) and ADA+ subjects (n=6). At Week 52, the mean (SD) plasma lyso-SPM level in ADA- subjects was 62.5 (27.9) ug/L compared to 83.6 (39.8) ug/L in ADA+ subjects. At Week 52, the mean (SD) ceramide level in ADA- subjects was 1.7 (0.4) mg/L compared to 4.2 (3.7) mg/L in ADA+ subjects.

Figure 86. Plasma Lyso-SPM Levels (A) by Sample and (B) by Subject ADA Status in Adults (ASCEND)



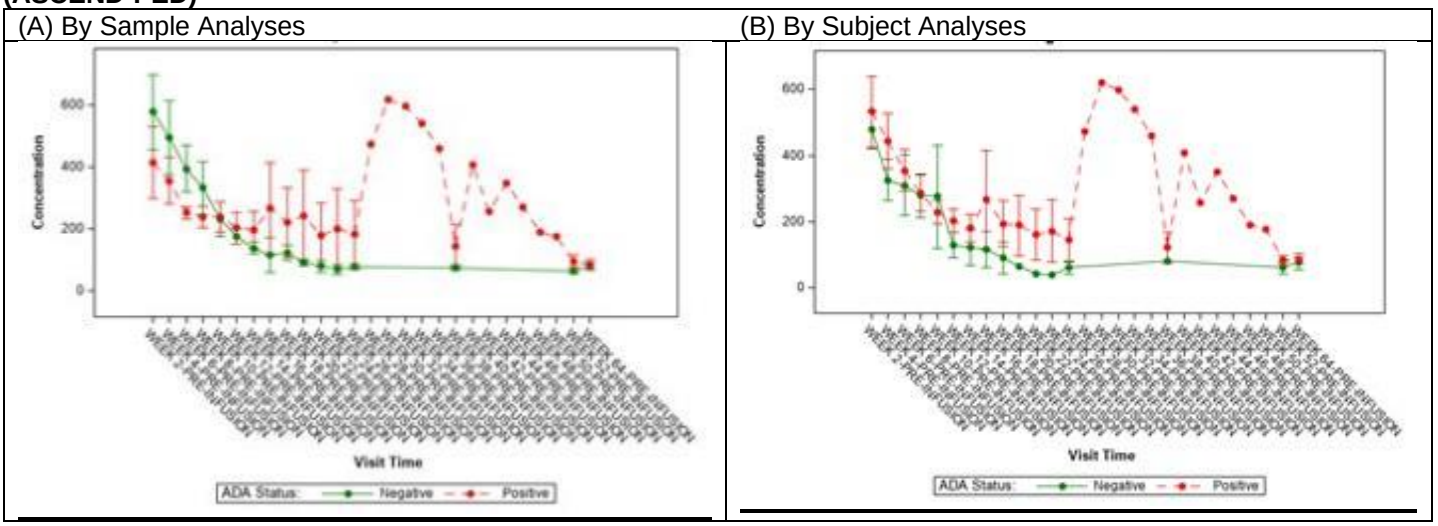
Source: Reviewer's analyses based on the ADIS, LB.XPT, and ADSL datasets.
Concentration (Y-axis)= Mean Lyso-SPM Levels in Plasma (ug/L)
Abbreviations: ADA, anti-drug antibody

Figure 87. Plasma Ceramide Levels (A) by Sample and (B) by Subject ADA Status in Adults (ASCEND)



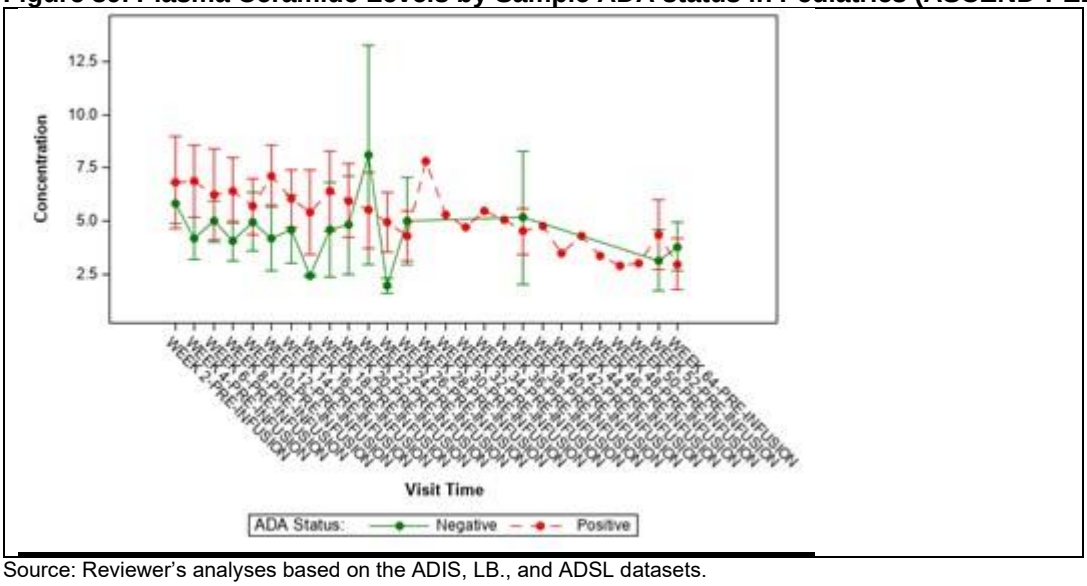
Source: Reviewer's analyses based on the ADIS, LB., and ADSL datasets.
Concentration (Y-axis)= Mean Ceramide Levels in Plasma (mg/L)
Abbreviations: ADA, anti-drug antibody

Figure 88. Plasma Lyso-SPM Levels (A) by Sample and (B) by Subject ADA Status in Pediatrics (ASCEND-PED)



Source: Reviewer's analyses based on the ADIS, LB.XPT, and ADSL datasets.
Concentration (Y-axis)= Mean Lyso-SPM Levels in Plasma (ug/L)
Abbreviations: ADA, anti-drug antibody

Figure 89. Plasma Ceramide Levels by Sample ADA status in Pediatrics (ASCEND-PED)



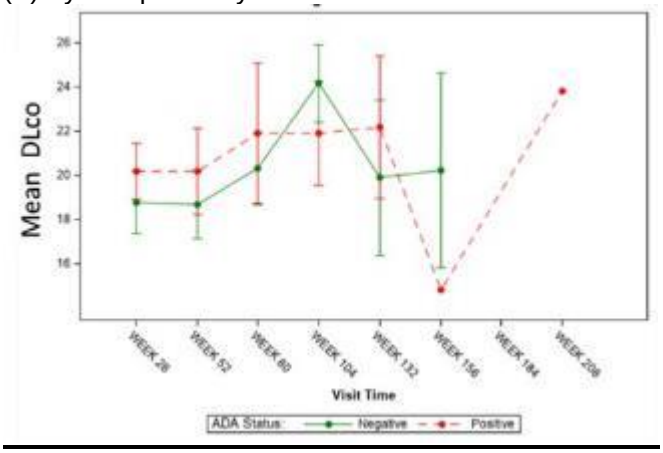
Source: Reviewer's analyses based on the ADIS, LB., and ADSL datasets.
Concentration (Y-axis)= Mean Ceramide Levels in Plasma (mg/L)
Abbreviations: ADA, anti-drug antibody

14.4.4. Impact of Immunogenicity of Efficacy

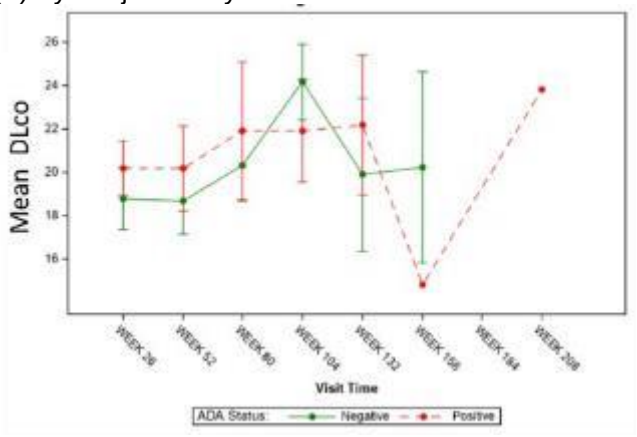
There was no apparent association between ADA status (positive versus negative) and the clinical efficacy results measured by DLco in ASCEND. The decline in mean DLco from baseline appeared to be similar between ADA+ subjects and ADA- subjects (Figure 90). However, because of the small number of subjects, the effect of ADA on efficacy of olipudase alfa could not be adequately determined.

Figure 90. DLco (A) by Sample and (B) by Subject ADA Status in Adults (ASCEND)

(A) By Sample Analyses



(B) By Subject Analyses



Source: Reviewer's analyses based on the ADIS, LB, and ADSL datasets.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide

14.4.5. Impact of Immunogenicity on Safety

The TEAEs and AEs by subject ADA status in pediatric and adult subjects are summarized in Table 181. Because of the small number of subjects, the effect of ADA on safety of olipudase alfa could not be adequately determined.

Table 181. Treatment Emergent Immunogenicity Events

	Pediatric		Adult		Overall	
Adverse Events	**TE-ADA Positive (N=6)**	**TE-ADA Negative (N=2)**	**TE-ADA Positive (N=9)**	**TE-ADA Negative (N=21)**	**TE-ADA Positive (N=15)**	**TE-ADA Negative (N=23)**
Most frequent TEAEs by ADA Patients with >=1 event	6	2	9	21	15	23
TESAEs	3	1	4	6	7	7
Summary of AEs leading to treatment interruption	4	0	4	7	8	7
TE IARs	6	0	5	10	11	10
Summary of hypersensitivity related IARs	4	0	4	1	8	1

Source: From the Applicant's response of the agency IR request dated June 16,2022,
Abbreviations: ADA, antidrug antibody; IAR, infusion associated reaction; N, number of subjects; TE, treatment emergent; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse events.

14.5. Pharmacometrics Review

14.5.1. Applicant's Population Pharmacokinetics Analysis POH0494

Objectives

To develop a population pharmacokinetics (PPK) model of olipudase alfa and to provide individual PK parameters for the population pharmacokinetics and pharmacodynamics (PPK/PD) study (POH0712)and exposure-response (E-R) analysis (POH0610).

Data

Five clinical studies included in the PPK POH0494 analysis (Table 182).

Table 182. Summary of Studies Included in the Population Pharmacokinetic Analysis

Study Protocol	N	Dose (mg/kg)	N_DV	Time after Dose by Schedule
Phase 1a, single dose, SPHINGO00605	11	0.03, 0.1, 0.3, 0.6, 1	136	Pre-dose, EOI, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72 h.
Phase 1b, DFI13412	5	0.1, 0.3, 0.6, 1, 2, 3	345	Pre-dose, EOI, 1, 4, 8, 12, 24, 48, 72 h at each new dose level ≥0.3 mg/kg and at Week 26.
Phase 1/2, DFI13803 (ASCEND-Peds)	20	0.03, 0.1, 0.3, 0.6, 1, 2, 3	387	At first dose of 0.3, 1.0 and 3.0 mg/kg and at Week 52. Adolescents (12 to <18 years): pre-dose, EOI, 2, 6, 24, 48, 72 h (replaced with 96h per FDA's recommendation) Child (6 to <12 years): pre-dose, 0-0.5, 2-4, 6-12, 24-36, 84-96 h. Early child/Infant (birth to <6 years): pre-dose, 0-0.5, 6-12, 24-36, 84-96 h
Phase 2, LTS13632 (patients from DF13412 or DF13803)	24	1, 2, 3	506	Every 12 months, same sampling scheme as in DFI13412 and DFI13803 (ASCEND-Peds)
Phase 2/3, DFI12712 (ASCEND)	33	0.1, 0.3, 0.6, 1, 2, 3	1726	Pre-dose, mid-way through, EOI, 1, 4, 8, 12, 24, 48, 96, and 168 h at Weeks 2, 10, 14, 26, 38, 52, 54, 68, 80, 132, 184, and 236.
Total	69		3100	

Source: Table 1 of Applicant's PPK report and PPK dataset "updated.xpt".
Abbreviations: EOI, end of infusion; N, number of subjects; N_DV, number of the dependent variable, i.e., number of drug concentration.

A summary of the demographics and laboratory variables of the PPK dataset is provided in Table 183.

Table 183. Baseline Characteristics of Subjects With ASMD in the Olipudase Alfa Population Pharmacokinetic Analysis

Baseline Characteristic	Pediatric Patients (N=20)		Adult Patients (N=49)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
Age (years)	7.6 (4.4)	7.5 (1.0-17.0)	34.0 (14.0)	29.9 (18.0-67.0)
Bod Weight (kg)	23.4 (10.8)	20.7 (9.9-51.5)	65.5 (13.8)	62.8 (44.3-107)
BMI (kg/m^2)	16.8 (1.48)	16.6 (14.9-20.4)	24.4 (4.3)	23.6 (17.6-40.2)
Bilirubin (µmol/L)	11.5 (5.0)	10.15 (5.0-22.0)	20.0 (15.2)	15.0 (5.13-88.0)
Ceramide (ng/mL)	6.74 (3.51)	5.55 (3.1-18.5)	3.95 (1.34)	3.7 (2.2-8.5)
Albumin (g/L)	43.9 (3.1)	44 (36-49)	41.8 (4.2)	42 (32-53)
AST (IU/L)	84.1 (52.2)	68 (35-242)	43.9 (30.3)	33 (12-135)
ALT (IU/L)	63.0 (32.2)	53.0 (22-140)	44.1 (30.2)	35 (9-126)
CLcr (ml/min/1.73 m^2)	215 (75)	195 (129-378)	125 (35.6)	120 (52.7-217)
Spleen Volume (multiples of normal)	19.0 (8.8)	16.8 (7.4-36.4)	11.4 (4.3)	10.5 (4.75-20.9)
Liver Volume (multiples of normal)	2.65 (0.74)	2.49 (1.69-4.19)	1.54 (0.43)	1.53 (0.827-3.11)

% Predicted DLco adjusted for Hb		54.8 (14.2)	57.8 (27.0-71.6)	50.4 (11.4)	50.1 (25.4-77.1)
Plasma sphingomyelin (µg/mL)		375 (137)	351 (100-709)	292 (63.7)	287 (200-467)
Plasma cholesterol (mg/dL)		208 (70)	192 (106-438)	186 (38.3)	181 (117-292)
Plasma HDL (mg/dL)		16.9 (6.1)	17.7 (7.73-28.6)	22.8 (11.1)	20.5 (6.0-66.0)
Plasma LDL (mg/dL)		151 (63)	129 (68.8-354)	130 (34.3)	131 (74-231)
Plasma VDL (mg/dL)		37.6 (16.4)	36.0 (12.4-66.9)	36.9 (15.9)	34.0 (11.0-73.0)
Plasma Triglycerides (mg/dL)		199 (93)	182 (62.8-402)	185 (89.2)	160 (52-400)
Plasma lysosphingomyelin		626 (277)	556 (293-1430)	422 (204)	353 (119-895)
ASM activity in leukocytes		0.135 (0.078)	0.12 (0-0.3)	2.03 (5.99)	0.15 (0-29)
Sex	Male (%)	50		44.9	
	Female (%)	50		55.1	
Race	White %	85		91.8	
	Other (%)	15		8.2	

Source: Applicant's PPK dataset "updated.xpt".
Abbreviations: ALT, alanine aminotransferase; ASMD, acid sphingomyelinase deficiency; AST, aspartate aminotransferase; BMI, body mass index; CLcr, creatine clearance; DLco, diffusion capacity for carbon monoxide; Hb, hemoglobin; HDL, high-density lipoprotein, LDL, low-density lipoprotein; VDL, very-low-density lipoprotein.

Methods

The popPK analysis was performed with the NONMEM (version 7.4.1) using the First Order Conditional Estimate method with Interaction option. Due to the specificity of the dataset (including adults, adolescents, children, and early children- infants), body weight dependent allometric scaling was tested before the covariate selection process. Forward selection method ($p<0.05$) and backward deletion ($p<0.01$) was performed to assess the covariate parameters relationships.

Results

A 3-compartment PPK model was developed for olipudase alfa with data for 20 pediatric and 49 adult subjects with ASMD from Phase I, Phase II, and Phase II/III studies for dose up to 3.0 mg/kg Q2W administered through IV infusion. Goodness-of-fit plots for the final model are shown in Figure 91.

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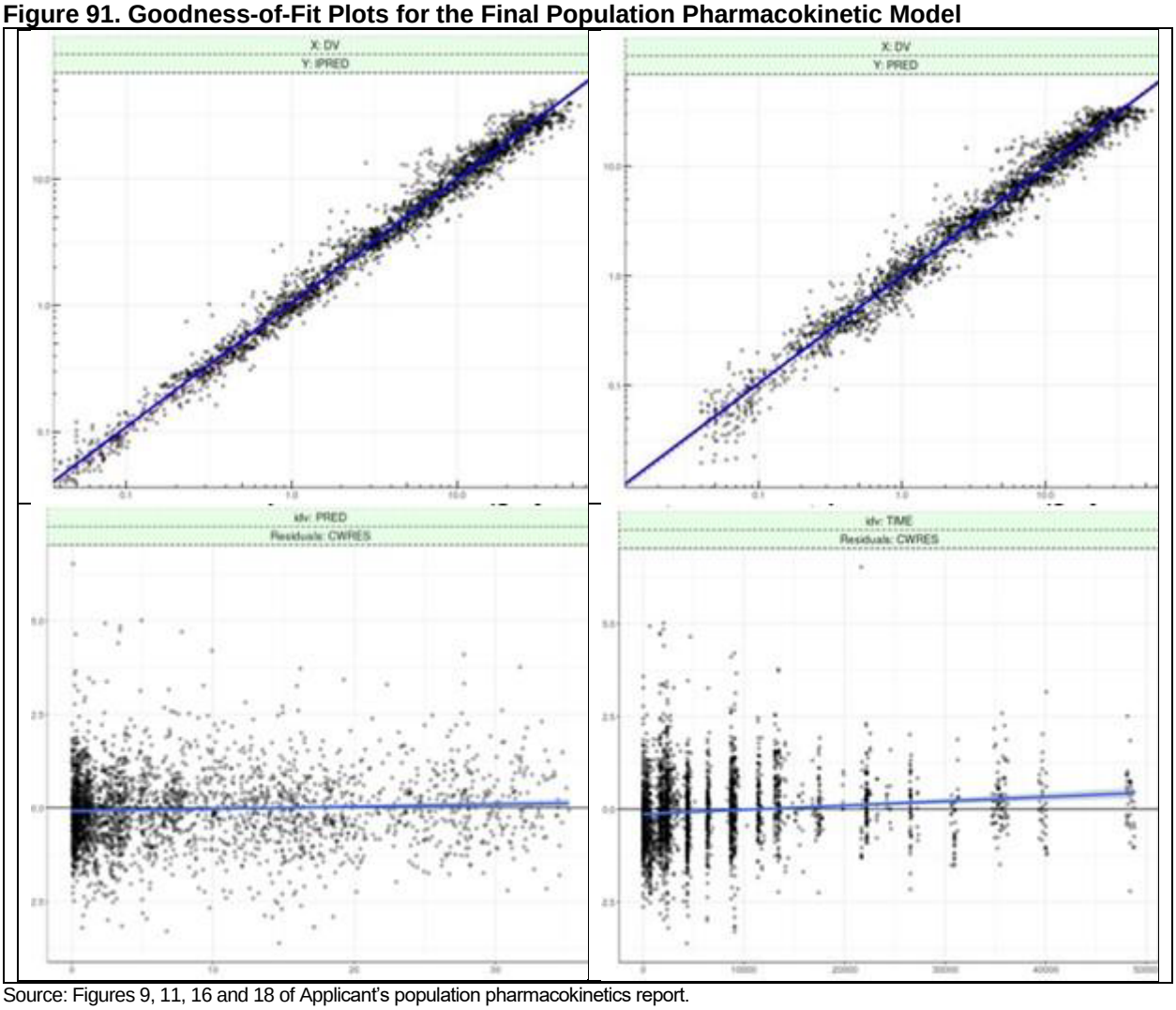
Figure 91. Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figures 9, 11, 16 and 18 of Applicant's population pharmacokinetics report.

The estimated PK parameter values and their associated variability for the selected final PK model are presented in Table 184.

Table 184. Parameter Estimates for Olipudase Alfa Final Population Pharmacokinetic Model

Parameter	Estimate (CV %)	% RSE	[95% CI] (% Shrinkage)
Typical value of CL (L/h)	0.307	2.71%	[0.29 ; 0.324]
Effect of PROD on CL	1.31	1.27%	[1.28 ; 1.34]
Effect of WT on CL	0.551	7.67%	[0.466 ; 0.635]
Typical value of V1 (L)	4.41	3.69%	[4.08 ; 4.73]
Effect of WT on V1 (L)	0.971	6.69%	[0.841 ; 1.10]
Effect of PROD on V1	1.18	3.12%	[1.11 ; 1.25]
Typical value of V2 (L)	3.90	3.81%	[3.61 ; 4.2]
Effect of WT on V2	0.918	5.78%	[0.812 ; 1.02]
Effect of PROD on V2	1.23	4.07%	[1.13 ; 1.33]
Typical value of V3 (L)	4.35	3.43%	[4.05 ; 4.65]
Effect of WT on V3	0.537	9.51%	[0.435 ; 0.64]
Typical value of Q2 (L/h)	0.587	4.40%	[0.536 ; 0.639]
Typical value of Q3 (L/h)	0.0704	5.65%	[0.0625 ; 0.0784]

Parameter	Estimate (CV %)	% RSE	[95% CI] (% Shrinkage)
Inter-individual variability			
ω² CL	0.0403 (20.3%)	22.9%	[0.0222 ; 0.0584] (2.29%)
ω² Block ηCL-ηV1	0.0405	24.1%	NA
ω² V1	0.0561 (24%)	23.8%	[0.0299 ; 0.0822] (5.96%)
ω² V2	0.0131 (11.5%)	48.1%	[0.000752 ; 0.0255] (41.2%)
ω² V3	0.0118 (10.9%)	40.8%	[0.00235 ; 0.0212] (39.5%)
Residual variability			
Proportional term	0.0444 (21.1%)	2.93%	[0.0419 ; 0.047] (2.46%)

Source: Table 12 of Applicant's population pharmacokinetics report.
Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; PROD, product; RSE, relative standard error; WT, weight.

Time-varying body weight dependent allometric scaling factors on CL, V1, V2, and V3 were included into the model. For the 3.0 mg/kg Q2W dose regimen, the body weight effect translated into an increase in C_{max} of 8% and $AUC_{0-\tau}$ of 16% for virtual patients weighing 77.6 kg and a decrease in C_{max} of 30% and $AUC_{0-\tau}$ of40% for virtual patients weighing 19.0 kg, when compared to virtual patients weighing 58.0 kg.

The drug substance manufacturing process, (Process A or Process B) versus Process C (b) (4) was identified as a significant covariate affecting CL, V_1, and V_2. Considering a typical patient, olipudase alfa manufactured by process C (b) (4) had lower CL (25%) and lower V1 and V2 (18% and 21% lower, respectively) compared to that manufactured by other process (process A or process B). Considering virtual patients, this translated into 16% and 24% higher C_{max} and $AUC_{0-\tau}$, respectively.

Reviewer's Comments: The Applicant's PPK analysis is generally acceptable for describing the PK of olipudase alfa in pediatric and adult patients with ASMD. Since some pediatric patients' body weight significantly increased during the PK data collection period, it is rational to consider the time varying effect of body weight on model parameters. However, it is questionable to fix Q2 and Q3 for the whole population with baseline age ranging from 1.5 to 67.0 years, and body weight ranging from 9.9 to 107 kg without including ETAs. FDA reviewer's analysis suggested that an alternative model would be adding ETAs to Q2 and Q3.

14.5.2. Applicant's Population Pharmacokinetics (PPK) Analysis POH0475

Objectives

The objective of this analysis is to assess the influence of anti-drug antibody factors (status and titers) on olipudase alfa PK in patients with ASMD using the previously developed popPK model (POH0494).

Method

Five clinical studies included in the PPK POH0494 analysis (Table 182). The previously reported POH0494 final PPK model was applied to this new analysis dataset ("poppk.xpt") to perform a covariate screening including:

- ADA: Anti-drug Antibodies (time varying – longitudinal- data). ADA assay results are reported either as negative ("0") or positive ("1").
- ADAMAX: binary yes (1) / no (0) variable. Should be 0 if ADA are always negative for the patient otherwise should be 1.
- ADAT: Anti-drug Antibodies titer (time varying – longitudinal-data).

Stepwise covariate selection (forward selection and backward elimination method as previously described) was applied to evaluate the ADA effect on PPK parameters.

Results

None of the evaluated ADA, ADAT and ADAMAX covariates showed significant effect in this analysis.

14.5.3. Exposure-Response Analysis POH0160

Objective

To explore the relationships between the primary efficacy endpoints (spleen volume, DL_{CO}, and platelets) and the exposure of olipudase alfa.

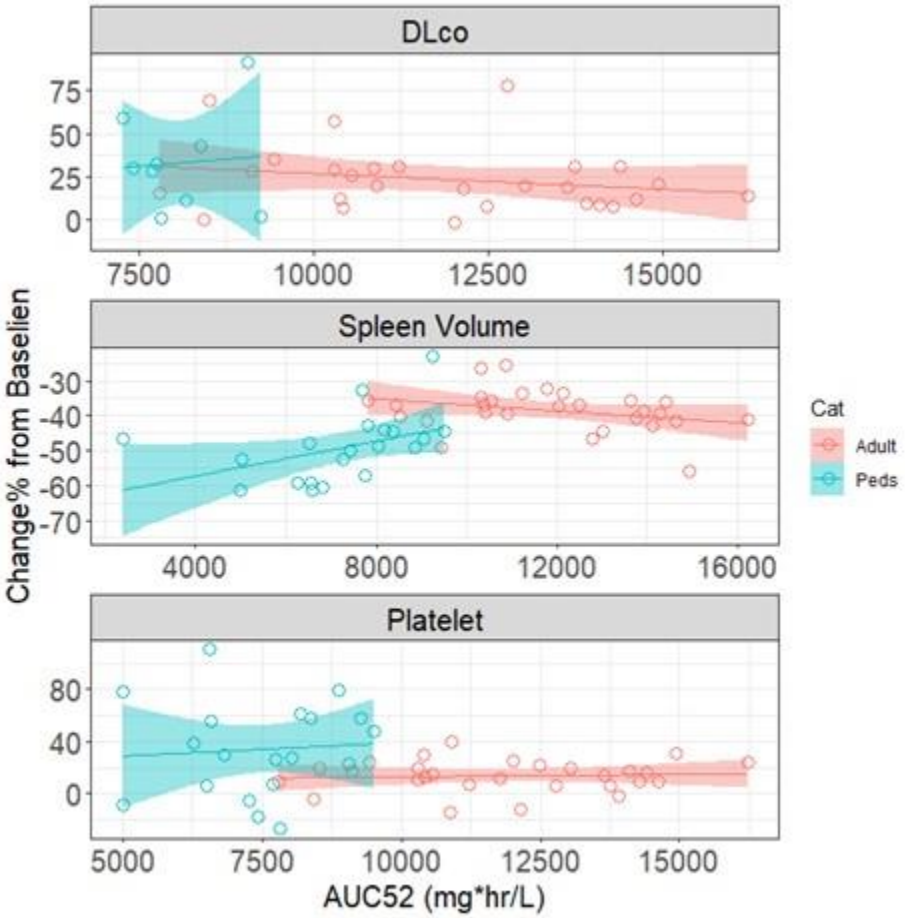
Method

Exposure and efficacy data are from all studies except for the Phase 1a study in Table 182. The exposure metrics were computed using the previously developed POH0494 PPK model for individual patients following their actual dosing regimen. The responses (spleen volume, DLco, and platelet) were analyzed using theindividual changes (percentage) from baseline at Week 52. Upon FDA information request, E-R analysis for safety data from the four studies was conducted using the same method.

Results

As shown in Figure 92, there appeared to be no E-R relationship for the three efficacy endpoints in the patients with ASMD. DLco and platelet increased after olipudase alfa treatment, and the response was similar between adult and pediatric patients. Spleen volume decreased after olipudase alfa treatment, and the response in pediatrics appeared greater than adult patients.

Figure 92. The Relationships Between Olipudase Alfa Exposure and Efficacy Endpoints



Source: FDA reviewer's analysis based on Applicant's datasets "dlco.xpt", "spleen.xpt", and "platelet.xpt"
Note: Olipudase alfa exposure metrics AUC52 is the cumulative AUC over the 52-week period per individual patient's actual olipudase alfa doses.
Abbreviations: AUC, area under the concentration-time curve; DL_{CO}, diffusion capacity for carbon monoxide.

The exposure-safety analyses suggested no apparent E-R relationship for serious adverse event (SAE), severe AE, TEAE leading to dose interruption/reduction (Figure 93), and other AEs.

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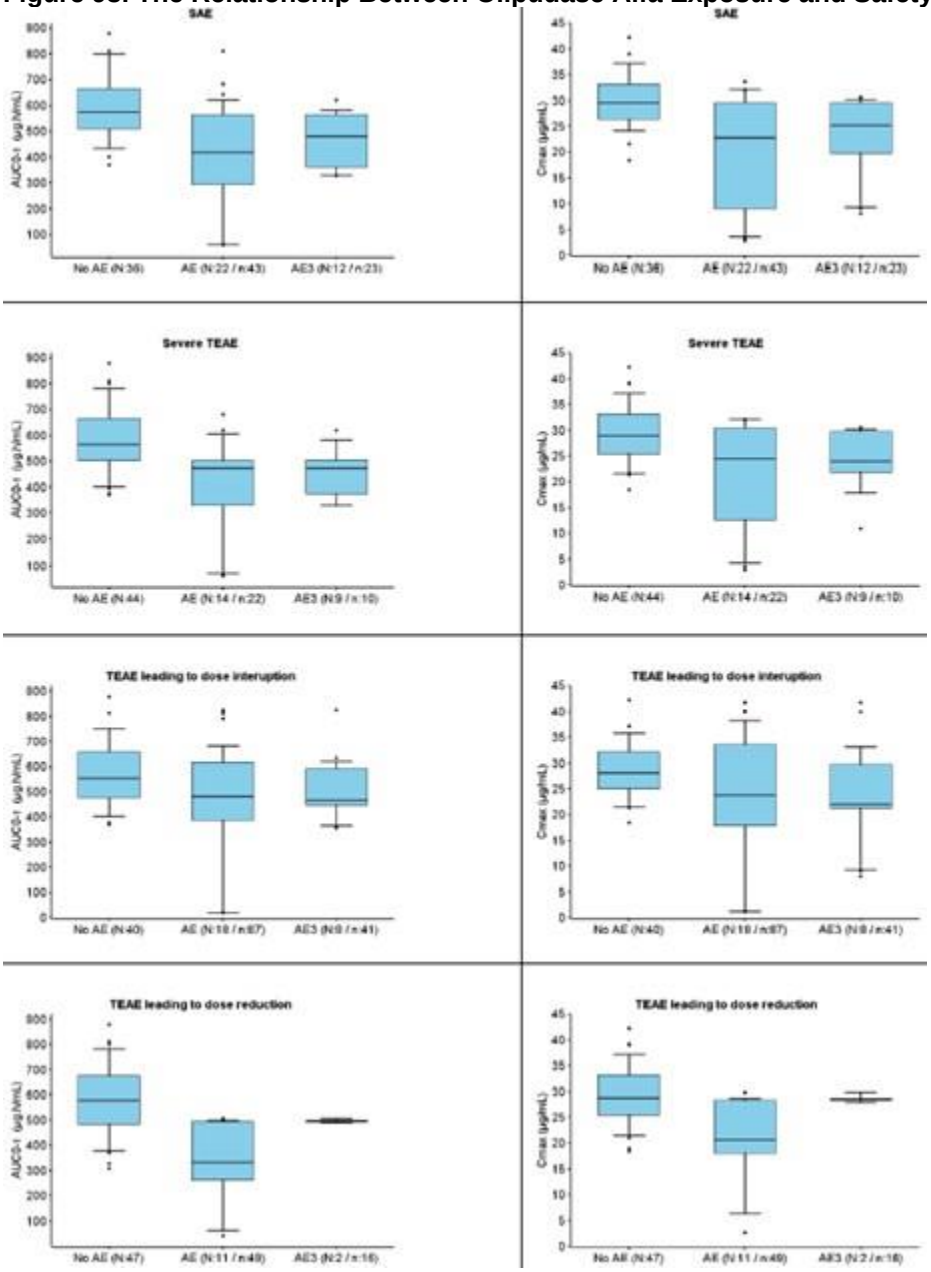
Figure 93. The Relationship Between Olipudase Alfa Exposure and Safety Endpoints



Source: Figure 3 of Applicant's response to FDA request for exposure-safety analysis.
Note: The box represents the interquartile range of C_{max} and $AUC_{0-\tau}$ at Week 52 and the whiskers represent 90% confidence interval. Lower and upper boundary of the box represents the 25th and 75th percentiles, respectively and the line within the box marks the median. No AE: olipudase alfa exposures at the maintenance dose of 3 mg/kg in patients with no AEs. AE: olipudase alfa exposures at the time of AE occurred at any dose in patients with AEs. AE3: olipudase alfa exposures at the time of AE occurred at 3 mg/kg in patients with AEs. N: the number of patients
n: the number AEs. $AUC_{0-\tau}$ and C_{max} values were included for each individual AE
Abbreviations: SAE, serious adverse event; TEAE, treatment emergent adverse event

14.5.4. Applicant's Population PK/PD Analysis POH0712

Objective

To develop Population PK/PD models for the plasma lysosphingomyelin (Lyso-SPM), spleen volume, and diffusing capacity of the lungs for carbon monoxide (DLco).

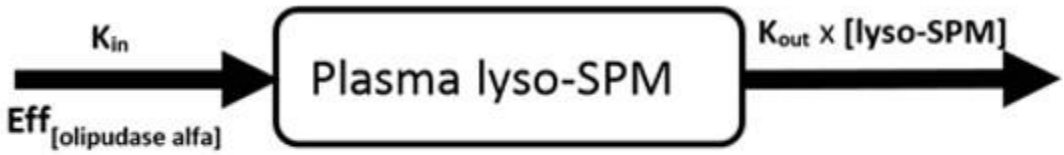
Method

Population PK/PD data are from all studies in Table 185 except for the Phase 1a study. The analyses were performed with the NONMEM computer program (version 7.4.1) using the First Order Conditional Estimate method with interaction option.

Results

The Lyso-SPM included 2739 plasma Lyso-SPM concentration measurements collected from 58 subjects (38 adult and 20 pediatric subjects). The relationship between the plasma Lyso-SPM concentrations and the plasma olipudase alfa concentrations was best characterized by a turnover response model (Figure 94) 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 thefirst order rate constant of lyso-SPM degradation Kout), Imax, the maximum drug induced inhibitory effect and half maximal inhibitory concentration (IC_{50}), the olipudase alfa plasma concentration at 50% of maximum drug inhibitory effect. The inter-individual variability was estimated for all parameters through exponential error models. A combined (proportional + additive) error model was used to model the residual variability. Time-varying bodyweight significantly influenced both I_{max} and IC_{50}, with a lower IC_{50} and a slightly higher I_{max} estimated in subjects with lower bodyweight. In addition, age was identified to significantly influence the plasma Lyso-SPM turnover time (T_{turn}), with longer T_{turn} estimated in younger patients. GOF plots are shown in Figure 95 and PPK/PD parameters are listed in Table 185.

Figure 94. Indirect Response Model for Plasma Lysosphingomyelin



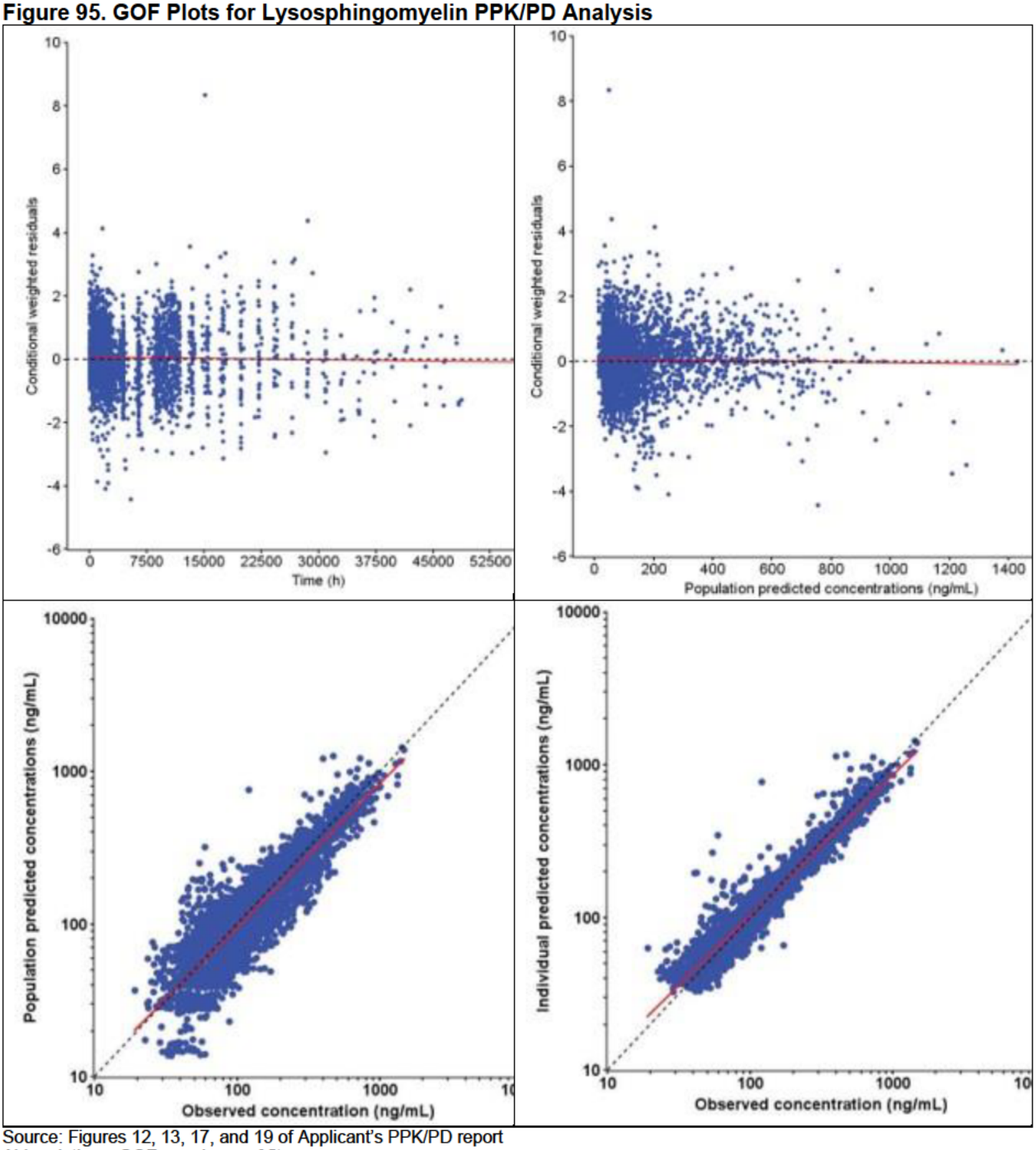
$$D[\text{lyso-SPM}]/dt = K_{in} * EFF - (1/T_{turn}) * [\text{lyso-SPM}]$$

$$T_{turn} = 1/K_{out}$$

$$EFF = 1 - (I_{max} * C / (IC_{50} + C))$$

Source: Figure 7 of Applicant's PPK/PD report.
Abbreviations: PD, pharmacodynamics; PPK, population pharmacokinetics; SPM, sphingomyelin.

Figure 95. GOF Plots for Lysosphingomyelin PPK/PD Analysis



Source: Figures 12, 13, 17, and 19 of Applicant's PPK/PD report
Abbreviations: GOF, goodness of fit.

Table 185. Population PK/PD Parameters for the Final Lyso-SPM Model

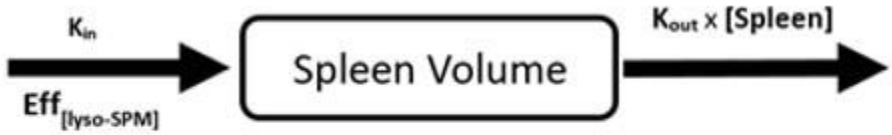
Parameter	Estimate	% RSE	[95%CI] (Shrinkage %)
Typical value of Tturn (h)	828	6.07%	[727 ; 928]
Effect of AGE on Tturn	-16.5	10.9%	[-20.1 ; -12.9]

Parameter	Estimate	% RSE	[95%CI] (Shrinkage %)
Typical value of Imax (θ2)	0.905	0.73%	[0.891 ; 0.918]
Effect of WT on Imax	-0.241	18.4%	[-0.33 ; -0.152]
Typical value of IC_{50} (θ3, mg/L)	0.00838	12.4%	[0.0063 ; 0.0105]
Effect of WT on IC_{50}	2.6	9.67%	[2.1 ; 3.11]
Inter-individual variability (CV%)			
ω ² Tturn	0.234 (51.4%)	24.7%	[0.121 ; 0.348] (6.56%)
ω ² Imax	0.14 (38.8%)	41.8%	[0.0254 ; 0.254] (28.2%)
ω ² IC50	2.43 (322%)	24.5%	[1.27 ; 3.6] (3.34%)
Residual variability			
Proportional term	0.035 (18.7%)	4.52%	[0.0319 ; 0.0381]
Additive term $(ng/mL)^2$	48.0	21.5%	[27.8 ; 68.1]

Source: Table III of Applicant's PPK/PD report.
Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; PD, pharmacodynamics; PPK, population pharmacokinetics; RSE, relative standard error; SPM, sphingomyelin

The Spleen Volume response model included 274 Spleen Volume data collected from 54 subjects (34 adult and 20 pediatric subjects). The relationship between the spleen volume data and the plasma Lyso-SPM concentrations was best described by a turnover response model (Figure 96) with a stimulatory effect of plasma lyso-SPM on the expansion rateof 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 alpha the coefficient of power function effect. The inter-individual variability was estimated for all parameters through exponential error models. A proportional error model was used to model the residual variability. None of the covariates considered in the present analysis could be included inthe spleen volume response model. GOF plots are shown in Figure 97 and PPK/PD parameters are listed in Table 186.

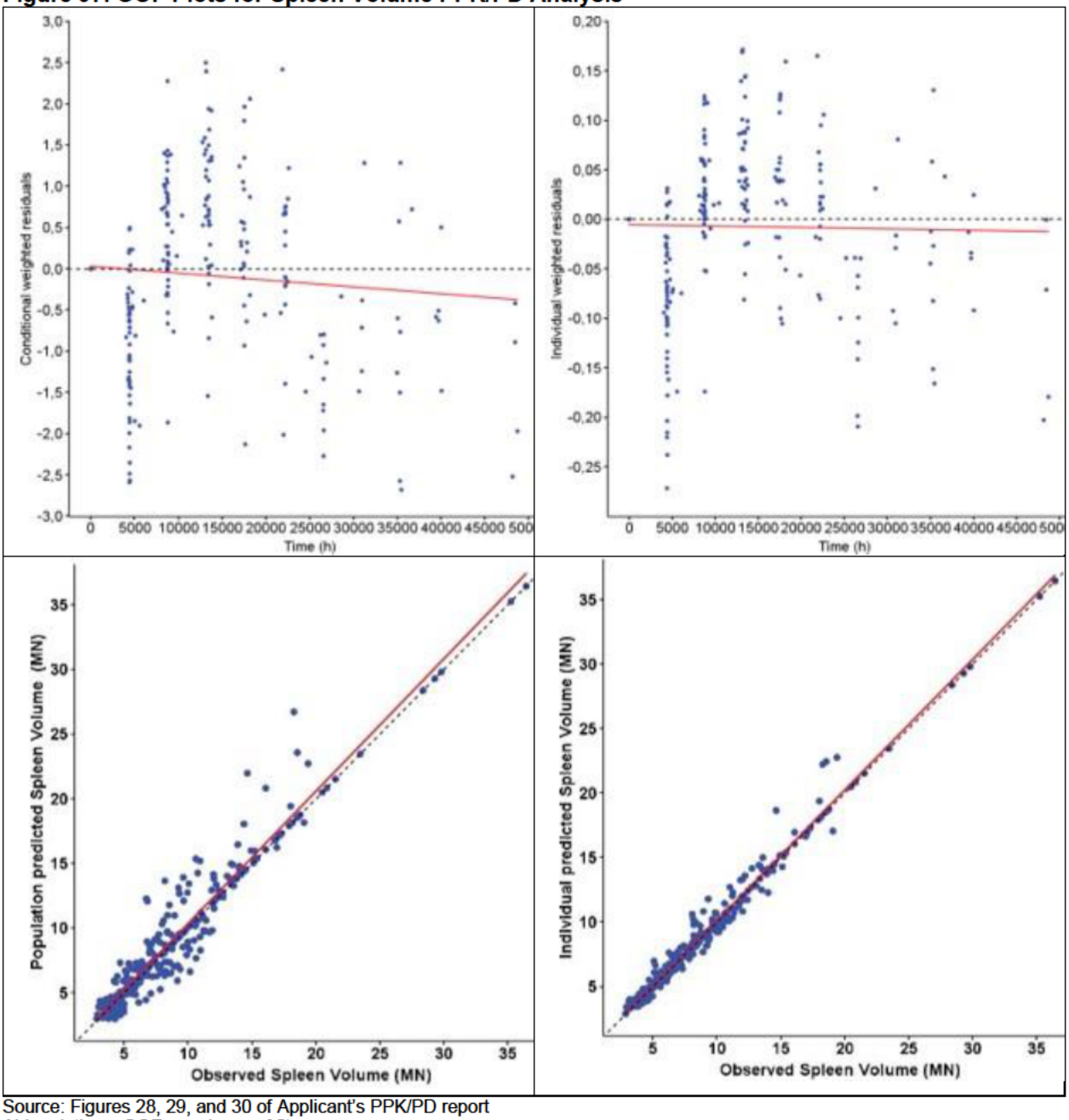
Figure 96. Indirect Response Model for Plasma Spleen Volume



$$D[Spleen]/dt = K_{in} * (1 + EFF) - (1/T_{turn}) * [Spleen]$$
$$T_{turn} = 1/K_{out}$$
$$EFF = (C_{lyso\text{-}SPM}) ** alpha$$

Source: Figure 26 of Applicant's PPK/PD report.

Figure 97. GOF Plots for Spleen Volume PPK/PD Analysis



Source: Figures 28, 29, and 30 of Applicant's PPK/PD report
Abbreviations: GOF, goodness of fit

Table 186. Population PK/PD Parameters for the Final Spleen Volume Model

Parameter	Estimate	% RSE	[95%CI] (Shrinkage %)
Typical value of Tturn (θ1, h)	3808	10.4%	[3017; 4600]
Typical value of alpha (θ2)	0.456	3.70%	[0.423 ; 0.490]
Inter-individual variability			
ω ² Tturn	0.221 (49.7%)	35.7%	[0.0664 ; 0.375] (19.8%)
ω ² alpha	0.0322 (18.1%)	28.9%	[0.0140 ; 0.0504] (18.9%)

Residual variability			
Proportional term	0.00778 (8.82%)	10.9%	[0.00613 ; 0.0944]

Source: Table IV of Applicant's PPK/PD report.
Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; PD; pharmacodynamics; PPK, population pharmacokinetics RSE, relative standard error.

The DLco PPK/PD analysis included 222 DLco data collected from 46 subjects (35 adult and 11 pediatric subjects). The relationship between the DLco data and the plasma Lyso-SPM concentration was best described by a turnover response model (Figure 98) with a stimulatory effect of plasma lyso-SPM on the reduction rate of DLco. For patients with missing baseline DLco values, a baseline parameter was a priori included and estimated in the model. The model was further parametrized with Kin, the zero-order rate constant of DLco recovery and alpha, the coefficient of the power effect function. The inter- individual variability was estimated for all parameters through exponential error. None of the covariates considered in the present analysis could be included in the DLco response model. GOF plots are shown in Figure 99 and PPK/PD parameters are listed in Table 187.

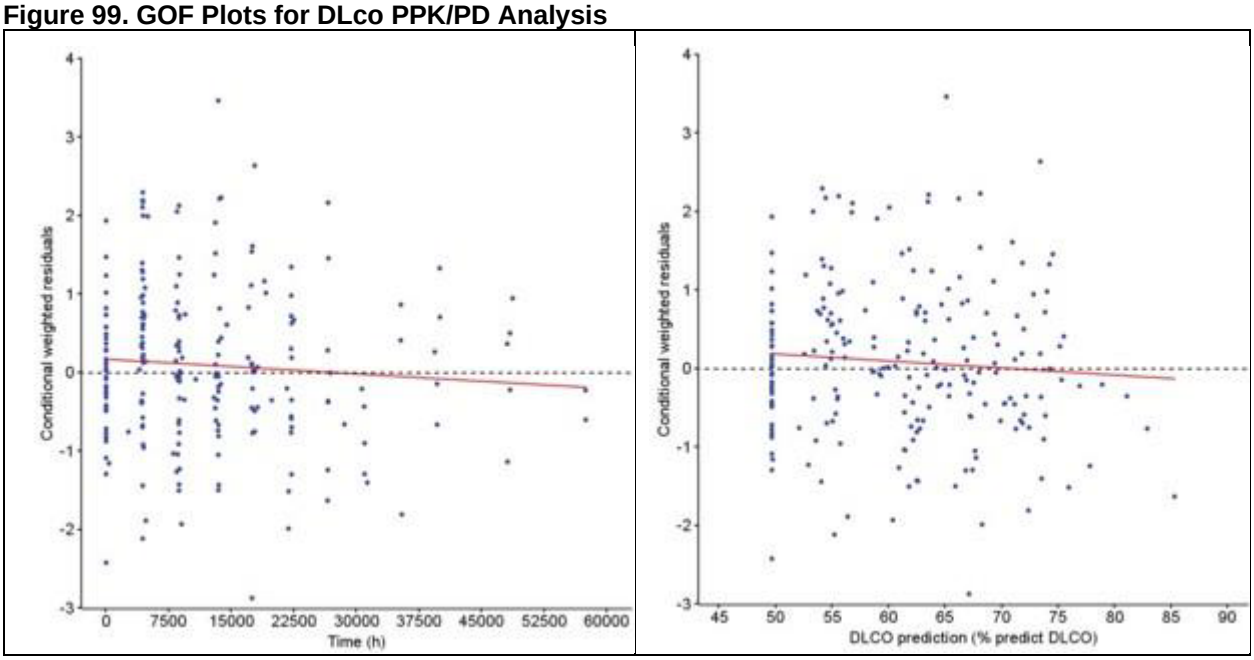
Figure 98. Indirect Response Model for Plasma DLco

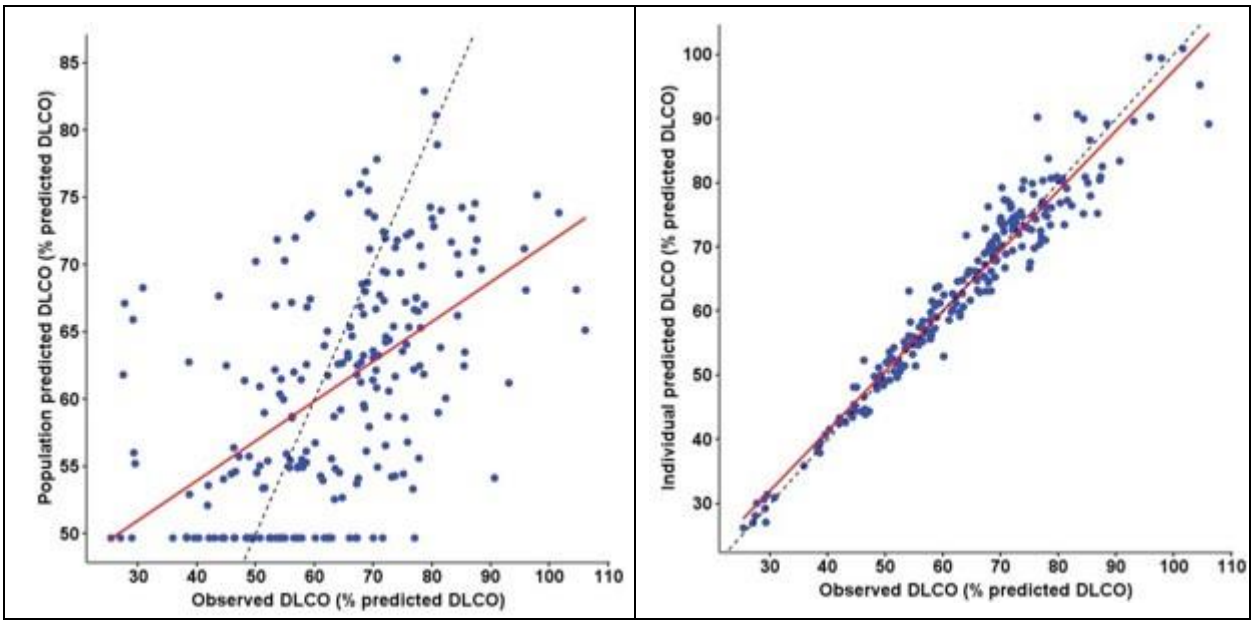
$$D[DL_{co}]/dt = K_{in} - K_{out} * (1+EFF) * [DL_{co}]$$

$$EFF = (C_{lyso\text{-}SPM}) ** alpha$$

Source: Figure 38 of Applicant's PPK/PD report.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; PD; pharmacodynamics; PPK, population pharmacokinetics..

Figure 99. GOF Plots for DLco PPK/PD Analysis





Source: Figures 40 and 42 of Applicant's PPK/PD report
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; GOF, goodness of fit; PD; pharmacodynamics; PPK, population pharmacokinetics.

Table 187. Population PK/PD Parameters for the Final DLco Model

Parameter	Estimate	% RSE	[95%CI] (Shrinkage %)
Typical value of Kin (θ1; (% predict DLco)/h)	0.00693	18.6%	[0.00436 ; 0.00951]
Typical value of alpha (θ2)	0.264	8.06%	[0.221 ; 0.306]
Typical value of Baseline (θ3, % predict DLco)	49.7	3.60%	[46.1 ; 53.2]
Inter-individual variability (CV%)			
ω ² alpha	0.202 (47.4%)	34.5%	[0.0656 ; 0.339] (4.86%)
Block ηBaseline – ηalpha	-0.103 b	27.4%	[-0.159 ; -0.048] (NA)
ω ² Baseline	0.0586 (24.6%)	22.2%	[0.0331 ; 0.084] (0.802%)
ω ² Kin	1.26 (159%)	30.7%	[0.502 ; 2.01] (18.6%)
Residual variability			
Proportional term	0.00426 (6.53%)	12.7%	[0.0032 ; 0.00531]

Source: Table V of Applicant's PPK/PD report.
Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; DLco, diffusion capacity for carbon monoxide; PD; pharmacodynamics; PPK, population pharmacokinetics RSE, relative standard error.

Reviewer's Comments: The Applicant's analyses are acceptable for characterizing the longitudinal PK/PD relationship for the 3 biomarkers in patients with ASMD. A covariance between ETA_Imax and ETA_IC50 was added in FDA's independent analysis.

14.5.5. Applicant's Simulations for Further Dose Exploration

Background

Upon FDA request, the Applicant conducted simulation analysis to compare the potential benefit of olipudase alfa 3 mg/kg Q1W dose regimen versus 3 mg/kg Q2W dose regimen in patients with ASMD.

Objective

To explore potential better olipudase alfa dose regimen than 3 mg/kg Q2W in patients with ASMD using PPK/PD modeling and simulation analysis.

Method

The Applicant conducted simulations to compare olipudase alfa pharmacokinetics (PK), responses of plasma lyso-sphingomyelin (lyso-SPM), and two efficacy endpoints of spleen volume and diffusing capacity of the lung for carbon monoxide (DLco) following the proposed dosing regimen in the BLA (3 mg/kg administered Q2W). An alternate dosing regimen was the maintenance dose of 3 mg/kg administered once weekly (Q1W) for the overall population, and separately for adult and pediatric acid sphingomyelinase deficiency (ASMD) patients. The simulations for the two dosing regimens are presented below.

Adult Proposed Dosing Regimen

Initiation of olipudase alfa administration with within-patient dose escalation of 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0 mg/kg Q2Wfollowed by the maintenance dose of 3.0 mg/kg Q2W up to Week 52.

Adult Alternate Dosing Regimen

Initiation of olipudase alfa administration with within-patient dose escalation of 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0 mg/kg Q2W followed by the maintenance dose of 3.0 mg/kg Q1W up to Week 52.

Pediatric Proposed Dosing Regimen

Initiation of olipudase alfa administration with within-patient dose escalation of 0.03, 0.1, 0.3, 0.3, 0.6, 1.0, 2.0 mg/kg Q2Wfollowed by the maintenance dose of 3.0 mg/kg Q2W up to Week 52.

Pediatric Alternate Dosing Regimen

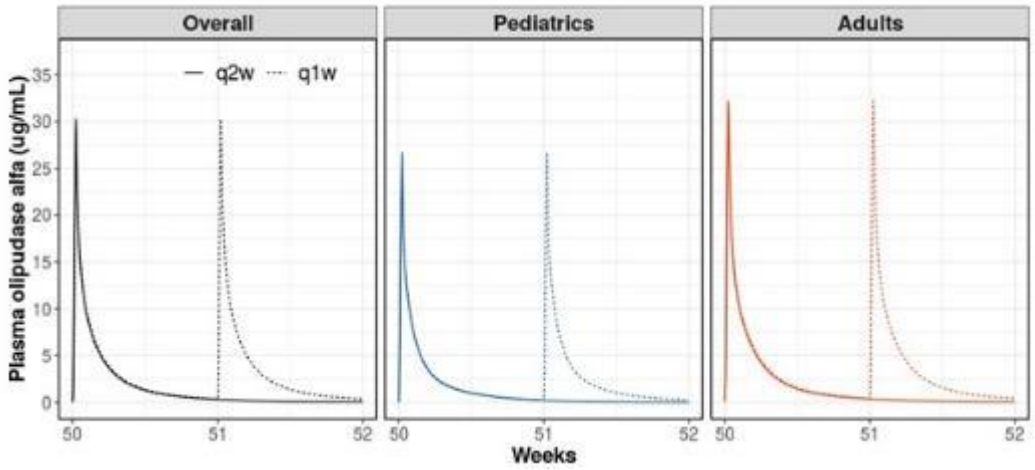
Initiation of olipudase alfa administration with within-patient dose escalation of 0.03, 0.1, 0.3, 0.3, 0.6, 1.0, 2.0 mg/kg Q2W followed by the maintenance dose of 3.0 mg/kg Q1W up to Week 52.

PPK POH0494 and Population PK/PD POH0712 models in the BLA of olipudase alfa were used for the analysis. Two sets of simulations were performed. Actual patient population from clinical studies were used for the simulation, which included adult patients from DFI13412 and DFI12712 (ASCEND), and pediatric patients from DFI13803 ASCEND-Peds.

Results

The predicted steady state olipudase alfa plasma concentration-time profiles over a 2-week interval at the maintenance dose of 3 mg/kg Q2W and Q1W in subjects with ASMD using the Pop PK model are presented in Figure 100. The C_{max}_ss are the same for Q2W and Q1W doses while AUCss is doubled for Q1W dose.

Figure 100. Predicted Mean Steady State Plasma PK Profiles of Olipudase Alfa Over a 2-Week Interval at the Maintenance Dose of 3 mg/kg Q2W and Q1W in Subjects With ASMD



Source: Figure 1 of Applicant's response to FDA Request Dated 11-Mar-2022
Abbreviations: ASMD, acid sphingomyelinase deficiency.

The plasma lyso-SPM profiles with the proposed 3 mg/kg Q2W regimen and the alternative 3 mg/kg Q1W regimen are presented in Figure 101. The predicted percent change from baseline in plasma lyso-SPM levels at Week 26 and Week 52 using the Pop PK/PD and QSP models are summarized in Table 188.

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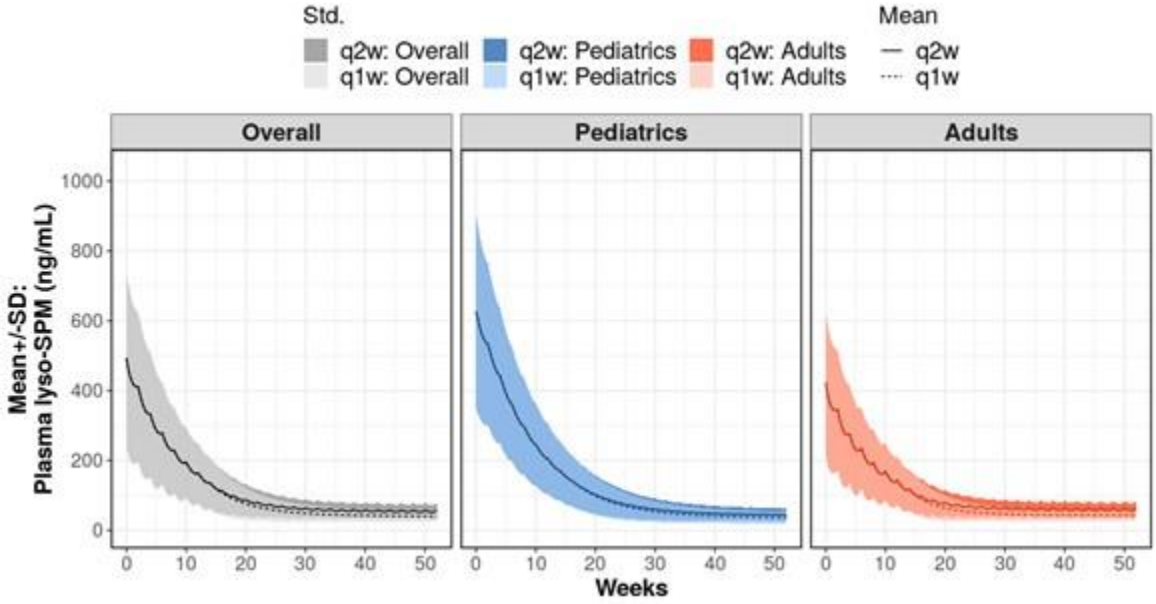
Figure 101. Predicted Plasma Lyso-SPM Levels With Olipudase Alfa 3 mg/kg Q2W and Q1W in Subjects With ASMD



Source: Figure 1 of Applicant's response to FDA Request Dated May 13, 2022
Abbreviations: ASMD, acid sphingomyelinase deficiency

Table 188. Predicted Percent Change From Baseline in Plasma lyso-SPM at Week 26 and Week 52 With Olipudase Alfa 3 mg/kg Q2W and Q1W Regimens in Subjects With ASMD

Dosing Regimen	Week	Patient Population Overall (N=58)	Pediatric (N=20)	Adult (N=38)
Q2W	26	-84.3±5.67	-88.6 ±2.69	-82.0 ± 5.51
Q1W	26	-88.3 ± 3.29	-89.8 ± 2.65	-87.5 ± 3.32
Q2W	52	-86.4 ± 6.33	-92.5 ± 2.10	-83.3 ± 5.45
Q1W	52	-90.8 ± 3.27	-94.0 ± 1.57	-89.1 ± 2.60

Source: Table 1 of Applicant's response to FDA Request Dated 13-May-2022

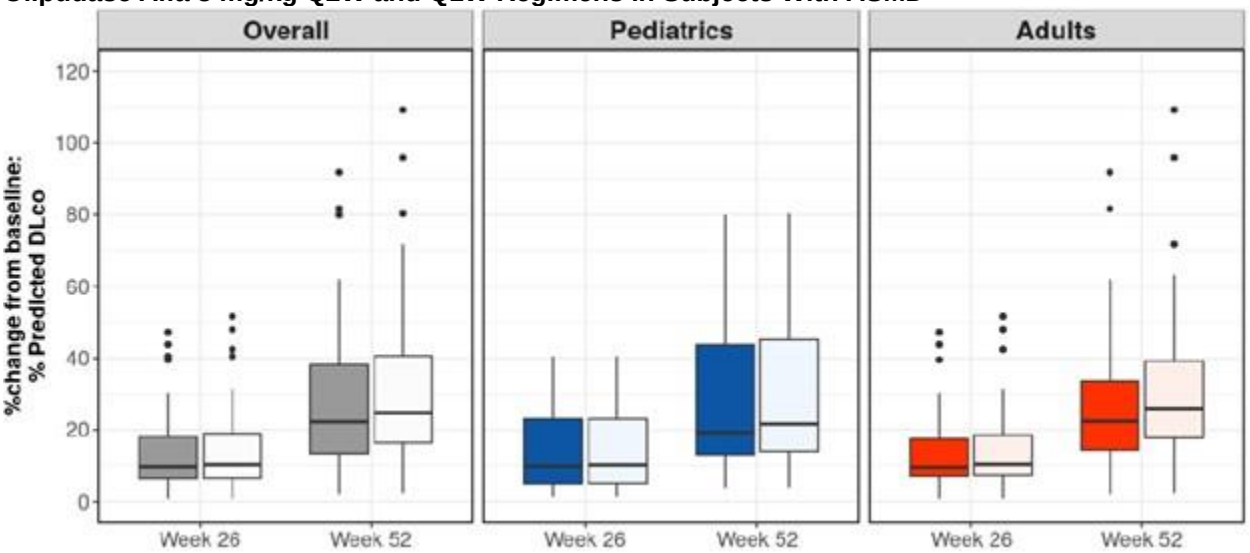
The predicted percent change from baseline in DLco and spleen volume at Week 26 and Week 52 based on the Pop PK/PD analysis are summarized in Table 189 and displayed in Figure 102 (DLco) and Figure 103 (spleen volume), respectively.

Table 189. Predicted Percent Change From Baseline in DLco and Spleen Volume at Week 26 and Week 52 With Olipudase Alfa 3 mg/kg Q2W and Q1W Regimens in Subjects With ASMD

Parameter	Dosing Regimen	Week	Patients in Clinical Studies (Mean ± SD) Overall (N=44)	Pediatrics (N=9)	Adults (N=35)
DLco (% predicted)	Q2W	26	13.9 ± 11.3	14.6 ± 12.0	13.7 ± 11.1
	Q1W	26	14.7 ± 12.0	14.7 ± 12.0	14.7 ± 12.0
	Q2W	52	28.5 ± 21.1	32.0 ± 24.4	27.6 ± 20.0
	Q1W	52	31.7 ± 23.5	32.7 ± 24.3	31.5 ± 23.3
			Overall (N=54)	**Pediatrics (N=20)**	**Adults (N=34)**
Spleen volume (MN)	Q2W	26	-28.7 ± 7.65	-31.4 ± 9.08	-27.1 ± 6.13
	Q1W	26	-29.8 ± 7.91	-31.7 ± 9.14	-28.8 ± 6.86
	Q2W	52	-48.0 ± 9.64	-55.0 ± 10.3	-43.9 ± 6.27
	Q1W	52	-51.3 ± 9.37	-56.6 ± 10.4	-48.2 ± 7.05

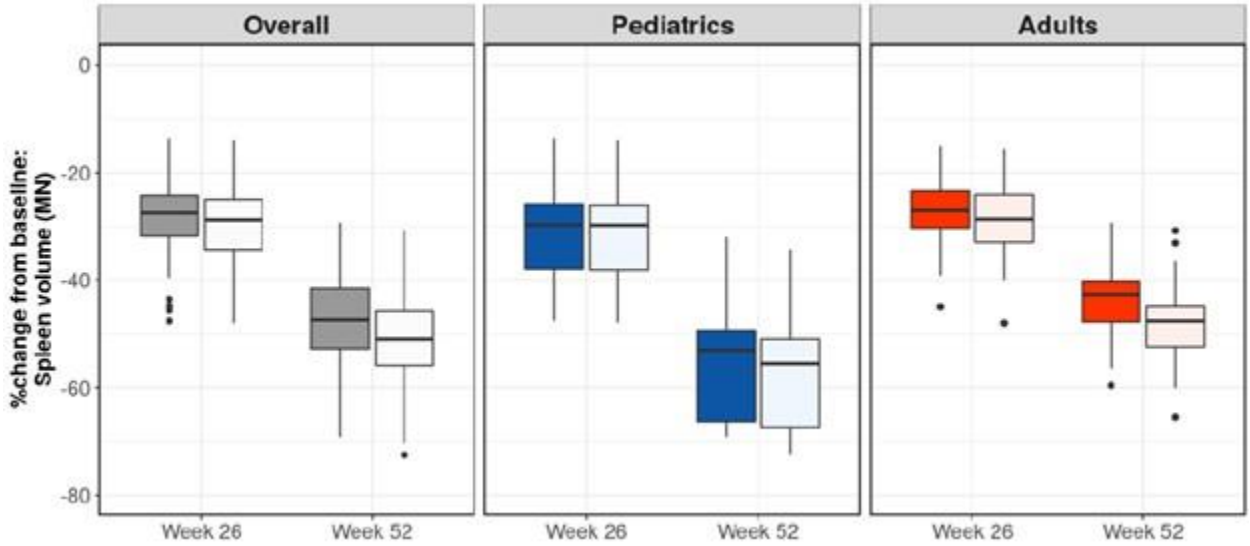
Source: Table 4 of Applicant's response to FDA Request Dated 13-May-2022.
Abbreviations: ASMD, acid sphingomyelinase deficiency; DLco, diffusion capacity for carbon monoxide; MN, multiples of normal; N, number of subjects; SD, standard deviation.

Figure 102. Predicted Percent Change From Baseline in DLco at Week 26 and Week 52 With Olipudase Alfa 3 mg/kg Q2W and Q1W Regimens in Subjects With ASMD



Source: Figure 2 of Applicant's response to FDA Request Dated 13-May-2022
Abbreviations: ASMD, acid sphingomyelinase deficiency; DL_{CO}, diffusion capacity for carbon monoxide.

Figure 103. Predicted Percent Change From Baseline in Spleen Volume at Week 26 and Week 52 With Olipudase Alfa 3 mg/kg Q2W and Q1W Regimens in Subjects With ASMD



Source: Figure 3 of Applicant's response to FDA Request Dated 13-May-2022
Abbreviations: ASMD, acid sphingomyelinase deficiency

Reviewer's Comments: The Applicant's original population PK/PD simulation in response to FDA Request Dated March 11, 2022 used incorrect input files. The corrected simulation results included in the Response to FDA Request Dated May 13, 2022 were consistent with FDA's analysis (See Section 14.4.5).

14.5.6. FDA's Analysis for Further Dose Exploration

Background

The need to explore a higher maintenance dose (e.g., 3 mg/kg every week; or 3 mg/kg QW) in patients with ASMD was assessed based on the following findings:

- The currently proposed maintenance dose of 3 mg/kg every other week (Q2W) was the highest dose studied, which was selected based on results of non-clinical studies in the absence of dose-ranging in ASMD patients.
- A dose-response relationship for PD biomarkers (e.g., plasma Lyso-SPM) was observed during the dose escalation phase of treatment with olipudase alfa in patients with ASMD across clinical trials. Notably, most patients did not achieve plasma Lyso-SPM levels within the normal range of healthy subjects at the proposed maintenance dose of 3 mg/kg Q2W, suggesting a higher dose may further improve the PD responses of olipudase alfa.
- Suboptimal or slow clinical response was observed in some patients in Study 012712. The patients with suboptimal response could be identified at Week 26 since the efficacy results were highly correlated between Week 26 and Week 52.
- The E-R analysis about adverse events (AEs) and QSP modeling and simulations on ceramide dynamics, in response to FDA information requests, did not suggest a signal for a safety concern about 3 mg/kg QW dose.

The collective review findings above strongly suggest a potential to improve clinical response at 3 mg/kg QW in patients who do not achieve optimal clinical response at the proposed 3 mg/kg Q2W regimen. These also indicated a higher or more frequent dose regimen may be needed.

Objective

To explore higher olipudase alfa maintenance dose regimens in patients with ASMD, and to identify potential patients that may benefit from a higher dose regimen.

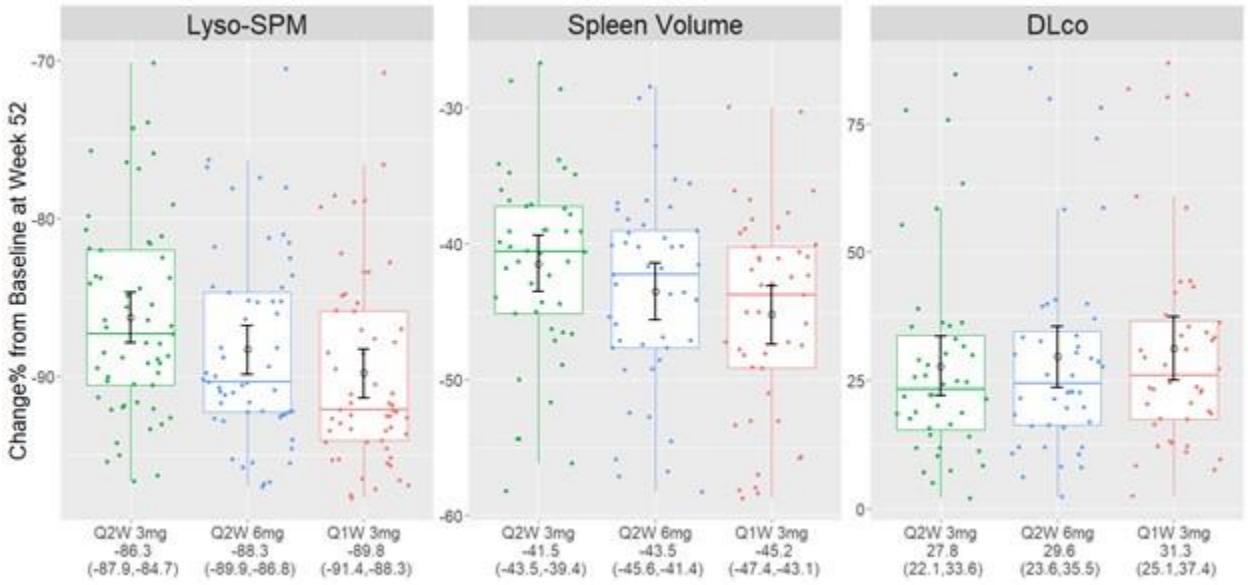
Method

Based on modified popPK model (ETA was added for Q2 and Q3) and modified PKPD model (covariance between ETA_IC_{50} and Imax for Lyso-SPM was added), the reviewer conducted independent PK/PD simulations to explore alternative maintenance dosing regimen.

Results

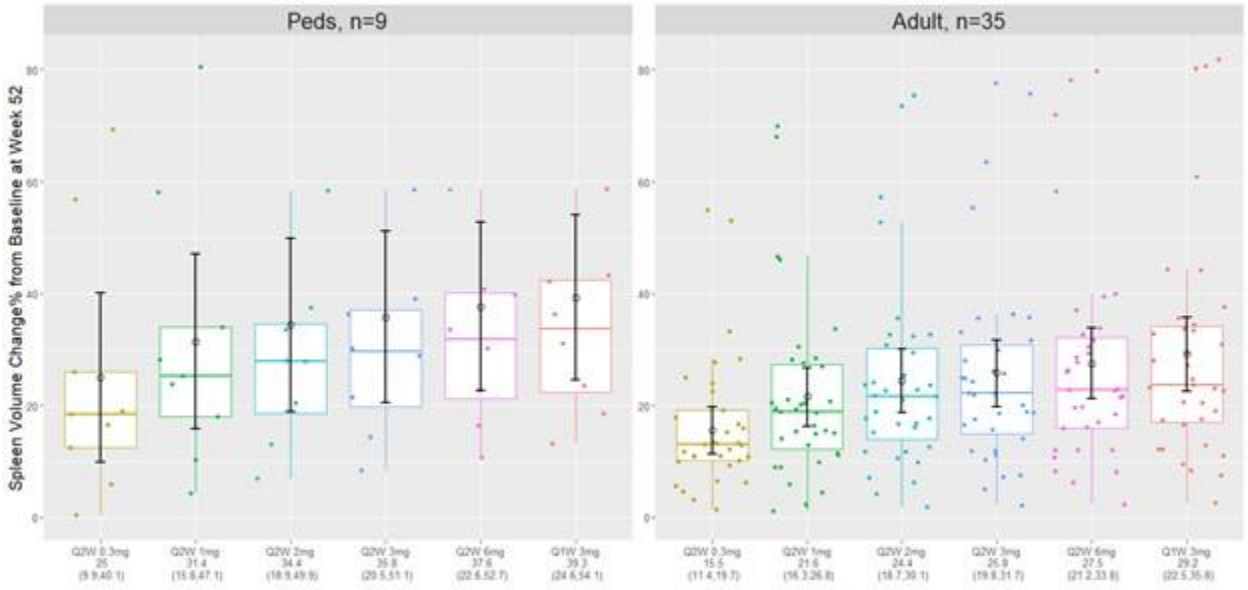
As shown in Figure 104, greater responses in Lyso-SPM, spleen volume and DLco are predicted with a higher maintenance dose of both 3 mg/kg QW and 6 mg Q2W, compared to the currently proposed 3 mg/kg Q2W. In addition, simulated dose-response relationship for the 3 biomarkers showed that pediatric patients are more responsive to olipudase alfa than adult patients; while 3 mg/kg Q2W dose is approaching efficacy plateau at the population level, some ASMD patients, potentially those with suboptimal or slower response, may benefit from 3 mg/kg QW dose (Figure 104, Figure 105, and Figure 106).

Figure 104. Comparison of the Three Dose Regimens in Change From Baseline of Lyso-SPM, Spleen Volume, and DLco at Week 52 for Olipudase Alfa



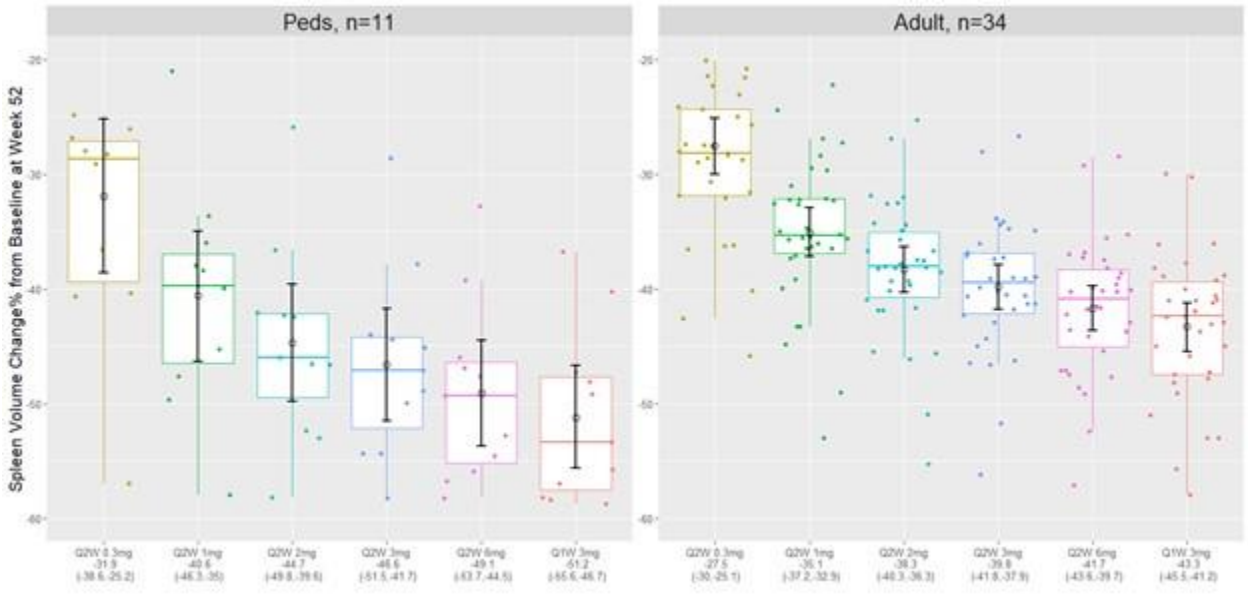
Source: FDA reviewer's analysis based on Applicant's PKPD datasets "dlco.xpt", "spleen.xpt", and "lysospm2.xpt".
Note: the 3 horizontal lines of each box represent Quartile 1, median, and Quartile 3 of the dots; the black circle represents the mean and the error bar represents the 95% confidence interval.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; SPM, sphingomyelinase.

Figure 105. Simulated Dose-Response in Change From Baseline of DLco at Week 52 for Olipudase Alfa



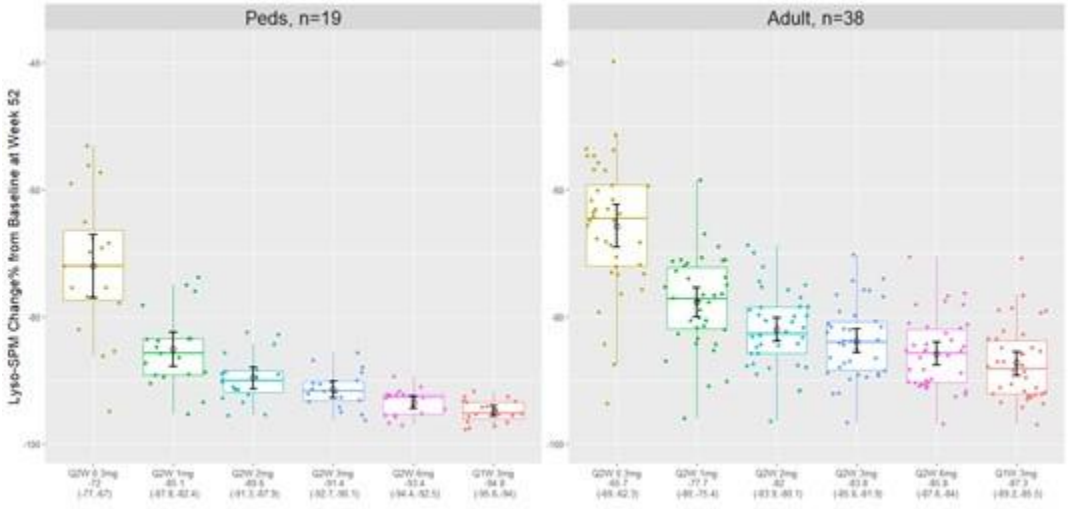
Source: FDA reviewer's analysis.
Note: The 3 horizontal lines of each box represent Quartile 1, median, and Quartile 3 of the dots; the black circle represents the mean and the error bar represents the 95% confidence interval.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; n, number of subjects.

Figure 106. Simulated Dose-Response in Change From Baseline of Spleen Volume at Week 52 for Olipudase Alfa



Source: FDA reviewer's analysis.
Note: The 3 horizontal lines of each box represent Quartile 1, median, and Quartile 3 of the dots; the black circle represents the mean and the error bar represents the 95% confidence interval.
Abbreviations: n, number of subjects; Peds, pediatrics.

Figure 107. Simulated Dose-Response in Change From Baseline of Lyso-SPM at Week 52 for Olipudase Alfa

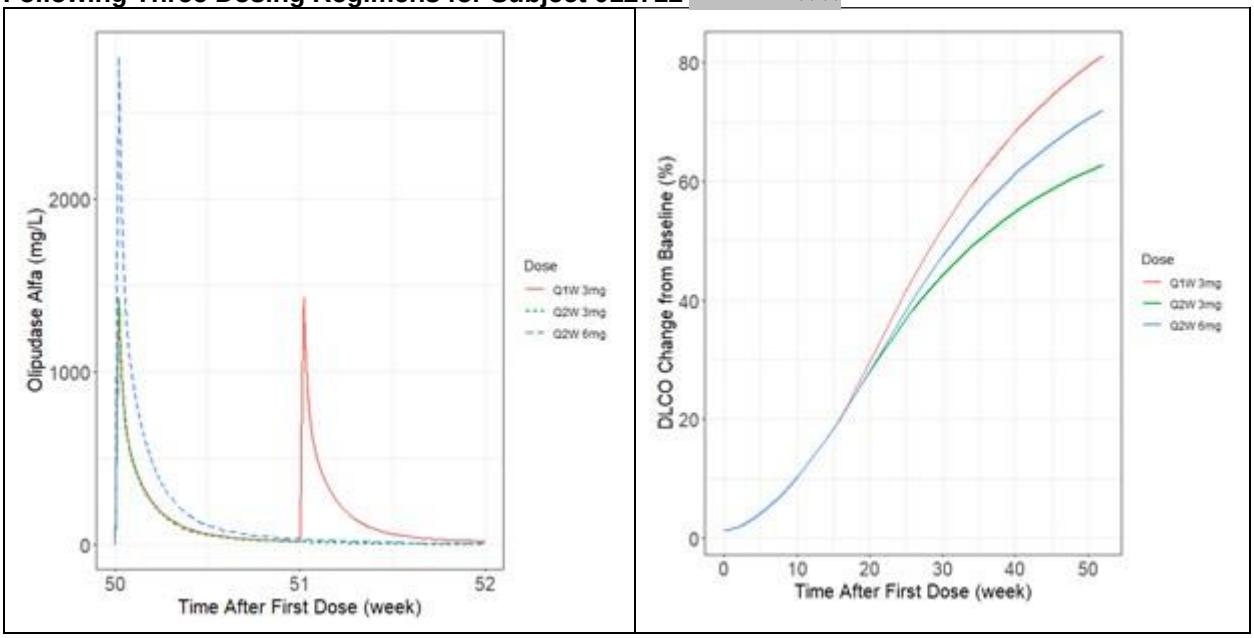


Source: FDA reviewer's analysis.
Note: The 3 horizontal lines of each box represent Quartile 1, median, and Quartile 3 of the dots; the black circle represents the mean and the error bar represents the 95% confidence interval.
Abbreviations: n, number of subjects; Peds, pediatrics.

It is noted that olipudase alfa QW 3 mg/kg dose may lead to better clinical outcome than Q2W 6 mg/kg dose although their weekly dose is the same. Based on simulation results in a typical patient (Subject 012712-[redacted] (b) (6)), there is almost no drug in the circulation during the 2nd week of the dosing interval for 3 or 6 mg/kg Q2W dose (left panel of Figure 108). In contrast, the 3 mg/kg QW dose avoids the high peak of the 6 mg/kg Q2W dose while maintain the drug exposure during 2nd weeks of the dosing interval as shown by the red line. These PK differences leads to predicted

PD differences shown in the right panel of Figure 108, where increasing olipudase alfa dose from 3 mg/kg Q2W to 6 mg/kg Q2W improves DLco CFB by 8.6% versus the improvement of 17.2% by increasing the dose from 3 mg/kg Q2W to 3 mg/kg QW.

Figure 108. Comparison of Simulated Olipudase Alfa Pharmacokinetics and DLco Dynamics Following Three Dosing Regimens for Subject 012712- (b) (6)



Source: FDA reviewer's analysis based on Applicant's PKPD dataset "dlco xpt".
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide

Further, additional exploration was carried out to identify those who may potentially benefit more from a higher maintenance dosing regimen, i.e., subjects predicted to have a remarkable difference in response following 3 mg QW versus 3 mg Q2W. Based on the simulation results, five subjects were identified and listed in Table 190**.** All five subjects had relatively high IC_{50} and high drug clearance compared to other subjects in the population. With olipudase alfa clearance ranged from 0.0795 to 0.480 (Q1=0.218, median =0.305, Q3=0.364, mean =0.289, and SD =0.103) L/h for the 58 patients in the popPK dataset, the CL of these 5 subjects were 0.278, 0.324, 0.338, 0.407, and 0.413, respectively. With IC_{50} on Lyso-SPM ranged from 0.000123 to 0.0321 (Q1=0.00376, median =0.00722, Q3=0.0116, mean =0.00887, and SD =0.007007) mg/L for the 58 patients in the population PK/PD dataset, and IC_{50} of these 5 subjects were 0.00510, 0.00590, 0.00997, 0.0181, and 0.0321, respectively. For these 5 patients, there were additional 5.8-17.2% increase in DLco, additional 5.0-13.6% decrease in spleen volume, and additional 3.7-13.9% decrease in Lyso-SPM by increasing the maintenance dosing frequency from Q2W to QW. The additional benefit of QW dose might be clinically meaningful.

Table 190. Comparison of Predicted Efficacy Results at Week 52 Between Olipudase Alfa 3 mg/kg Q2W and QW Regimens in Five Identified Subjects With ASMD

USUBJID	Efficacy Biomarker	Baseline	Prediction at Week 52 (CFB%) Q2W	QW	Difference
012712 (b) (6)	DLco (%)	41.8	49.7 (18.8%)	52.1 (24.6%)	2.4 (5.8%)
012712		44.5	56.2 (26.1%)	59.2 (32.9%)	3.0 (6.8%)
012712		48.5	79.3 (63.4%)	87.6 (80.6%)	8.3 (17.2%)
012712		54.3	67.8 (25.0%)	72.6 (33.8%)	4.8 (8.8%)
013803		27.0	36.8 (36.3%)	38.7 (43.4%)	1.9 (7.1%)
012712	Spleen Volume (MN)	18.5	11.7 (-36.8%)	10.5 (-43.1%)	-1.2 (-6.3%)
012712		18.8	10.5 (-44.3%)	9.2 (-51.0%)	-1.3 (-6.7%)
012712		9.65	5.7 (-41.3%)	4.9 (-49.2%)	-0.8 (-7.9%)
012712		10. 7	6.1 (-42.3%)	4.7 (-55.9)	-1.4 (-13.6%)
013803		13.8	7.7 (-44.4%)	7.0 (-49.4)	-0.7 (-5.0%)
012712	Lyso-SPM (ng/mL)	729	95.7 (-86.9%)	54.0 (-92.6%)	-41.7 (-5.7%)
012712		601	69.2 (-88.5%)	35 (-94.2%)	-34.2 (-5.7%)
012712		365	59.7 (-83.7%)	30.4 (-91.7%)	-29.3 (-8.0%)
012712		260	67.8 (-73.9%)	31.6 (-87.8%)	-36.2 (-13.9%)
013803		692	67.3 (-90.3%)	41.2 (-94.0%)	-26.1 (-3.7%)

Source: FDA reviewer's analysis.
Abbreviations: CFB%, change from baseline in percent; QW, once a week; Q2W, once every 2 weeks; USUBJID, unique subject identity.

14.6. QSP Review

Quantitative Systems Pharmacology Modeling Review

Division Of Pharmacometrics, Office Of Clinical Pharmacology

Executive Summary

The objective of this analysis is to assess the degree of mechanistic similarity of disease and response to olipudase alfa in pediatric and adult ASMD patients by applying a Quantitative Systems Pharmacology (QSP) model of ASMD that describes key pathophysiology of ASMD and the mechanism of action of olipudase alfa.

The Division of Pharmacometrics has reviewed the QSP analysis report (Study: QSP0068), supporting modeling files, and the Applicant's responses to Clinical Pharmacology Information Requests (IR). The QSP review team concluded that QSP analysis, in addition to the observations from clinical trials in pediatric and adult patients, can be used to support the approval of olipudase alfa in pediatric patients based on:

- The QSP analysis provided supportive evidence that the pathophysiology of ASMD and the pharmacology of olipudase alfa are similar between adult and pediatric patients.
- The QSP analysis can describe the pharmacokinetic profiles of olipudase alfa, dynamics of plasma levels of ceramide and lyso-sphingomyelin (SPM), spleen volume, and percentage predicted diffusing capacity of the lung for carbon monoxide (DLco) after olipudase alfa treatment.

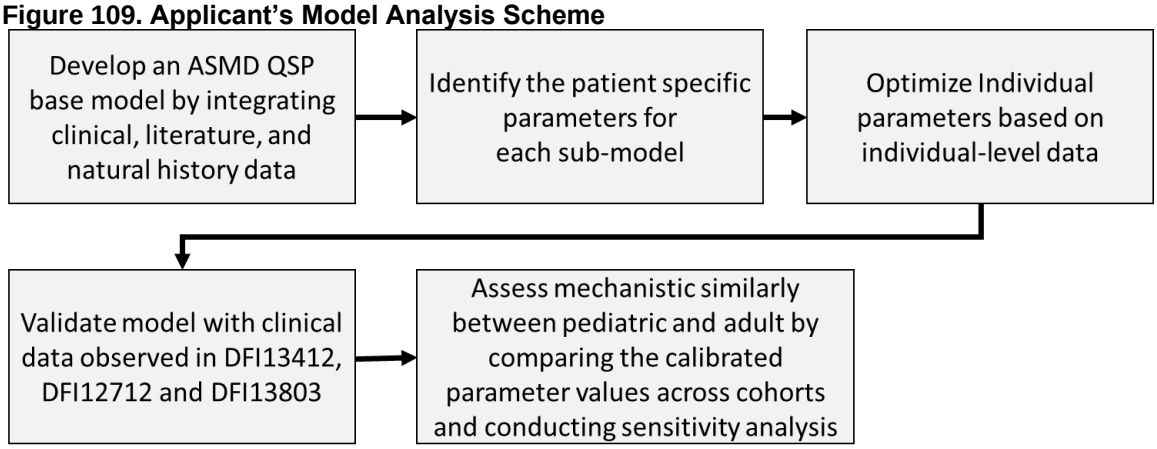
Background

Olipudase alfa is used in the intravenous enzyme replacement therapy (ERT) for the treatment of the non-neurological manifestations of ASMD. Olipudase alfa was designed to replace deficient or defective endogenous enzyme, acid sphingomyelinase (ASM), allowing the breakdown of accumulated sphingomyelin (SM) in hepatocytes and macrophages (lung and spleen). The Applicant developed a QSP model which provides a multiscale representation of ASMD and olipudase alfa mode of action to describe the dynamics of ASMD biomarkers and clinical endpoints following the olipudase alfa treatment. The ASMD QSP model is proposed as a quantitative platform to assess the degree of mechanistic similarity of disease and treatment response between adult and pediatric ASMD patients.

Methods

An overview of the steps of the QSP modelling effort conducted by the Applicant is shown in Figure 109.

Figure 109. Applicant's Model Analysis Scheme



Source: adapted from QSP analysis report Figure 1

Model Structure

The submitted QSP model comprised four sub-models: a PK sub-model, a molecular-level sub-model, a cellular-level sub-model, and an organ-level sub-model. A PBPK sub-model was used to describe the distribution and clearance of olipudase alfa in plasma and in tissues of interest. The PBPK sub-model included representations of liver, spleen, lung, plasma, lymph, and other organs (i.e., small intestine, large intestine, and pancreas) contributing to liver blood flow. Other body compartments were lumped. Figure 110 presents a diagram of selected representation of sub-models in the Applicant's QSP model.

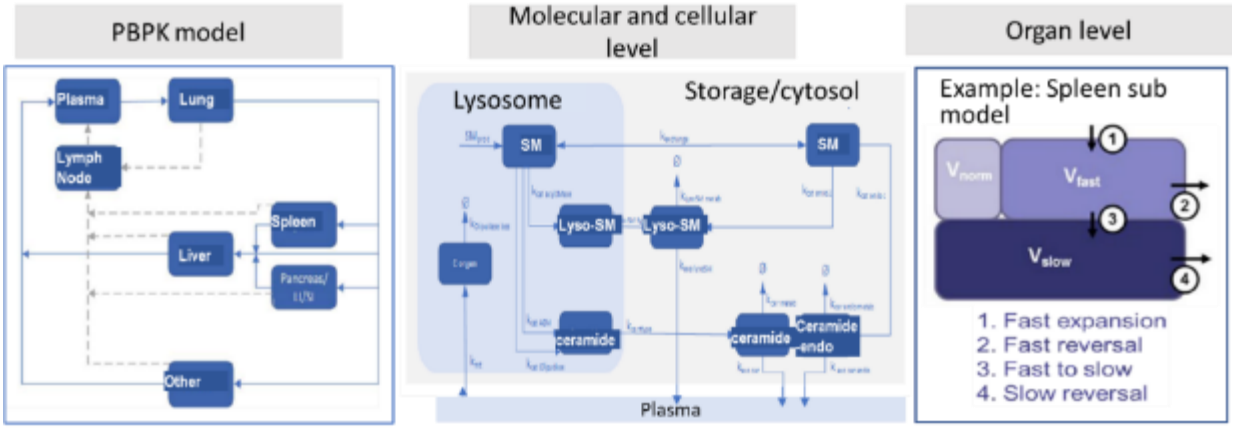
The molecular sub-model describes the production and clearance of SM in the lysosomal and or extra lysosomal compartments within the macrophages and hepatocytes **(**Figure 110**)**. In the lysosome, sphingomyelin will be converted to ceramide or lyso-sphingomyelin (lyso-SPM). Ceramide was catalyzed by endogenous residual ASM and olipudase alfa (rhASM), and lyso-SPM was catalyzed by acid ceramidase. In addition, the model also includes the production of ceramide and lyso-SPM outside the lysosome via a stored SM pool, catalyzed by other endogenous enzymes. This was referred by Applicant as "two-pool" theory. Two pools of SM inside the cell were hypothesized based on plasma biomarker data and review of the SM

metabolism pathway. SM could be exchanged between the two pools based on concentration differential and the exchange rate of SM between lysosome and storage was same across all cell types.

Sphingomyelin accumulation in splenic macrophages and alveolar macrophages causes impairment of macrophage function in both organs. The cellular level sub-model (i.e., macrophages and hepatocytes) therefore serves as the connecting point translating cellular SM levels into organ dysfunction and the empirical measure of macrophage function serves as the input into each organ sub-models.

Sub-models to describe two organ level biomarkers for ASMD patients: spleen volume related to the normal spleen volume (as 1 MN unit), and diffusing capacity of the lung for carbon monoxide DLco were included in the model. In the QSP model, total spleen volume is the sum of three interconnected sub-volumes: V_{norm}, the normal spleen volume; V_{fast}, a quickly reversible saturable enlarged sub-volume, representing temporary build-up of SM and foamy macrophages, and V_{slow}, a slowly reversible volume, representing less pliable tissue possibly due to fibrotic damage (see Figure 110 for example). As for the lung sub-model, no clear distinction in the DLco time course data to suggest such a structure (slow and fast component) as the spleen model.

Figure 110. Diagram of Selected Representation of QSP Sub-Models



Source: Figure 3, Figure 10, and Figure 21 of the Applicant's QSP report

Parameter Values

Various sources of data were used to inform the development of the QSP model as summarized in Table 191**.** The QSP model contained several types of parameters which are classified into three categories based on their sources and uncertainty. The values of the first category parameters were obtained directly from the literature or nonclinical studies and were considered "fixed" and not varied across patients. The second category includes parameters with mean values that were estimated based on literature values, preclinical and clinical data. The third category consists of parameters that were allowed to vary among individual patients and estimated based on data collected in the clinical drug development. Parameters in this category were selected based on prior clinical knowledge and sensitivity analysis. Model calibration was conducted to capture the individual level variability and to identify the source of the variability.

For a full list of parameters in details, refer to Appendix 2.2 of the QSP analysis report (Study of QSP0068).

Table 191. Various Sources of Data Informing the QSP Model

Modeling stage	Study	Description	QSP modeling parameters obtained
Development	3.2.S.3.1	Nonclinical data	Molecular and cellular sub-model parameters (i.e., k_{cat} and K_M for olipudase alfa)
Development	03-0380Pnp	Preclinical data	**PBPK sub-model parameters** (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	02-0266Pnp	Preclinical data	**PBPK sub-model parameters** (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	03-0142Pnp	Preclinical data	**PBPK sub-model parameters** (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	05-0094Pnp	Preclinical data	**PBPK sub-model parameters** (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	SPHINGO-001-00	Natural History study	**Spleen sub-model parameters** (i.e., maximum spleen volume)
Development	SPHINGO-006-05	Phase 1a clinical trials (Adult ASMD patients, SD, 0.03, 0.1,0.3,0.6 and 1.0 mg/kg)	**Molecular and cellular sub-model parameters** (i.e., Rate of transit of ceramide; rate of SM exchange; rate of export of ceramide into plasma)
Development/ Validation/ Refinement	DFI13412	Phase 1b clinical trials (Adult ASMD patients, Intrapatient dose escalation 0.1- 0.3- 0.3- 0.6- 1.0- 2.0 and -3.0 (target) mg/kg, Q2W, 26 weeks)	**PBPK sub-model parameters** (i.e., Organ vascular reflection coefficient) **Molecular and cellular sub-model parameters** (i.e., Number of ASM, acylSMase molecules per cell; rate of olipudase alfa clearance; rate of ceramide production; rate of lyso-SPM production; rate of transit of ceramide; Rate of transit of lyso-SPM; rate of SM exchange; rate of export of ceramide into plasma; rate of export of lyso-SPM into plasma; rate of clearance of lyso-SPM from plasma; parameters controlling lyso-SPM export; maximum SM amount in hepatocytes/macrophages in ASMD; parameters controlling macrophage function in lung/spleen;) **Spleen sub-model parameters** (i.e., Rates controlling spleen sub-volumes; maximum spleen volume) **Lung sub-model parameters** (i.e., Rates controlling Hb-adjusted percent predicted DLco; maximum and minimum Hb-adjusted percent predicted DLco)
Development/ Refinement/ Validation	DFI13803 (ASCEND-Peds)	Phase 1/2 clinical trials (Pediatric ASMD patients, Intrapatient dose escalation 0.03 - 0.1 - 0.3 - 0.3 - 0.6 - 1.0 - 2.0 - 3.0 (target) mg/kg, Q2W, 64 weeks)	**Spleen sub-model parameters** (i.e., Rates controlling spleen sub-volumes; maximum spleen volume) **Lung sub-model parameters** (i.e., Rates controlling Hb-adjusted percent predicted DLco; maximum and minimum Hb-adjusted percent predicted DLco)

Modeling stage	Study	Description	QSP modeling parameters obtained
Development/ Refinement	LTS13632	Phase 2 clinical trials (ASMD adult and pediatric patients rolled over from DFI13412 and DFI13803, 9 years or marketing approval)	**Spleen sub-model parameters** (i.e., Rates controlling spleen sub-volumes; maximum spleen volume) **Lung sub-model parameters** (i.e., Maximum Hb-adjusted percent predicted DLco)
Development/ Validation/ Refinement	DFI12712 (ASCEND)	Phase 2/3 clinical trials (Adult ASMD patients, Intrapatient dose escalation 0.1- 0.3- 0.3- 0.6- 0.6- 1.0- 2.0- 3.0 -3.0 (target) mg/kg, Q2W, in total (PAP + ETP), the trial will last for to up to 5 years and 3 months))	**Spleen sub-model parameters** (i.e., Maximum spleen volume) **Lung sub-model parameters** (i.e., Maximum and minimum Hb-adjusted percent predicted DLco)

Source: Reviewer's summary

Parameter Sensitivity Analysis

Both local sensitivity analysis (LSA) and global sensitivity analysis (GSA) were performed at baseline and week 52 treatment to identify key parameters affecting the variability of PK, PD, and clinical endpoints. More than hundred model parameters were used in the QSP model, and 72 relevant parameters were subjected to LSA to identify sensitive model parameters based on the average Ph1b patient's calibration. Applicant excluded PBPK sub-model related parameters, any constants, or unit conversion factors, and olipudase alfa kinetics parameters (k_m and k_{cat}) from this LSA analysis. Parameters LSA was run with each parameter value increased by 20% and simulated results were compared to the original simulated results using the original parameter value (base value). The sensitivity index (SI) of the output to the 20% parameter change was calculated and further normalized within each group for interpretation and identification purposes. Global sensitivity analysis, Extended Fourier amplitude sensitivity test (eFAST) was performed to further evaluate the interactions and effects of parameters identified during LSA.

Model Calibration

Two calibration methodologies were employed during model development. Grid searches were utilized when the parameter space was small enough to explore thoroughly in a reasonable amount of time. When the dimension and size of the parameter space was large, Covariance Matrix Adaptation Evolution Strategy (CMA-ES), was used to minimize the cost function generated by the data. Model calibration was performed in a sequential manner with each level utilizing a different cost function due to the varying nature of the data from the PK, biomarkers, and clinical endpoints. Optimized parameter sets from each sub-model were assessed for unintended detrimental effects on outputs not included in the original optimization.

The QSP model was calibrated to data from 38 individual patients (22 adults, 4 adolescents, 7 children and 5 infants) in Trials DFI13412, DFI13803 (ASCEND-Peds), LTS13632 and DFI12712 (ASCEND). The parameters to be calibrated were chosen based on local sensitivity analysis (LSA), biological knowledge, and availability of literature reference values. Parameters

with high sensitivity that were known sources of variability, such as REA, were chosen to be calibrated to capture the individual-level clinical data. A total of 12 parameters as shown in Table 192 were selected for calibration accordingly. The parameters were optimized in sequence. $k_{deg\ plasma}$, which describes the degradation of olipudase alfa in plasma was first calibrated for the PK sub-model using a grid search. During calibration, the plasma concentration of olipudase alfa was used as input data for the cost function. Parameters for molecular sub-model, such as SM_prod and ASM REA, was calibrated using CMA-ES algorithm, using the plasma ceramide and plasma lyso-SPM concentrations. Next, the lung portion of the organ level sub-model was calibrated, utilizing the CMA-ES algorithm as well based on the percent predicted DLco data for each patient. Finally, the spleen portion of the organ level sub-model was calibrated based on the observed spleen volume data for each patient.

Table 192. Parameters for Calibration

Parameter	Data calibrated to	Parameter Description	Reason for inclusion in indiviual calibration
Step 1 - PK sub-model			
kdeg plasma (1/hr)	olipudase alfa in plasma	Clearance rate of olipudase alfa from plasma compartment	Biological plausibility
Step 2 - Molecular sub-model			
SM Prod (uM/hr)	plasma lyso-SPM and plasma ceramide	Uptake rate of SM into lysosome	Biological plausibility
ASM REA (unitless)	plasma lyso-SPM and plasma ceramide	Proportion of residual ASM activity	Biological plausibility
k exo lysoSM (1/hr)	plasma lyso-SPM and plasma ceramide	Export rate of lysoSM into plasma	Lumping of multiple reactions
k clear lysoSM (1/hr)	plasma lyso-SPM and plasma ceramide	Clearance rate of lysoSM from plasma	Lumping of multiple reactions
k clear cer (1/hr)	plasma lyso-SPM and plasma ceramide	Clearance rate of ceramide from plasma	Lumping of multiple reactions
Step 3a - Spleen sub-model			
spleen fast expansion (MN/hr)	spleen volume	Expansion rate of quickly reversible spleen volume	Empirical nature of submodel
spleen fast reversal (MN/hr)	spleen volume	Reversal rate of quickly reversible spleen volume	Empirical nature of submodel
spleen fast to slow (MN/hr)	spleen volume	Transition rate of spleen volume from quickly to slowly reversible	Empirical nature of submodel
spleen slow reversal (MN/hr)	spleen volume	Reversal rate of slowly reversible spleen volume	Empirical nature of submodel
Step 3b - Lung sub-model			
lung beta decline	% predicted DLco	Decline rate of % predicted DLco	Empirical nature of submodel
lung beta reversal	% predicted DLco	Reversal rate of % predicted DLco	Empirical nature of submodel

Source: QSP analysis report, Table 15

Reviewer's Comments:

As indicated above, the individual model calibrations were performed in a sequential manner (PK sub-model-> molecular level sub-model-> lung portion of the organ level sub-model->

spleen portion of the organ level sub-model). However, the robustness of model performance when dealing with different optimization sequences was not considered by the Applicant. This concern was communicated via FDA's information request (dated Jan 31st, 2022). The Applicant then explored the robustness of the model behavior to the calibration sequence by comparing parameter values and model simulation outcomes after calibration with different calibration sequences. Detailed comparison results suggested that the modular and sequential parameterization of upstream sub-models of the QSP model increases the identifiability of the downstream parameters, as it reduces the size of the plausible parameter space searched during the optimization procedure resulting in more accurate fits. Moreover, this type of sequential sub-model calibration allows the empirical representations of the organ-sub models to be constrained by the mechanistic features of the molecular sub-model, justifying the model structure and the current representation of the disease processes by more accurately capturing corresponding datasets, which seems to be reasonable to the reviewers.

Model Validation

The QSP model was validated by comparing the simulation with the clinical datasets which were not utilized during model development. These validation exercises included: a) validation of olipudase alfa-mediated liver SM reductions; b) validation of simulated healthy plasma ceramide and lyso-SPM levels; c) validation of simulated biomarkers and clinical endpoints in adult virtual population; d) validation of simulated biomarkers and clinical endpoints in pediatric virtual population; e) validation of spleen SM levels from Type A patients untreated with olipudase alfa. Virtual populations for adults were constructed based on the adult derived parameterization from DFI13412 and DFI12712 (ASCEND). Instead, virtual populations for each individual pediatric patient from DFI13803 (ASCEND-Peds) were generated by using a bootstrapping approach.

Model Application

The following assessment were proposed by Applicant to assess the disease similarity between adult and pediatric population.

- Comparison of averaged individual fit accuracy metrics between adult and pediatric cohorts.
- Comparison of distributions of calibrated parameters from adult and pediatric cohorts.
- Comparison of the sensitivity of model parameters on the variability observed in PK, PD, and clinical outputs between adult and pediatric population.

Software and Code Verification

The QSP analysis was conducted using MATLAB® R2019a (The MathWorks, Natick, MA) and MIST-C based upon data pooled from different studies. R statistical software© (version 4.0.2) (The R Foundation, Vienna, Austria) was used for data tabulation, and visualization activities.

Reviewer's Comments:

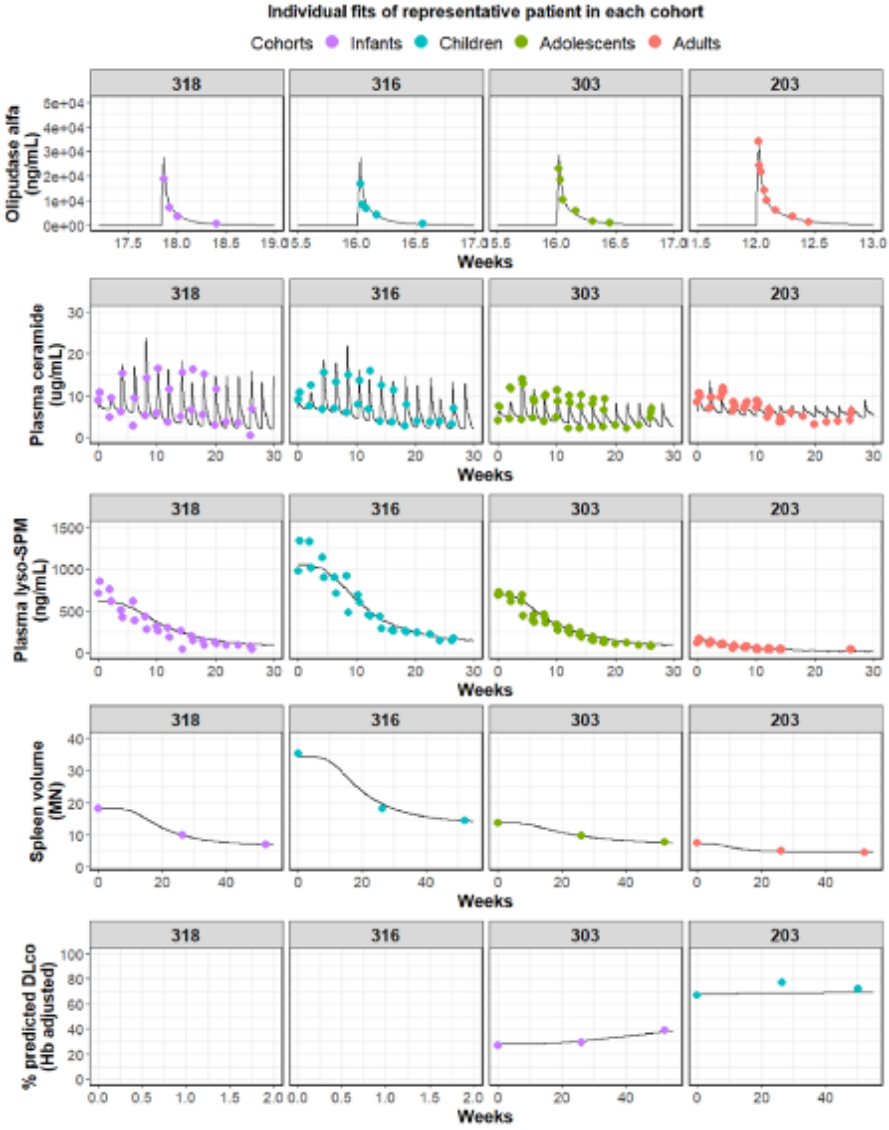
a.) Applicant's technical documentation is well-organized and referenced.
b.) Mathematical equation and methodology have been checked against the reference code and reviewer can reproduce the results in the report.
c.) Reviewer noted that an early communication of software requirement will help with timely review.

Result

Can the Submitted QSP Model Support the Similarity in Disease Progression and Treatment Response Between Pediatric and Adult ASMD Patients?

Yes. Mechanistic similarity on pathophysiology and pharmacology of ASMD between pediatric and adult patients were assessed by the agreement between the observed plasma levels of olipudase alfa, ceramide, lyso-SPM, spleen volume and % predicted DLco with those simulated under the same model structure. As shown in Figure 111, the model was able to simultaneously describe various biomarker data which presented the direct and/or indirect PK/PD response to disease and treatment despite the wide range of baseline values observed.

Figure 111. Individual Calibrations for Representative Patient of Each Cohort

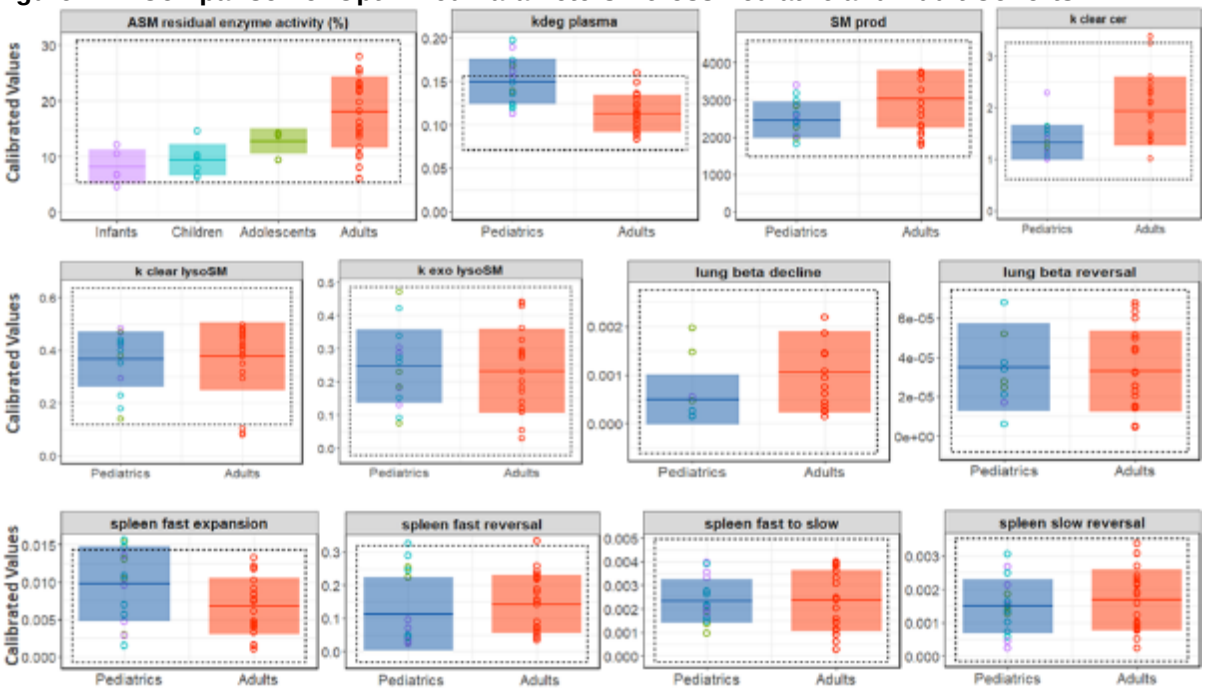


** Patient 318 (age 2) and 316 (age 5) lack % predicted DLco measurements due to age limits*

Source: QSP analysis report, Figure 36) using the QSP model for the selected patients
* Patient 318 (age 2) and 316 (age 5) lack percent predicted DLco measurements due to age limits

Mechanistic similarity can be further supported by comparing the calibrated parameter values across cohorts and sensitivity analysis. As shown in Figure 112, the distributions of the majority of calibrated parameters showed significant overlap except k_{deg_plasma}, k_{clear_cer} and ASM REA. Further analyses were conducted for k_{deg_plasma}, k_{clear_cer} and ASM REA as described in the next paragraph.

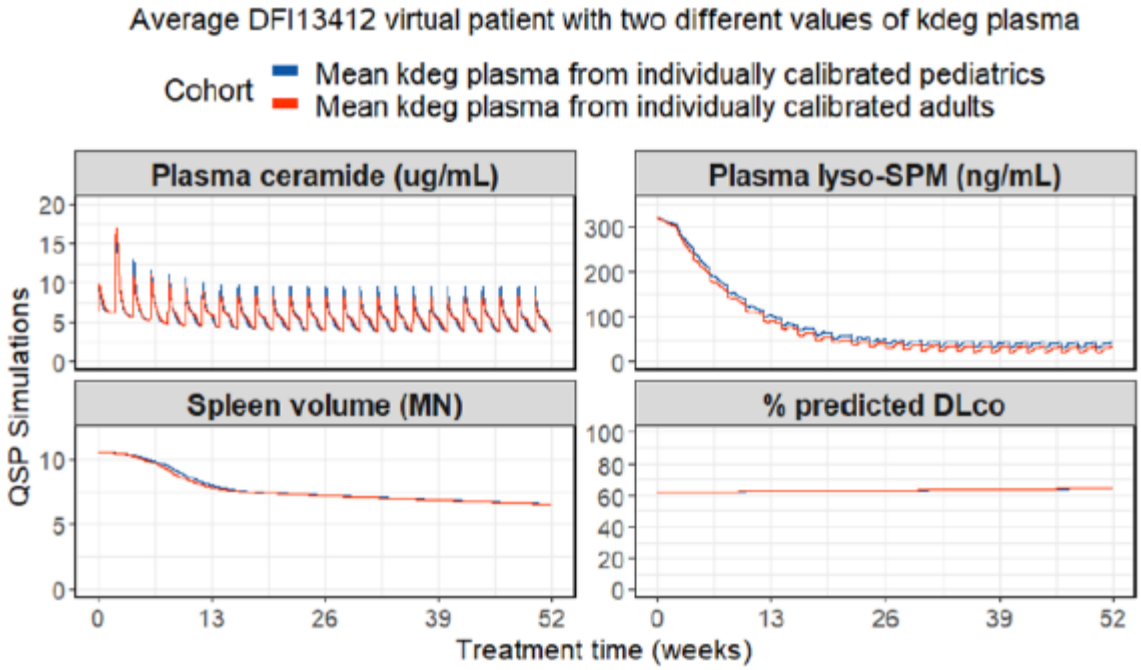
Figure 112. Comparison of Optimized Parameters Across Pediatric and Adult Cohorts



Source: QSP analysis report, Figure 38
Open dots are individual optimized parameter values, color coded by cohorts. Solid line: mean optimized parameter value of corresponding cohorts; shaded area: mean +/- σ of optimized parameter value of corresponding cohorts; dashed open rectangular: mean +/- 2σ of average calibrations from adults

Applicant also conducted statistically analyses to evaluate the similarity between the optimized parameters in the pediatric and adult cohort. Two-sample Kolmogorov-Smirnov (KS) test and comparison of group-wise sample medians between pediatric and adult cohorts were chose to compare the distributions of parameters. Applicant defined the pediatric parameters sets were different from those in adult patients if there was consensus based on the two stringent metrics (KS test and group-wise sample medians analysis). The results of the statistical analysis are consistent with the distribution plots which suggested that most parameters are not significantly different between pediatric and adult cohorts except k_{deg_plasma}, k_{clear_cer} and ASM REA. To evaluate the effect of these differences in parameter values on the biomarker or clinical endpoint represented in the model, the Applicant performed simulations by using the mean estimated parameter from all pediatric patients or the mean estimated parameter from all adult patients. The rest of other parameters were based on the parametrization of the average Ph1b DFI13412. As exhibited in Figure 113, no clinical meaningful effects on the biomarkers or endpoints were simulated when using mean estimated parameter (k_{deg_plasma}) from pediatric or adult patients. Similar results were simulated when using mean estimated parameter, k_{clear_cer} (result not shown).

Figure 113. Average Ph1b DFI13412 Virtual Patient's Trajectories for Mean Adult and Pediatric Values for kdeg Plasma. Average DFI13412 Virtual Patient With Two Different Values of kdeg Plasma

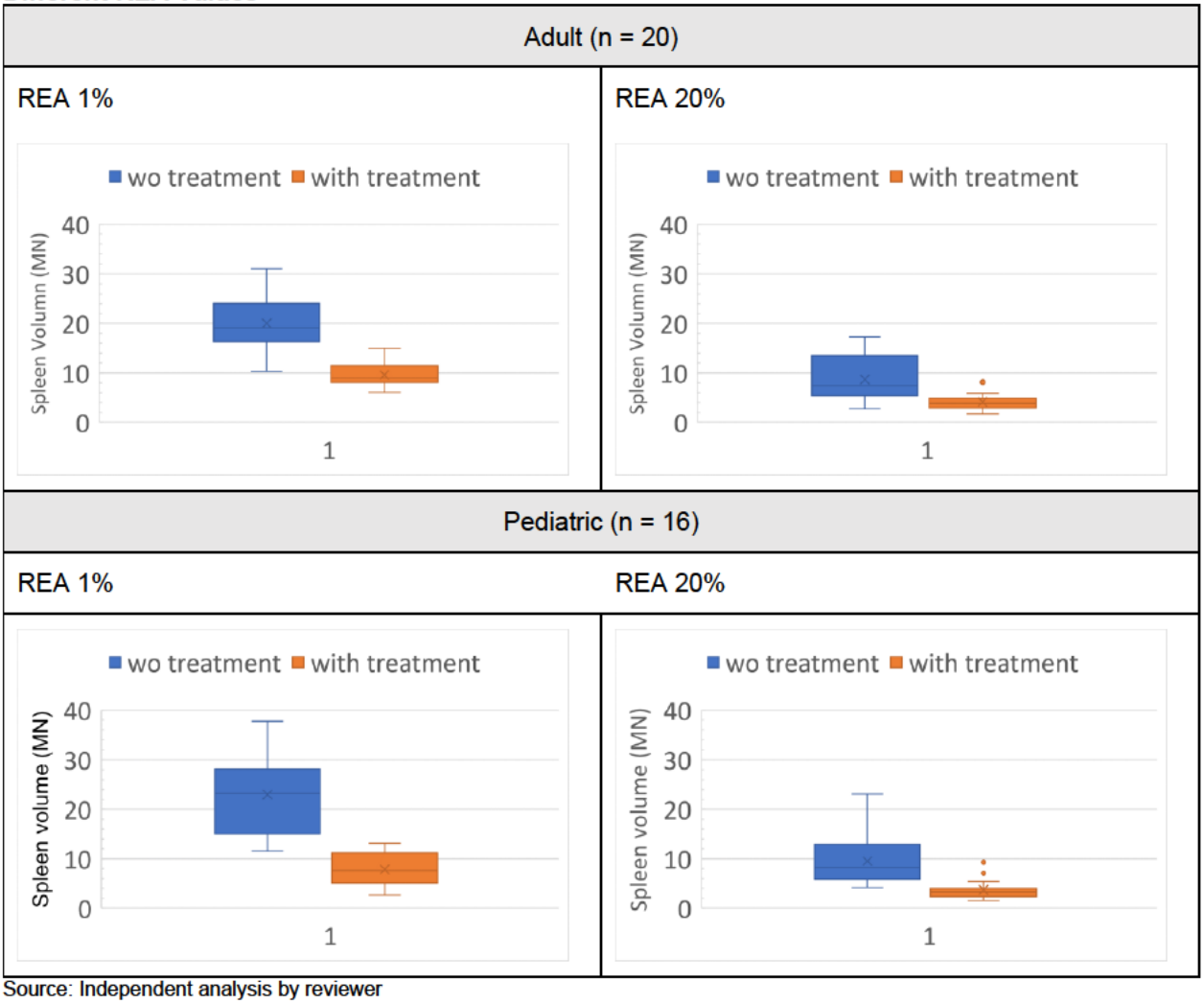


Source: QSP analysis report, Figure 39

Reviewers' Comments

The parameter ASM REA, which defines the degree of lipid accumulation and represents disease severity tended to be lower in pediatric than adult patients and when specific pediatric age groups were plotted, REA was increased with patient age (Figure 112, first panel). REA values were estimated during individual model calibrations using each patient's observed plasma lyso-SPM and ceramide datasets. Therefore, pediatric patients that exhibited higher observed baselines values for plasma lyso-SPM and ceramide were predicted to have lower residual activities. Additional simulations were performed by FDA reviewer to determine the effect of REA on the simulated spleen volume in the model. The simulations were performed using the pediatric and adult virtual patients whose parameters were calibrated with clinical dataset included in the submitted QSP analysis. For each individual, simulations were performed using the REA value of 1% or 20% while other parameters were remained the same. As shown in Figure 114, there is a clear relationship between REA and simulated spleen volumes. The predicted baseline spleen volumes at steady state were higher in patients with lower REA for both cohorts (averaged value of blue bar in (a) vs.(b) and (c) vs. (d) panels). However, the magnitude of reductions in the spleen volume with 52 weeks treatment were comparable between pediatric and adult cohort regardless the REA values. For example, the simulated fold of reduction in averaged spleen volume were 2.6 (averaged value of blue vs. orange bar in panel (c))and 3.0 (averaged value of blue vs. orange bar in panel (d)) in pediatric cohort for REA values of 1% and 20% respectively following olipudase alfa treatment. A similar trend was simulated for adult cohort.

Figure 114. Comparison of the Predicted Treat and Untreated Spleen Volume in Patients With Different REA Values

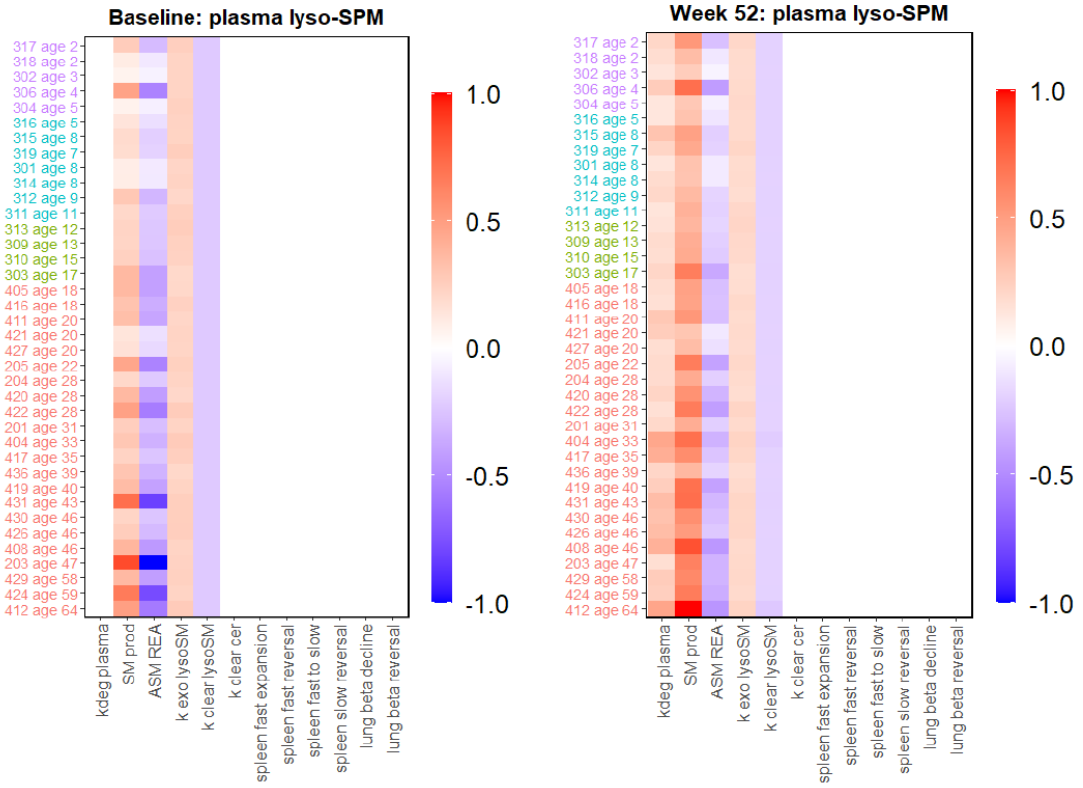


Source: Independent analysis by reviewer
Lines within the boxplot represent the median and the upper and lower quartiles and 'x' is the averaged value.

Similar sensitivity parameter profiles across cohorts would support mechanistic similarity. To evaluate the parameter sensitivity profile for each patient, the Applicant run a simulation using the optimized parameter values of each individual patient calibration, followed with 20% increase in each parameter value. Then the resulting simulated results were compared to the original simulated results. Applicant stated this analysis aimed to assess whether both cohorts shared similar parameter influences on their outputs, supporting mechanistic similarity. Figure 115 presents the heatmaps of parameters sensitivities influencing plasm lyso-SPM at baseline and week 52 treatment timepoint. As shown in the Figure 115, there are differences in the magnitude of the parameter sensitivity for each individual patient (different intensity of the color), however the trend (positive or negative correlation) is consistent across all patients, regardless of age cohort.

Reviewer noted that the assessments of similarity of sensitivities were qualitative, as similarity was defined, irrespective of magnitude, as consistent directionality trends across cohorts. Overall, the Applicant's analysis support that the similar parameter sensitivities were shared in both pediatric and adult cohorts.

Figure 115. Heatmap of Parameter Sensitivities for Plasma lyso-SPM at Baseline (Left Panel) and at 52 Weeks Olipudase Alfa Treatment (Right Panel). Sensitivities of Each Parameter of Each Individual Calibration Were Color Coded as Red When Positive, White When Zero or Blue When Negative



** Sensitivities of each parameter of each individual calibration were colour coded as red when positive, white when zero or blue when negative.*

Source: QSP analysis report, Figure 41

Can the QSP Model Describe the PK Profiles of Olipudase Alfa and Dynamics of Biomarkers, Spleen Volume and Percent Predicted DLco After Olipudase Alfa Treatment?

Yes. The model can describe the dynamics of biomarkers, spleen volume and percent predicted DLco observed in individual patients following the clinical treatment of olipudase alfa. As shown in Figure 111, the model was able to simultaneously describe various biomarker data which presented the direct and/or indirect PK/PD response to disease and treatment.

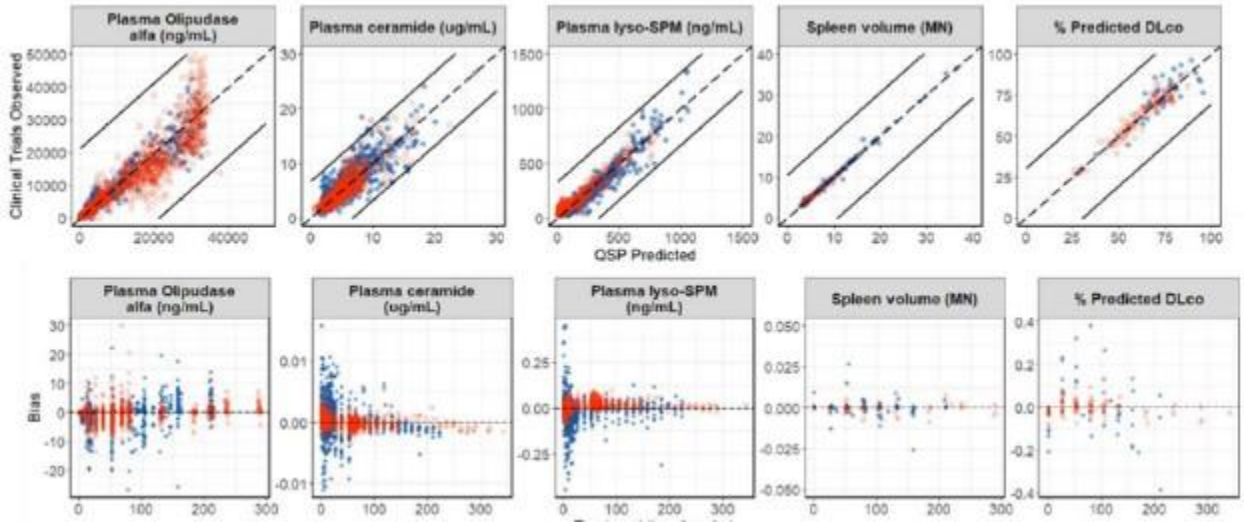
In addition, the Applicant compared prediction performance metrics between pediatric and adult patients. These evaluation metrics showed that the QSP model can capture the dynamic changes of plasma levels of olipudase alfa, ceramide, lyso-SPM, and clinical endpoints (spleen volume and percent predicted DLco) in both pediatric and adult patients (Table 193). Particularly, the model fits showed similar accuracy between pediatric and adult patients at all outputs. Bias analysis was also conducted (Figure 116) by the Applicant and the bias plots showed similar model behavior between pediatric and adult patients at all outputs. Thus, the QSP model structure reasonably represents the disease presentation and olipudase alfa response in patients and can recapitulate pediatric and adult clinical patient data with similar accuracy.

Table 193. Evaluation Metrics to Assess the Goodness of Fit

	Pearson Correlation Coefficient		Absolute Average Fold Error		Normalized Root Mean Squared Error		Percent predicted within two standard deviations of observed	
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric
Plasma olipudase alfa	0.93	0.96	1.47	1.64	0.43	0.34	99.77	100
Plasma Ceramide	0.88	0.86	1.21	1.32	0.28	0.35	99.78	99.08
Plasma LysoSM	0.96	0.96	1.60	1.24	0.30	0.27	100	100
Spleen Volume	1.00	1.00	1.03	1.03	0.04	0.05	100	100
% predicted DLco	0.96	0.90	1.05	1.07	0.06	0.10	100	100

Source: QSP analysis report, Table 16

Figure 116. Goodness of Fit and Bias Plots Comparing Predicted Model Outputs to the Corresponding Observed Data



Source: QSP analysis report, Figure 37
Black solid lines are 2σ of clinical data from all patients included in QSP analysis. Blue dots represent pediatrics, red dots represent adults

RISK ASSESSMENT

Model Risk Assessment

Table 194 showed the highlights of the regulatory impact of the Applicant's QSP model.

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Table 194. Highlights of the Regulatory Impact of the QSP Model

Impact on Drug Approval and/or Labeling	Reviewer Team's Comments
Supporting evidence. Applicant states that this QSP model is proposed to facilitate the comparison of disease and response to olipudase alfa in adult and pediatric ASMD patients. Applicant noted that QSP model was not applied to support the dosing recommendation for olipudase alfa	Agree
Additional Review Team's Modeling and Simulation	
Clinical data is available to describe the efficacy of olipudase alfa in pediatric population. The impact of the QSP modeling analysis on the United States Prescribing Information (USPI) is low. Review team has re-run the submitted model and assessed the in vitro and in vivo dataset used to develop, refine, and validate the submitted QSP model. Information requests were issued to communicate Reviewer's concerns regarding model script deficiencies and model parameter calibration. Applicant was able to update the model and conduct additional analysis to address Reviewer's concern. Review team conclude that the submitted QSP provide insight on mechanism of ASMD progression and response to olipudase alfa treatment in pediatric and adult ASMD patients. The simulation results supported the mechanistic similarity of disease and response to olipudase alfa between pediatric and adult ASMD patients. These results support the approval of olipudase in pediatric patients, in addition to the observations from clinical trials in pediatric and adult patients.	

Source: Review Team
Table 195 and Source: Review Team

Table 196 summarized the overall model risk assessment of the Applicant's QSP modeling analysis.

Table 195. Overall Model Risk Assessment for Type A/B and Type B Patient Population

Variable	Description	Applicant's position	FDA Assessment
Model influence	Describe the model influence, i.e., what is the weight of model predictions in decision-making considering the totality of evidence	Low.	Low. The primary evidence to support the pediatric indication was the pediatric clinical trial (DFI13803 ASCEND-Peds) which enrolled patients ages 18 months to 17 years and the long-term extension trial LTS13632.
Decision consequence	Discuss your decision consequence based on all available evidence i.e., potential safety or efficacy risk to patients if an incorrect decision is made.	Low.	Low. The safety and efficacy of olipudase alfa treatment at the proposed dose is supported by clinical data up to 52 weeks. Dose titration will be used to prevent the adverse infusion-associated reactions (IAR). Monitoring tool (such as IgE testing) can be used to manage adverse IAR.
Model Risk	Provide an assessment of overall risk of a wrong model prediction based on answers in 'Model influence' and 'Decision consequence'.	Low.	Low.

Source: Review Team

Table 196. Overall Model Risk Assessment for Type A Patient Population

Variable	Description	Applicant's position	FDA Assessment
Model influence	Describe the model influence, i.e., what is the weight of model predictions in decision-making considering the totality of evidence	Medium.	Medium. All the data used to support parameter optimization and validation to the clinical data were based on Type B patients. The extrapolation of disease response from Type B and Type A patients based on simulations without proper validation would traditionally be considered as exploratory. As no other treatment currently is available in this patient group, the integration of scientific understanding of the mechanism of action of olipudase alfa and mechanics-based modeling could aid the decision regarding the approval of olipudase alfa in Type A patient
Decision consequence	Discuss your decision consequence based on all available evidence i.e., potential safety or efficacy risk to patients if an incorrect decision is made.	Low.	Medium. From mechanism perspective, the etiology (ASM deficiency) is likely the same between the Type A and B patients. Thus, the safety data of olipudase alfa obtained from Type B population might be applicable to Type A patients. However, only few clinical data available to inform the safety/efficacy of olipudase alfa treatment in Type A patients. Therefore, decision consequence is considered *medium*.
Model Risk	Provide an assessment of overall risk of a wrong model prediction based on answers in 'Model influence' and 'Decision consequence'.	Low.	Low. The development and conclusion of QSP is in line with current scientific understanding where etiology is likely the same between the Type A and B patients. No quantitative information derived from the QSP analysis is proposed to support the decision-making process. The risk of a wrong model prediction to the patients is *low.*

Source: Review Team

Conclusion

The submitted QSP model and analyses provided mechanistic insight of ASMD and support the similarity in the disease and response to olipudase alfa in adult and pediatric ASMD patients.

Specifically, the model was able to describe the clinical biomarker data representing different aspect of disease and treatment response in patients. Under the same model structure, individual model fits to each patient showed comparable value ranges for parameters that control key disease processes across age or disease severity. Consistent parameter sensitivities were also identified in both pediatric and adult cohort. Therefore, the QSP model, in context with other clinical data, support the similarity in the disease and response to olipudase alfa in adult and pediatric ASMD patients.

Appendix

Summary of QSP Modeling Assessment Matrix and Criteria

Table 197 summarized various methods used to evaluate the acceptance of model parameters and model performance, as well as mechanistic similarity and QSP modeling assessment matrix and criteria were summarized in the following Table 197.

Table 197. Assessment Matrix and Criteria

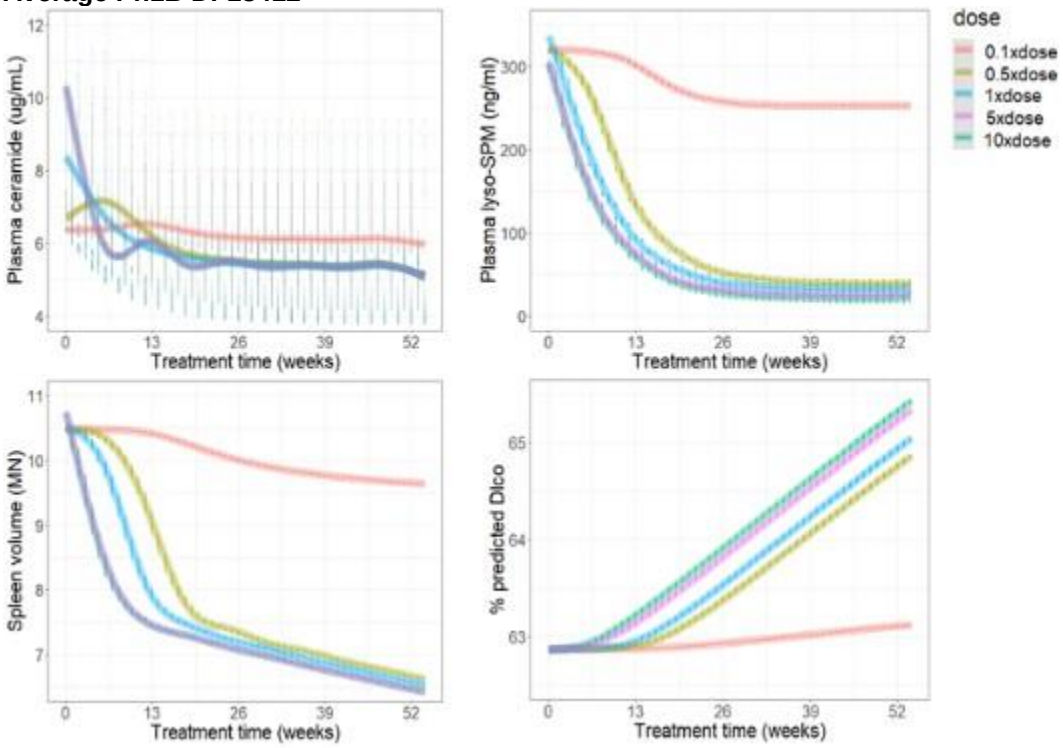
Assessment Matrix			Criteria
Model Fit Assessment	Graphical examination	Individual fit plot	Visual check
		Goodness of fit Plot	
		Bias Plot	
	Individual fit accuracy metrics	Pearson correlation coefficient (R^2)	Range of 0 to 1, the higher R^2 indicates the better model fit
		Absolute Average Fold Error (AAFE)	The smaller error value, the better model fit
		Normalized Root Mean Squared Error (nRMSE)	The smaller error value, the better model fit
		Percent predicted within two standard deviations of observed	The higher percentage value, the better model fit
Cohorts Similarity Comparison	Comparison of averaged individual fit accuracy metrics between adult and pediatric cohorts	R^2	Agreement in the averaged metrics values between pediatric and adult cohorts.
		AAFE	
		nRMSE	
		% predicted within 2σ of observed	
	Comparison of distributions of calibrated parameters from adult and pediatric cohorts	% of pediatric patient parameters within 2σ of the adult mean	The higher percentage value, the more similarity in parameter for the two cohorts
		Two-sample K-S test at 5% significance (p-value)	p>0.05, failure to reject null hypothesis, population distributions are the same
		95% CI (on the estimated difference between the group-wise sample medians)	If 95% CI includes zero: The centers of the individual cohorts were similar, or dissimilar otherwise.
	Sensitivity analysis	LSA for individual patient calibration; heat map of calculated sensitivities was generated	Qualitive assessments on similarity of sensitivities: visual check on sensitivities heat map

Source: Summary by reviewer

Exploration of Clinical Biomarker Response to Different Dose of *Olipudase Alfa*

Reviewer conducted additional analysis using the scripts provide by the Applicant to simulate four identical virtual patients derived for Study DF13412 except with *olipudase alfa* dose ranging 0.1 to 10-fold of the clinical dose, 3mg/kg. As shown in Figure 117, the most prominent difference in response only observed with the lowest dose level (0.1× dose). After treated with 0.5× of default dose or higher, the predicted plasma ceramide, plasma lyso-SPM, spleen volume and percentage predicted DLco levels reached similar values at the end of week 52.

Figure 117. Simulation of Different Dose-Response Curved Based on Parameterization of the Average Ph1B DF13412



Source: Independent analysis by reviewer

14.7. Summary of Bioanalytical Method Validation and Performance

Summary of Bioanalytical Method Validation and Performance

PK Assay: Bioanalytical Methods for the Measurement of Olipudase Alfa Concentrations in Human Plasma

The Applicant used two validated bioanalytical methods to quantify olipudase alfa in human plasma. Both methods used enzyme-linked immunosorbent assay (ELISA) platform. The first validated assay (Reports of Bioanalytical and Analytical Methods for Human Studies [ITR-432-0409]) used a mouse monoclonal antibody against olipudase alfa as the detection reagent. This method was used for the two Phase 1 clinical trials, SPHINGO-006-05 and DFI13412 and had a lower limit of quantitation (LLOQ) of 0.125 µg/mL [125 ng/mL] in neat plasma. Because the mouse monoclonal antibody used as the detection reagent could no longer be supplied, the Applicant developed the second method utilizing a rabbit polyclonal antibody against olipudase alfa as the detection agent ([ITR-653-0813]). This new method had an LLOQ of 0.04 µg/mL [39 ng/mL] in neat plasma and was used for clinical trials (DFI13803 ASCEND-Peds, LTS13632, and DFI12712 ASCEND).

Summary of life cycle information of assay methods used during development, assay validation parameters, and performance of assays used in clinical trials are provided in Table 198, Table 199, Table 200, and Table 201 below.

Table 198: Bioanalytical Method Life Cycle Information – Olipudase alfa

Variable	Method Validation #1	Method Validation #2	Method Validation #3	Phase 1a Study	Phase 1b Study DFI13412	Long-Term Safety Study LTS13632	Pediatric Study (ASCEND-Peds)	Adult Pivotal Study (ASCEND)
Analyte	Olipudase alfa	Olipudase alfa	Olipudase alfa	Olipudase alfa	Olipudase alfa	Olipudase alfa	Olipudase alfa	Olipudase alfa
Validation type	Full validation	Full validation	Full validation	In-study	In-study	In-study	In-study	In-study
CTD reference #	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4
Method ID	**ITR-432-0409**	**ITR-653-0813**	**PDV0079**	**ITR-432-0409**	**ITR-432-0409**	**ITR-653-0813; PDV0079**	**ITR-653-0813**	**ITR-653-0813; PDV0079**
Duration of time method is in use	04/2009-02/2014	08/2014-01/2020	09/2020-11/2020	05/2009	09/2013-02/2014	08/2014-12/2019; 11/2020-present	01/2016-10/2019	08/2016-01/2020; 11/2020-present
Bioanalytical site	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	(b) (4)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences); (b) (4)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences); (b) (4)

Variable	Method Validation #1	Method Validation #2	Method Validation #3	Phase 1a Study	Phase 1b Study DFI13412	Long-Term Safety Study LTS13632	Pediatric Study (ASCEND-Peds)	Adult Pivotal Study (ASCEND)
Matrix	Sodium Heparin Plasma							
Platform	enzyme-linked immunosorbent assay (ELISA)							
Format	A validated sandwich format using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a second non-competing purified mouse monoclonal anti-olipudase alfa monoclonal antibody (4G11) for detection	A validated sandwich format using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a purified rabbit polyclonal for detection	A validated sandwich format using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a purified rabbit polyclonal for detection	A validated sandwich format using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a second non-competing purified mouse monoclonal anti-olipudase alfa monoclonal antibody (4G11) for detection		A validated sandwich format using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a purified rabbit polyclonal anti-olipudase alfa antibody for detection		

Variable	Method Validation #1	Method Validation #2	Method Validation #3	Phase 1a Study	Phase 1b Study DFI13412	Long-Term Safety Study LTS13632	Pediatric Study (ASCEND-Peds)	Adult Pivotal Study (ASCEND)
Stock reference, lot number, expiration date	Drug lot SM076DP, Standard lot# 17044-150A, exp 08-Apr-2011	Drug lot SM079DP, Standard lot# 19063-72a, exp 27-Feb-2015	Drug batch # 9W2177, Standard lot# 20NP009, exp 30-Apr-2024	Drug lot SM076DP, Standard lot# 17044-150A, exp 08-Apr-2011	Drug lot SM079DP, Standard lot# 19037-179A, exp 04-Sep-2014	Lot 1: Drug lot SM079DP, Standard lot# 19063-72a, exp 27-Feb-2015 Lot 2: Drug lot 13CT116; Standard lot# 15-CRE-042, exp 19-May-2017 Lot 3: Drug batch number C6642; Standard lot# 17NP022, exp 31-Aug-2019 Lot 4: Drug batch number C6642; 19NP032, exp 30- Jun-2021 Lot 5 (CRL): Drug batch number 9W2177, Standard lot# 20NP009, exp 30-Apr- 2024	Lot 1: Drug lot 13CT116; Standard lot#15- CRE-042, exp 19-May-2017 Lot 2: Drug batch number C6642; Standard lot# 17NP022, exp 31-Aug-2019 Lot 3: Drug batch number C6642; 19NP032, exp 30-Jun-2021	Lot 1: Drug lot 13CT116; Standard lot# 15-CRE- 042, exp 19-May-2017 Lot 2: Drug batch number C6642; Standard lot# 17NP022, exp 31-Aug-2019 Lot 3: Drug batch number C6642; 19NP032, exp 30-Jun-2021 Lot 4 (CRL): Drug batch number 9W2177, Standard lot# 20NP009, exp 30-Apr-2024
Calibration range from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ)	2.5 ng/mL to 50 ng/mL in 1/50 human plasma (125 ng/mL to 2500 ng/mL in neat plasma)	0.78 ng/mL to 50 ng/mL in 1/50 human plasma (39 ng/mL to 2500 ng/mL in neat plasma)	39 ng/mL to 2500 ng/mL in neat plasma	3.13 ng/mL to 25 ng/mL (provisional LLOQ) in 1/50 human plasma (156 ng/mL to 1250 ng/mL in neat plasma)	2.5 ng/mL to 50 ng/mL in 1/50 human plasma (125 ng/mL to 2500 ng/mL in neat plasma)	0.78 ng/mL to 50 ng/mL in 1/50 human plasma (39 ng/mL to 2500 ng/mL in neat plasma)	0.78 ng/mL to 50 ng/mL in 1/50 human plasma (39 ng/mL to 2500 ng/mL in neat plasma)	0.78 ng/mL to 50 ng/mL in 1/50 human plasma (39 ng/mL to 2500 ng/mL in neat plasma)

Variable	Method Validation #1	Method Validation #2	Method Validation #3	Phase 1a Study	Phase 1b Study DFI13412	Long-Term Safety Study LTS13632	Pediatric Study (ASCEND-Peds)	Adult Pivotal Study (ASCEND)
Matrix study population	Normal Plasma	Normal Plasma	Normal Plasma	ASMD Population	ASMD Population	ASMD Population	ASMD Population	ASMD Population
Relevant reference and applicable report amendment	ITR-432-0409	[I TR-653-0813]	[PDV0079]	SPHINGO00605]	[DFI13412]	[LTS13632]	[DFI13803 ASCEND-Peds]	[DFI12712 (ASCEND)-interim2]
Synopsis of amendment history	N/A	Long-term storage ability	N/A	N/A	N/A	Amendment 1 adds data from additional runs performed between database lock 1 and database lock 2.	N/A	Amendment 1 adds data from additional runs performed between database lock 1 and database lock 2.

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 199: Summary Method Performance Validation of a Method for the Determination of Olipudase Alfa in Human Plasma Used in DFI13803 (ASCEND-Peds), LTS13632 Through 12/2019, DFI12712 (ASCEND) Through 01/2020)

Method Parameter	**Method Information**	
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Recombinant Human Acid Sphingomyelinase PK ELISA for the Quantitation of rhASM in Human Plasma Using Rabbit Detection Antibody**	
Method description	A validated sandwich ELISA using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a purified rabbit polyclonal anti-olipudase alfa antibody for detection.	
Materials used for standard calibration curve and concentration	Olipudase alfa reconstituted at 4 mg/mL	
Validated Assay Range	Curve range: 0.78 ng/mL to 50 ng/mL or 0.04 µg/mL to 2.5 µg/mL in neat plasma	
Material used for quality controls (QCs) and concentration	Olipudase alfa spiked into normal human plasma ULOQ=2500 ng/mL HQC=2000 ng/mL MQC=250 ng/mL LQC=100 ng/mL LLOQ=39 ng/mL	
Minimum required dilutions (MRDs)	50	
Source and lot of reagents	Genzyme, lot# SM0079DP	
Regression model and weighting	4-parameter curve fit, no weighting	
Validation Parameters		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7 (plus 1 anchor point)
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.1% to 1.8%
	Cumulative precision (%CV) from LLOQ to ULOQ	NA
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs	-5.9% to 5.0%
	Interbatch %CV	≤9.3%
	Total error (TE)	≤14.6%
Selectivity and matrix effect	10 individual lots tested at 2 concentrations	2 ng/mL spiked samples - 10/10 recovered with acceptable precision and accuracy. 40 ng/mL spiked samples - 8/10 samples recovered with acceptable precision and accuracy.
Interference and specificity	Lack of detection of the three irrelevant recombinant human enzyme spikes	Acceptable with results <LLOQ
Hemolysis effect	Not Performed	
Lipemic effect	Not Performed	

Method Parameter	Method Information	
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Recombinant Human Acid Sphingomyelinase PK ELISA for the Quantitation of rhASM in Human Plasma Using Rabbit Detection Antibody**	
Dilution linearity and hook effect	A high level of olipudase alfa (10 µg/mL) was independently spiked into pooled normal human plasma three times. Each spiked sample was diluted 1/50 in Sample Dilution Buffer. Nine subsequent serial 2-fold dilutions were performed in Standard Dilution Buffer so that the first two dilutions were above the range of the standard curve and one dilution was below the range of the standard curve.	2 of the 3 samples in serial dilutions resulted in acceptable %Bias and precision for concentrations that fell on the rhASM standard curve with % bias of -15.0% to 3.5% and -18.0% to 7.7% for sample 1 and sample 2, respectively. The third sample did not meet acceptance criteria; bias ranged from -31.5% to -13.4% and failed at 4 concentrations (50, 25, 3.13 and 1.56 ng/mL) within the curve and at the LLOQ (-23.1% bias). Overall data indicated acceptable bias with dilutions up to 12 800. No hook effect observed with concentrations up to 200 ng/mL (10 µg/mL in neat plasma).
Bench-top/process stability	Short-Term Stability: Stable for up to 3 hours at ambient temperature	Acceptable up to 3 hours (% Bias ranged -7.5% to 8.5% for all timepoints)
Freeze-thaw stability	5 F/T cycles evaluated	Stable for up to 5 F/T cycles. % Bias ranged -10.2% to 7.2% for all timepoints (except for HQC Cycle 2F/T = 22.9%)
Long-term storage	Up to 34 months assessed	Stable for up to 34 months at ≤-60°C %Bias ranged -11.0% to 9.8% for all timepoints
Parallelism	Not Performed	
Carryover	Not Applicable	
Method Performance in Trial #DFI12712 (ASCEND) (method used until 01/2020)		
Assay passing rate	97.5% passing rate (116 passed out of 119 total.	
Standard curve performance	Cumulative bias range: -1.37% to 0.62%	
	Cumulative precision: 0.73% to 2.83% CV	
QC performance	Cumulative bias range: -8.69% to 5.64%	
	Cumulative precision: 7.9% to 9.4% CV	
	TE: ≤16.6%	
Method reproducibility	ISR results met the predefined acceptance criteria with an overall pass rate of 96.7%	
Study sample analysis/stability	Long term stability is currently established up to 34 months at ≤-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	
Standard calibration curve performance during accuracy and precision runs	7 standard curve points from LLOQ to ULOQ (plus 1 anchor point).	
Method Performance in Trial #DFI13803 (ASCEND-Peds)		
Assay passing rate	97.2% passing rate (35 passed out of 36 total)	
Standard curve performance	Cumulative bias range: -0.95% to 0.47%	
	Cumulative precision: ≤4.20% CV	

Method Parameter	Method Information
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Recombinant Human Acid Sphingomyelinase PK ELISA for the Quantitation of rhASM in Human Plasma Using Rabbit Detection Antibody**
QC performance	Cumulative bias range: -11.85% to -1.51%
	Cumulative precision: ≤14.8% CV
	TE: ≤21%
Method reproducibility	Incurred sample re-analysis was performed in 11.7% of non-placebo study samples, and 88.6% of the samples met the pre-specified criteria.
Study sample analysis/stability	Long term stability is currently established up to 34 months at ≤-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.
Standard calibration curve performance during accuracy and precision runs	7 standard curve points from LLOQ to ULOQ (plus 1 anchor point)
Method Performance in Trial # LTS13632 (method used until 12/2019)	
Assay passing rate	90.9% passing rate (40 passed out of 44 total)
Standard curve performance	Cumulative bias range: -0.43% to 0.72%
	Cumulative precision: ≤ 3.31% CV
QC performance	Cumulative bias range: -7.91% to 2.15%
	Cumulative precision: ≤ 11.3% CV
	TE: ≤16%
Method reproducibility	Incurred sample reanalysis was not performed in this study.
Study sample analysis/stability	Long term stability is currently established up to 34 months at ≤-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.
Standard calibration curve performance during accuracy and precision runs	7 standard curve points from LLOQ to ULOQ (plus 1 anchor point)

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; LLOQ, lower limit of quantification; QC, quality check; ULOQ, upper limit of quantification

Table 200: Summary Method Performance Validation of a Method for the Determination of Olipudase Alfa in Human Plasma Used in LTS13632 Starting 11/2020, DFI12712 (ASCEND) Starting 11/2020

Method Parameter	Method Information
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Recombinant Human Acid Sphingomyelinase PK ELISA for the Quantitation of rhASM in Human Plasma Using Rabbit Detection Antibody**
Method description	A validated sandwich ELISA using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a purified rabbit polyclonal anti-olipudase alfa antibody for detection.
Materials used for standard calibration curve and concentration	Olipudase alfa reconstituted at 4 mg/mL
Validated Assay Range	Curve range: 39 to 2500 ng/mL (0.039 µg/mL to 2.5 µg/mL) in neat plasma
Material used for quality controls (QCs) and concentration	Olipudase alfa spiked into normal human plasma ULOQ=2500 ng/mL, HQC=1900 ng/mL, MQC=500 ng/mL, LQC=117 ng/mL, LLOQ=39 ng/mL

Method Parameter	Method Information		
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Recombinant Human Acid Sphingomyelinase PK ELISA for the Quantitation of rhASM in Human Plasma Using Rabbit Detection Antibody**		
Minimum required dilutions (MRDs)	50		
Source and lot of reagents	Drug batch number 9W2177		
Regression model and weighting	4-parameter (Marquardt) curve fit, with weighting factor of 1 /Y^2		
Validation Parameters			
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ		9 (plus 2 anchor points)
	Cumulative accuracy (%bias) from LLOQ to ULOQ		-2.3% to 2.5%
	Cumulative precision (%CV) from LLOQ to ULOQ		2.0% to 5.6%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 validation samples		-5.7% to 1.3%
	Inter-batch %CV		7.1% to 12.4%
	Total Error (TE)		≤13.9%
Selectivity and matrix effect	10 individual lots tested at 2 concentrations	39 ng/mL spiked samples: -8/10 recovered with acceptable precision and accuracy. 1900 ng/mL spiked samples: 8/10 samples recovered with acceptable precision and accuracy. (Note: Initially 5/10 samples spiked at 39 ng/mL failed to meet criteria. Five failed samples were retested in triplicate with 3 of the 5 meeting criteria for precision and accuracy.)	
Interference and specificity	Not Performed	N/A	
Hemolysis effect	Hemolytic sample tested at 2 spiked levels (39 and 1900 ng/mL)	Selectivity acceptable for 5% (v/v) hemolysis	
Lipemic effect	Lipemic sample tested at 2 spiked levels (39 and 1900 ng/mL)	Selectivity acceptable in the presence of lipemic human plasma	
Dilution linearity and hook effect	High levels of olipudase alfa (400, 40 and 5 µg/mL) were spiked into pooled normal human plasma and diluted up to 10 000-fold with blank matrix.	Measured results within ±20% relative error (±25% relative error at the LLOQ level) with CV(%) ≤20% between replicates and cumulative precision within 20% for each dilution tested down to 5-fold in blank human plasma. High concentration samples of GZ402665 in human plasma can be diluted within the range of the standard curve up to 10 000-fold with blank human plasma. No hook effect observed with concentrations up to 400 000 ng/mL	
Bench-top/process stability	Short-term stability assessed at ambient temperature at 4^0C	Stable for up to 21 hours at ambient temperature and at 4^0C	
Freeze-thaw stability	5 F/T cycles evaluated	Acceptable up to 5 Freeze/Thaw cycles	

Method Parameter	Method Information	
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Recombinant Human Acid Sphingomyelinase PK ELISA for the Quantitation of rhASM in Human Plasma Using Rabbit Detection Antibody**	
Long-term storage	Up to 34 months assessed	Stable for up to 34 months at ≤-60°C %Bias ranged -11.0% to 9.8% for all timepoints
Parallelism	Not Performed	
Carryover	Not Applicable	
Method Performance in Trial #DFI12712 (ASCEND) (method in use starting 11/2020)		
Assay passing rate	95.2% passing rate (20 passed out of 21 total)	
Standard curve performance	Cumulative bias range: -6.2% to 5.3%	
	Cumulative precision: 2.0% to 6.7% CV	
QC performance	Cumulative bias range: -4.0% to 9.4%	
	Cumulative precision: 6.2% to 8.3% CV	
	TE: ≤17.7%	
Method reproducibility	ISR results met the predefined acceptance criteria with an overall pass rate of 89.1%	
Study sample analysis/stability	Long term stability is currently established up to 34 months at ≤-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	
Standard calibration curve performance during accuracy and precision runs	9 standard curve points from LLOQ to ULOQ (plus 2 anchor points)	
Method Performance in Trial #LTS13632 (method in use starting 11/2020)		
Assay passing rate	85.7% passing rate (12 passed out of 14 total)	
Standard curve performance	Cumulative bias range: -7.6% to 8.7%	
	Cumulative precision: 1.8% to 7.8% CV	
QC performance	Cumulative bias range: -3.5% to 8.5%	
	Cumulative precision: 6.9% to 7.9% CV	
	TE: ≤16.1%	
Method reproducibility	ISR results met the predefined acceptance criteria with an overall pass rate of 92.9%	
Study sample analysis/stability	Long term stability is currently established up to 34 months at ≤-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	
Standard calibration curve performance during accuracy and precision runs	9 standard curve points from LLOQ to ULOQ (plus 2 anchor points)	

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; LLOQ, lower limit of quantification; QC, quality check; ULOQ, upper limit of quantification

Table 201: Summary Method Performance Validation of a Method for the Determination of Olipudase Alfa in Human Plasma Used in Phase 1a and Phase 1b Studies

Method Parameter	**Method Information**		
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Acid Sphingomyelinase PK Quantitation Immunoassay**		
Method description	A validated sandwich ELISA using a purified mouse anti-olipudase alfa monoclonal antibody (clone 1H7) as capture and a second non-competing purified mouse monoclonal anti-olipudase alfa monoclonal antibody (4G11) for detection		
Materials used for standard calibration curve and concentration	Olipudase alfa reconstituted at 4 mg/mL		
Validated Assay Range	Curve range: 2.5 ng/mL to 50 ng/mL or 0.125 µg/mL to 2.5 µg/mL in neat plasma		
Material used for quality controls (QCs) and concentration	Olipudase alfa spiked into normal human plasma at 750 ng/mL, 375 ng/mL, 187.5 ng/mL, 93.8 ng/mL, and 46.9 ng/mL (VS) and 20, 10, and 2.5 ng/mL (QCs		
Minimum required dilutions (MRDs)	50		
Source and lot of reagents	Genzyme, lot# SM0076DP		
Regression model and weighting	4-parameter curve fit, no weighting		
Validation Parameters			
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ		6 (plus 2 anchor points)
	Cumulative accuracy (%bias) from LLOQ to ULOQ		Curve data not shown in report
	Cumulative precision (%CV) from LLOQ to ULOQ		Curve data not shown in report
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 validation samples		-15% to 16%
	Inter-batch %CV		≤16.3%
	Total Error (TE)		≤30.3%
Selectivity and matrix effect	3 plasma lots tested by 2 operators at multiple concentrations (starting at 2500 ng/mL and serially diluted 1/2 in matching human plasma for a total of seven additional points to 19.5 ng/mL).		Percent recovery for values in reportable range: 83.4% to 109.7% for all but one point at the ULOQ for 1 pool by 1 operator (acceptable recovery for the second operator)
Interference and specificity	Lack of detection of three irrelevant recombinant human enzyme spikes	Acceptable with results <LLOQ	
Hemolysis effect	Not performed	N/A	
Lipemic effect	Not Performed	N/A	

Method Parameter	Method Information	
Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation Report: Acid Sphingomyelinase PK Quantitation Immunoassay**	
Dilution linearity and hook effect	Three normal human plasma samples were spiked with 20 µg/mL of olipudase. Each sample was diluted 1/50 in Sample Dilution Buffer (SDB) and twelve serial ½ dilutions were made in SDB for each spiked sample.	% Recovery of slope: 94.6%-98.1%. All recover within 10% of the slope of the standard curve and meet acceptance criteria. Supports dilution up to at least 6400. Percent recovery of samples diluted in parallel demonstrates acceptable recovery with dilution up to 2500. No hook observed up to 8 x above ULOQ
Bench-top/process stability	Short-term stability	Stable for up to 4 hours at ambient temperature (%Bias ranged -11.8% to 17.1% for all timepoints)
Freeze-thaw stability	5 F/T cycles evaluated	Stable for up to 5 F/T cycles. % Bias ranged -13.9% to 17.7% from nominal for all timepoints. 3 data points exceeded 20% bias (1 and 2 F/T for VS3 and 5F/T for VS1)
Long-term storage	up to 26 months assessed	Stable for up to 26 months at ≤ -60°C % Bias ranged -8.2% to 19.1% from nominal for all timepoints (for samples >LLOQ)
Parallelism	Not Performed	
Carryover	Not Applicable	
Method Performance in Trial # #SPHINGO-006-05		
Assay passing rate	63.2% passing rate (12 passed out of 19 total)	
Standard curve performance	Cumulative bias range: -1.23% to 1.25%	
	Cumulative precision: 2.86% to 5.08% CV	
QC performance	Cumulative bias range: -8.47% to -7.88%	
	Cumulative precision: 6.22% to 6.92% CV	
	TE: ≤14.8%	
Method reproducibility	Incurred sample re-analysis was not performed.	
Study sample analysis/stability	Long term stability is currently established up to 34 months at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	
Standard calibration curve performance during accuracy and precision runs	4 standard curve points from LLOQ (3.13 ng/mL) to ULOQ (25.0 ng/mL) (plus 4 anchor points)	

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; LLOQ, lower limit of quantification; QC, quality check; ULOQ, upper limit of quantification

Pharmacodynamic Biomarker

Ceramide

Total ceramide in plasma was quantified using liquid-liquid and solid-phase extraction procedures followed by liquid chromatography with tandem mass spectrometry (LC/MS/MS) with multiple reaction monitoring (5.3.1.4 [ITR-377-1207], [BMV0028]). Summary of life cycle information of assay methods used during development, assay validation parameters, and performance of assays used in clinical trials are provided in Table 202 and Table 203.

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Table 202: Bioanalytical Method Life-Cycle Information- Ceramide

Variable	Method Validation	Phase 1b Study DFI13412	Long-Term Safety Study LTS13632	Pediatric Study DFI13803 (ASCEND-Peds)	Adult Pivotal Study DFI12712 (ASCEND)
Analyte	Ceramide	Ceramide	Ceramide	Ceramide	Ceramide
Validation type	Full validation	In-study	In-study	In-study	In-study
CTD reference #	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4
Method ID	**ITR-377-1207/ BMV0028**	**ITR-377-1207**	**ITR-377-1207/ BMV0028**	**ITR-377-1207/ BMV0028**	**ITR-377-1207/ BMV0028**
Duration of time method is in use	01/2008- present	05/2013-01/2014	05/2014-present	09/2015-12/2019	08/2016-present
Bioanalytical site	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)				
Matrix	Heparin Plasma				
Platform	LC/MS/MS assay				
Format	Validated assay for quantification of total ceramide levels using liquid-liquid and solid-phase extraction procedures followed by liquid chromatography with tandem mass spectrometry (LC/MS/MS) with multiple-reaction monitoring.				
Stock reference, lot number, expiration date	Lot# BCER-23, expiration 6 months from date of receipt (received on multiple occasions)/ Lot# BCER-27 exp. 27Apr2022 (expiry extended to 6 years from receipt)	860052P Lot# BCER-25, expiration 6 months from date of receipt	Lot# BCER-26, expiration 6 months from date of receipt Lot# BCER-27 exp. 27Apr2022	Lot# BCER-25, expiration 6 months from date of receipt Lot# BCER-26, expiration 6 months from date of receipt Lot# BCER-27 exp. 27Apr2022	Lot# BCER-27 exp. 27Apr2022
Calibration range from the LLOQ to the ULOQ	1-32 µg/mL	1-32 µg/mL	1-32 µg/mL	1-32 µg/mL	1-32 µg/mL
Matrix study population	Normal Plasma	ASMD Population	ASMD Population	ASMD Population	ASMD Population

(b) (4)

Variable	Method Validation	Phase 1b Study DFI13412	Long-Term Safety	Pediatric Study	Adult Pivotal Study
Relevant reference and applicable report amendment	[ITR-377-1207] and [BMV0028]	[DFI13412]	[LTS13632]	[DFI13803 ASCEND-Peds]	[DFI12712 ASCEND-interim2]
Synopsis of amendment history	Amendment 1 of ITR-377- 1207 corrects errors, provides overall precision and bias calculations, and clarifies the interpretation of the stability data. BMV0028 captures the revalidation of the method using the API4000 mass spectrometer with the inclusion of the C16:0 isomer in calculation of total CER. In addition, a human QC with endogenous CER is added and stability for endogenous CER determined.	N/A	Amendment 1 adds data from additional runs performed between database lock 1 and database lock 2	Amendment 1 corrects errors and adds a calculation of total error for QCs	Amendment 1 adds data from additional runs performed between database lock 1 and database lock 2

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: ASMD, acid sphingomyelinase deficiency; LLOQ, lower limit of quantification; QC, quality check; ULOQ, upper limit of quantification

Table 203: Summary Method Performance Validation of a Method for the Determination of Ceramide in Human Plasma used in DFI13803 (ASCEND-Peds), LTS13632 through 12/2019, DFI12712 (ASCEND) Through 01/2020)

Method Parameter	Method Information		
Bioanalytical method validation report name, amendments, and hyperlinks	**Validation Report ITR-377-1207: Quantitation of Total Ceramide in Human Plasma by LC/MS/MS**		
Method description	A validated assay to detect ceramide in human plasma by LC/MS/MS. Liquid-Liquid extraction, then solid phase extraction (SPE) followed by liquid chromatography with tandem mass spectrometry (LC/MS/MS) detection with electrospray ionization.		
Materials used for standard calibration curve and concentration	Porcine brain ceramide, (b) (4) Spiking solution prepared at 10 µg/mL in 2:1 (volume/volume) chloroform/ methanol		
Validated Assay Range	1.0-32 µg/mL		
Material used for quality controls (QCs) and concentration	Plasma samples spiked with porcine ceramide LLOQ: 1 µg/mL Low: 2 µg/mL Mid: 8 µg/mL High: 24 µg/mL		
Minimum required dilutions (MRDs)	N/A		
Source and lot of reagents	Brain Porcine Ceramide: (b) (4), Lot#BCER-23 Internal Standard (IS): C19-D-erythro-Ceramide: (b) (4)		
Regression model and weighting	Linear regression with 1/X weighting		
Validation Parameters			
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ		7
	Cumulative accuracy (%bias) from LLOQ to ULOQ		-4.5% to 2.3%
	Cumulative precision (%CV) from LLOQ to ULOQ		3.2% to 7.6%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs		1.6% to 5.8%
	Cumulative accuracy (%bias) at LLOQ (1µg/mL)		-3.67%
	Interbatch %CV in 3 QC		5.1% to 11.4%
	Total error (TE) in 3 QC		6.7% to 17.2%
	LLOQ		19.76%
Selectivity and matrix effect	Porcine ceramide spiked into plasma compared to porcine ceramide spiked into 80% methanol/20% water/ 0.1% formic acid	% difference of curve slopes <15%. %bias of QCs <15%. No significant difference in QC values (p>0.05). Matrix effect not significant.	
Interference and specificity	Parent ion scanning showed similar profiles in 10 donor samples spiked and unspiked with porcine, ceramide Human plasma with 8 µg/mL ceramide spiked with low (20 µg/mL) and high (600 µg/mL) of bilirubin	Assay specific for ceramide monitoring No interference effect from bilirubin was observed	
Hemolysis effect	Human plasma with 8 µg/mL ceramide spiked with low (6 µg/mL) and high (100 µg/mL) of hemoglobin	No interference effect from hemoglobin was observed	
Lipemic effect	Human plasma with 8 µg/mL ceramide spiked with low (0.67 mg/mL) and high (10 mg/mL) of intralipid	No interference effect from lipids was observed	

Method Parameter	Method Information	
Bioanalytical method validation report name, amendments, and hyperlinks	**Validation Report ITR-377-1207: Quantitation of Total Ceramide in Human Plasma by LC/MS/MS**	
Dilution linearity and hook effect	Samples prepared at 5, 10, 20, 40, 80 and 160 µg/mL and tested in triplicate.	Samples dilution linearity demonstrated from 5 to 160 µg/mL Hook effect N-/A
Bench-top/process stability	Stability of porcine ceramide spiked into human plasma evaluated at 2-8°C Stability at ambient not performed Processed sample stability assessed after extraction	Samples are stable up to 5 days at 2-8°C. Extracted samples stable after storage at 2-8°C for up to 3 days
Freeze-thaw stability	5 F/T cycles evaluated porcine ceramide spiked into human plasma	Acceptable for up to 5 Freeze/Thaw cycles
Long-term storage	Assessed for up to 2.5 years	Samples spiked with 24 µg/mL porcine ceramide were stable up to 2.5 years at -20°C and -80°C. Samples spiked with 2 µg/mL porcine ceramide were stable up to 3 weeks at -20°C and for 1 month at -80°C
Parallelism	Not Performed	
Carryover	Not Performed	
Method description	A validated assay to detect ceramide in human plasma by LC/MS/MS. Liquid-liquid extraction, then solid phase extraction (SPE) followed by liquid chromatography with tandem mass spectrometry (LC/MS/MS) detection with electrospray ionization.	
Materials used for standard calibration curve and concentration	Porcine brain ceramide, (b) (4) Spiking solution prepared at 10 µg/mL in 2:1 (volume/volume) chloroform/ methanol	
Validated Assay Range	1.0-32 µg/mL	
Material used for quality controls (QCs) and concentration	Plasma samples spiked with porcine ceramide LLOQ: 1 µg/mL Low: 3 µg/mL Mid: 10 µg/mL High: 25 µg/mL	
Minimum required dilutions (MRDs)	N/A	
Source and lot of reagents	Brain Porcine Ceramide: (b) (4) Lot#BCER-23 Internal Standard (IS): C19-D-erythro-Ceramide: (b) (4)	
Regression model and weighting	Linear regression with 1/X weighting	
Validation Parameters		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.6% to 8.8%
	Cumulative accuracy (%CV) from LLOQ to ULOQ, API-4000	-7.1% to 4.4%
	Cumulative precision (%CV) from LLOQ to ULOQ, Premier	1.5% to 9.1%
	Cumulative precision (%CV) from LLOQ to ULOQ, API-4000	4.0% to 7.4%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	-2.7% to 7.0%
	Cumulative accuracy (%bias) in 4 QC, AOI-400 LLOQ	-7.7% to 3.0%
	Interbatch %CV in 4 QC	4.5% to 13.8%
	Inter-batch %CV in 4 QC, API-4000	5.1% to 15.2%

Method Parameter	Method Information	
Bioanalytical method validation report name, amendments, and hyperlinks	**Validation Report ITR-377-1207: Quantitation of Total Ceramide in Human Plasma by LC/MS/MS**	
	Total error (TE), Premier	≤14.3%
	Total error (TE), API-4000	≤22.9%
Selectivity and matrix effect	Nor performed	N/A
Interference and specificity	Nor performed	N/A.
Hemolysis effect	Nor performed	N/A.
Lipemic effect	Nor performed	N/A.
Dilution linearity and hook effect	Nor performed	N/A.
Bench-top/process stability	Evaluated at ambient temperature and 2-8°C using pooled human plasma with endogenous ceramide Processed sample stability assessed after extraction.	Samples are stable up to 65 hours at ambient temperature; up to 72 hours at 2-8°C. Reconstituted extracted samples are stable for at least 74 h at 2-8ºC. Reconstituted extracted samples are stable for at least 74 hr at 2-8ºC plus 7 days at ≤-14ºC. Dried extracted samples are stable for at least 7 days at ≤-60ºC.
Freeze-thaw stability	5 F/T cycles evaluated using pooled human plasma with endogenous ceramide	Acceptable for up to 5 Freeze/Thaw cycles
Long-term storage	Assessed for up to 752 days using pooled human plasma with endogenous ceramide	Acceptable up to 752 days at ≤-60°C
Parallelism	Not Performed	
Carryover	The carryover impact to LLOQ was evaluated by injecting methanol (MeOH) solvent after STD8 (32 µg/mL)	The mean carryover impact was 3.7 % for CER and 0.1% for C19:0-Ceramide.
Method Performance in Trial #DFI12712 (ASCEND) (CER)		
Assay passing rate	92% passing rate (22 passed out of 24 total)	
Standard curve performance	Cumulative bias range: -2.3% to 1.9%	
	Cumulative precision: 3.4% to 13.0% CV	
QC performance	Cumulative bias range: -7.0% to 3.3%	
	Cumulative precision: 5.8% to 30.8% CV	
	TE: ≤37.8%	
Method reproducibility	Incurred sample reanalysis was not performed in this study.	
Study sample analysis/stability	Long term stability of endogenous ceramide in human plasma is currently established up to 752 days at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability	
Standard calibration curve performance during accuracy and precision runs	7 standard curve points from LLOQ to ULOQ	
Method Performance in Trial #DFI13803 (ASCEND-Peds) (CER)		
Assay passing rate	70% passing rate (68 passed out of 97 total)	
Standard curve performance	Cumulative bias range: -1.9% to 2.0%	
	Cumulative precision: 3.1% to 8.8% CV	

Method Parameter	Method Information
Bioanalytical method validation report name, amendments, and hyperlinks	**Validation Report ITR-377-1207: Quantitation of Total Ceramide in Human Plasma by LC/MS/MS**
QC performance	Cumulative bias range: -2.7% to 3.3%
	Cumulative precision: 5.9% to 15.5% CV
	TE: ≤18.8%
Method reproducibility	Incurred sample reanalysis was not performed in this study.
Study sample analysis/stability	Long term stability of endogenous ceramide in human plasma is currently established up to 752 days at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability
Standard calibration curve performance during accuracy and precision runs	7/8 standard curve points from LLOQ to ULOQ
Method Performance in Trial # LTS13632 (CER)	
Assay passing rate	69.0% passing rate (49 passed out of 71 total)
Standard curve performance	Cumulative bias range: -1.3% to 0.6%
	Cumulative precision: 4.2% to 9.2% CV
QC performance	Cumulative bias range: -2.9% to 2.7%
	Cumulative precision: 5.1% to 12.8% CV
	TE: ≤14.3%
Method reproducibility	Incurred sample reanalysis was not performed in this study.
Study sample analysis/stability	Long term stability of endogenous ceramide in human plasma is currently established up to 752 days at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability
Standard calibration curve performance during accuracy and precision runs	7/8 standard curve points from LLOQ to ULOQ

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Lyso-SPM

Lyso-SPM in human plasma was quantified using protein precipitation and filtration followed by LC/MS/MS with multiple-reaction monitoring (5.3.1.4 [ITR-731-1014]). Summary of life cycle information of assay methods used during development, assay validation parameters, and performance of assays used in clinical trials are provided in Table 204 and Table 205.

Table 204: Bioanalytical Method Life-Cycle Information- Lyso-SPM

Variable	Method Validation	Phase 1b study DFI13412 (SPHINGO-008-12)	Long-Term Safety Study LTS13632	Pediatric Study DFI13803 (ASCEND-Peds)	Adult Pivotal Study DFI12712 (ASCEND)
Analyte	Lyso Sphingomyelin (Sphingosylphosphorylcholine)				
Validation type	Full validation	In-study (retrospective)	In-study	In-study	In-study
CTD reference #	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4
Method ID	**ITR-731-1014**	**ITR-731-1014**	**ITR-731-1014**	**ITR-731-1014**	**ITR-731-1014**
Duration of time method is in use	11/2014-present	09/2016-10/2016	03/2015-present	10/2015-12/2019	08/2016-present
Bioanalytical site	Sanofi US, Biomarkers and Clinical Bioanalyses-Boston, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)				
Matrix	Heparin Plasma				
Platform	LC/MS/MS assay				
Format	Validated assay to quantify Lyso-SPM in plasma using protein precipitation and filtration followed by LC/MS/MS with multiple-reaction monitoring.				
Stock reference, lot number, expiration date	[redacted] (b) (4)				Lot#24175, exp. 09Jun2021
	Lot#23846, exp. 23Oct2019; Lot#24175, exp. 09Jun2021 [redacted] (b) (4) Lot#24175, exp. 09Jun2021	Lot#23846, exp. 23Oct2019; Lot#24175, exp. 09Jun2021	Lot#23846, exp. 23Oct2019; Lot#24175, exp. 09Jun2021	Lot#23846, exp. 23Oct2019;	
	[redacted] (b) (4) stock used to prepare dry vials at 20 µg and 100 µg with an additional 4 years stability				
Calibration range from the lower limit of quantitation (LLOQ) to the upper limit of quantitation (ULOQ)	10-1000 ng/mL	10-1000 ng/mL	10-1000 ng/mL	10-1000 ng/mL	10-1000 ng/mL

Variable	Method Validation	Phase 1b study DFI13412 (SPHINGO-008-12)	Long-Term Safety Study LTS13632	Pediatric Study DFI13803 (ASCEND-Peds)	Adult Pivotal Study DFI12712 (ASCEND)
Matrix study population	Normal Plasma	ASMD Population	ASMD Population	ASMD Population	ASMD Population
Relevant reference and applicable report amendment	5.3.1.4 [ITR-731-1014]	Retrospective analysis; no phase report prepared	5.3.5.2 [LTS13632]	5.3.5.2 [DFI13803]	5.3.5.1 [DFI12712-interim2]
Synopsis of amendment history	Add additional long-term stability data for lyso-SPM stock solution and dried vials and Lyso-SPM in plasma.	N/A	Amendment 1 adds data from additional runs performed between database lock 1 and database lock 2	N/A	Amendment 1 adds data from additional runs performed between database lock 1 and database lock 2

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 205: Summary Method Performance Validation of a Method for the Determination of Lyso-SPM in Human Plasma Used in DFI13803 (ASCEND-Peds), LTS13632 Through 12/2019, DFI12712 (ASCEND) Through 01/2020)

Method Parameter	Method Information		
Bioanalytical method validation report name, amendments, and hyperlinks	**Validation Report: Quantitation of Lyso Sphingomyelin (Lyso-SPM) in Human Plasma by LC/MS/MS**		
Method description	A validated assay to quantify Lyso-SPM in plasma using protein precipitation and filtration followed by LC/MS/MS with multiple-reaction monitoring		
Materials used for standard calibration curve and concentration	Delipidized plasma spiked with lyso-SPM at 10, 20, 50, 150, 300, 500, 800, 1000 ng/mL		
Validated assay range	10.0-1000 ng/mL		
Material used for quality controls (QCs) and concentration	Plasma samples spiked with porcine ceramide LLOQ: 1 µg/mL Low: 2 µg/mL Mid: 8 µg/mL High: 24 µg/mL		
Minimum required dilutions (MRDs)	N/A		
Source and lot of reagents	Sphingosylphosphorylcholine, (b) (4) Lot#23846 and 24175 (for Amendment 1) Internal Standard (IS): D-9 Lyso SPM: (b) (4) (b) (4)		
Regression model and weighting	Linear regression with 1/X weighting		
Validation Parameters			
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ		8
	Cumulative accuracy (%bias) from LLOQ to ULOQ		-1.8% to 3.8%
	Cumulative precision (%CV) from LLOQ to ULOQ		0.8% to 3.0%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs		-2.8% to 1.0%
	Interbatch %CV in 5 QC		2.7% to 5.1%
	Total error (TE)		≤ 7.9%
Selectivity and matrix effect	Heparin plasma from 6 donors were spiked with lyso- SPM at 30 and 750 ng/mL and tested in triplicate	No matrix effect was observed. Accuracy (%bias) was 1.3% to 10.4%. Precision (%CV) was 0.6% to 3.5%.	
Interference and specificity	Delipidized plasma prepared at the LQC and HQC levels with Lyso-SPM were spiked with 0.600 mg/mL bilirubin	% difference from unspiked was within ±15%. No interference effect was observed with bilirubin	
Hemolysis effect	Delipidized plasma prepared at the LQC and HQC levels with Lyso-SPM were spiked with 10 mg/mL hemoglobin	% difference from unspiked was within ±15%. No interference effect was observed with hemoglobin	
Lipemic effect	Delipidized plasma prepared at the LQC and HQC levels with Lyso-SPM were spiked with 10 mg/mL intralipid	% difference from unspiked was within ±15%. No interference effect was observed with intralipid	
Dilution linearity and hook effect	Human plasma was spiked with 1500 ng/mL lysoSPM and diluted 2X and 5X with normal human plasma (endogenous levels <LLOQ)	Dilution integrity was acceptable at factor 2x and factor 5x. Hook effect - not applicable	

Method Parameter	Method Information	
Bioanalytical method validation report name, amendments, and hyperlinks	**Validation Report: Quantitation of Lyso Sphingomyelin (Lyso-SPM) in Human Plasma by LC/MS/MS**	
Bench-top/process stability	Sample stability assessed at ambient temperature and 2-8°C. Processed sample stability assessed for reinjection stability and reinjection reproducibility	Samples are stable up to 24 hours at ambient temperature; up to 5 days at 2-8°C Reinjection Stability: stable up to 72 hours at 2°C to 8°C Reinjection Reproducibility: stable up to 3 days at 2°C to 8°C
Freeze-thaw stability	5 F/T cycles evaluated	Samples are stable for 5 freeze-thaw cycles at both -20°C and -80°C.
Long-term storage	Assessed up to 69 months for spiked QCs and 38 months at -80°C for incurred samples	Spiked samples are stable for up to 69 months at -80°C, incurred samples are stable for up to 38 months at -80°C.
Parallelism	Not Performed	
Carryover	Evaluated by injecting solvent after the highest calibration standard.	Overall % carryover was 0.1% and IS % carryover was 0.0%. Both analyte and IS carryover were acceptable.
Method Performance in Trial # DFI12712 (ASCEND) (Lyso-SPM)		
Assay passing rate	98.2%% passing rate (55 passed out of 56 total)	
Standard curve performance	Cumulative bias range: -3.7% to 2.2%	
	Cumulative precision: 1.7% to 3.9% CV	
QC performance	Cumulative bias range: -2.0% to 2.7%	
	Cumulative precision: 5.1% to 9.0% CV	
	TE: ≤11.7%	
Method reproducibility	Incurred sample reanalysis was not performed in this study.	
Study sample analysis/stability	Long term stability is currently established up to 38 months at <-80°C for endogenous samples and 69 months for QCs. All standards, QCs and samples tested in this assay were analyzed within established stability.	
Standard calibration curve performance during accuracy and precision runs	8 standard curve points from LLOQ to ULOQ	
Method Performance in Trial # DFI13803 ASCEND-Peds (Lyso-SPM)		
Assay passing rate	95% passing rate (37 passed out of 39 total)	
Standard curve performance	Cumulative bias range: -3.7% to 1.6%	
	Cumulative precision: 1.4% to 3.4% CV	
QC performance	Cumulative bias range: -2.0% to 5.7%	
	Cumulative precision: 4.7% to 7.4% CV	
	TE: ≤13.1%	
Method reproducibility	Incurred sample reanalysis was not performed in this study.	
Study sample analysis/stability	Long term stability is currently established up to 38 months at <-80°C for endogenous samples and 69 months for QCs. All standards, QCs and samples tested in this assay were analyzed within established stability.	
Standard calibration curve performance during accuracy and precision runs	8 standard curve points from LLOQ to ULOQ	

Method Parameter	Method Information
Bioanalytical method validation report name, amendments, and hyperlinks	**Validation Report: Quantitation of Lyso Sphingomyelin (Lyso-SPM) in Human Plasma by LC/MS/MS**
Method Performance in Trial #LTS13632 (Lyso-SPM)	
Assay passing rate	100% passing rate (29 passed out of 29 total)
Standard curve performance	Cumulative bias range: -3.0% to 2.0%
	Cumulative precision: 1.4% to 5.0% CV
QC performance	Cumulative bias range: -1.2% to 4.3%
	Cumulative precision: 5.0% to 7.4% CV
	TE: ≤11.7%
Method reproducibility	Incurred sample reanalysis was not performed in this study.
Study sample analysis/stability	Long term stability is currently established up to 38 months at <-80°C for endogenous samples and 69 months for QCs. All standards, QCs and samples tested in this assay were analyzed within established stability.
Standard calibration curve performance during accuracy and precision runs	8 standard curve points from LLOQ to ULOQ

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods

15. Trial Design: Additional Information and Assessment

Not applicable

16. Efficacy: Additional Information and Assessment

Figure 118, Figure 119, and Figure 120 show the individual changes from baseline at Week 52 for the three components of the primary endpoints.

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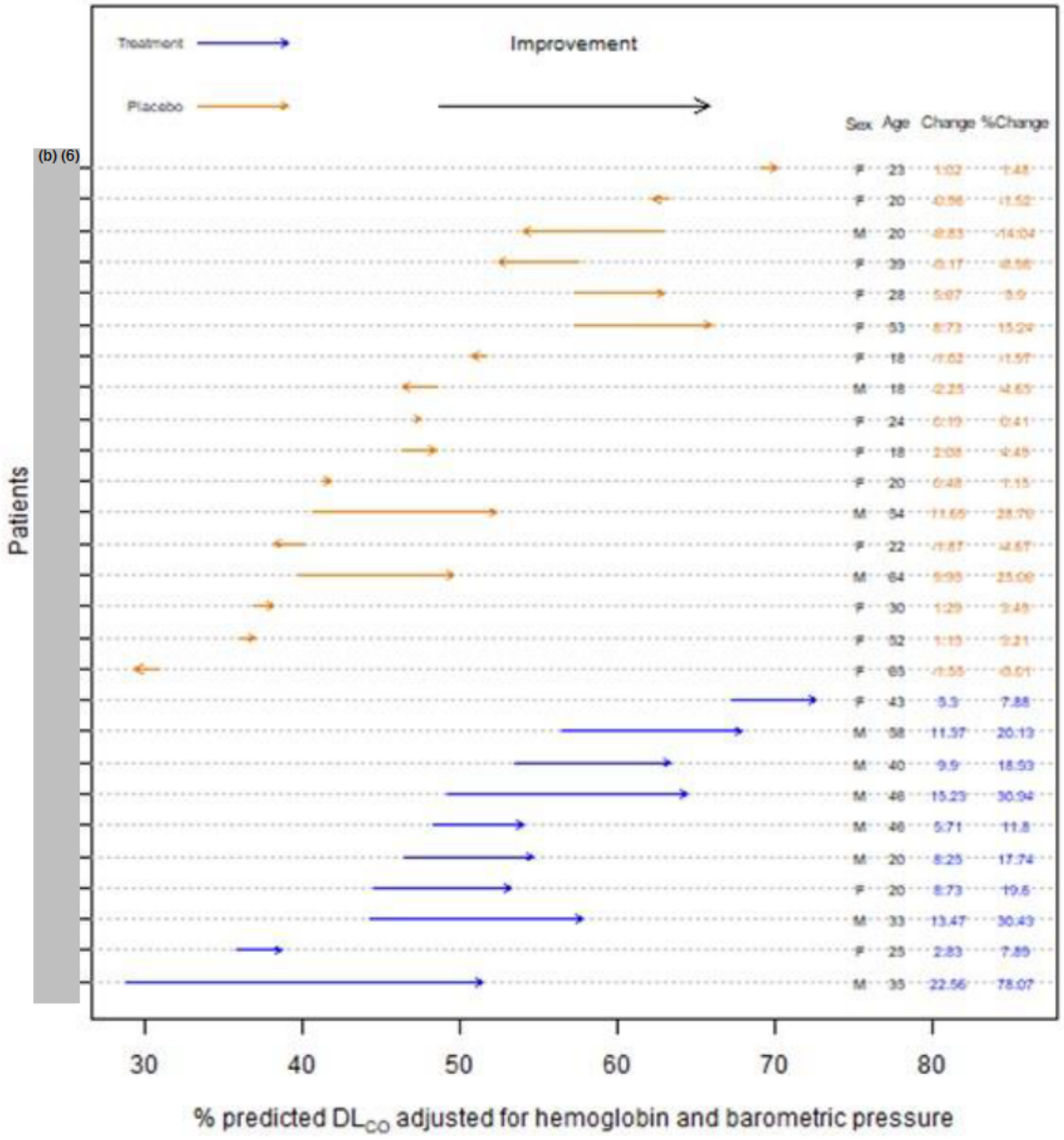
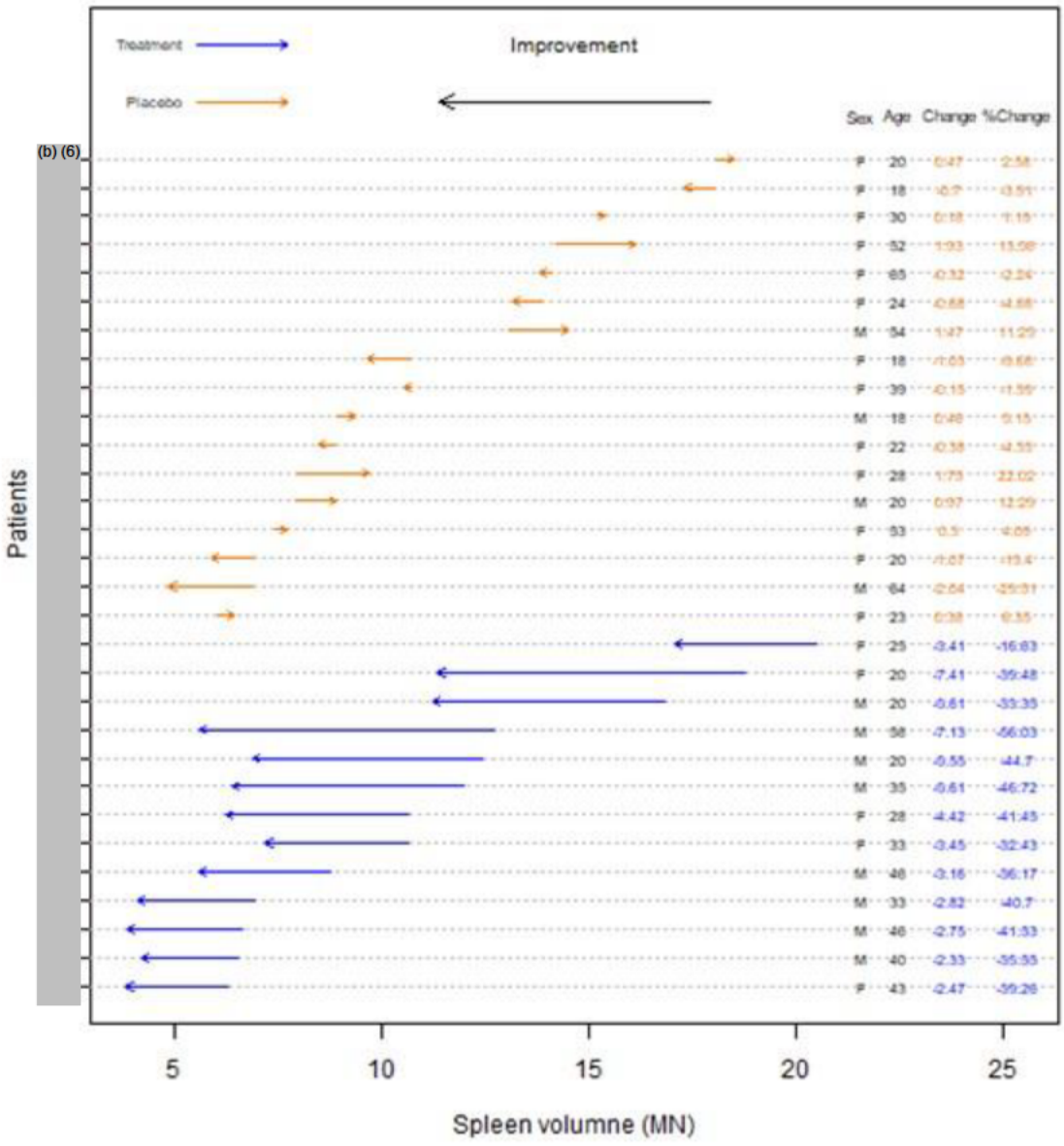
Figure 118. Individual Changes in % Predicted DL_{CO} at Week 52 Among mITT Population, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: DL_{CO}, diffusion capacity for carbon monoxide; F, female; M, male; mITT, modified intent to treat.

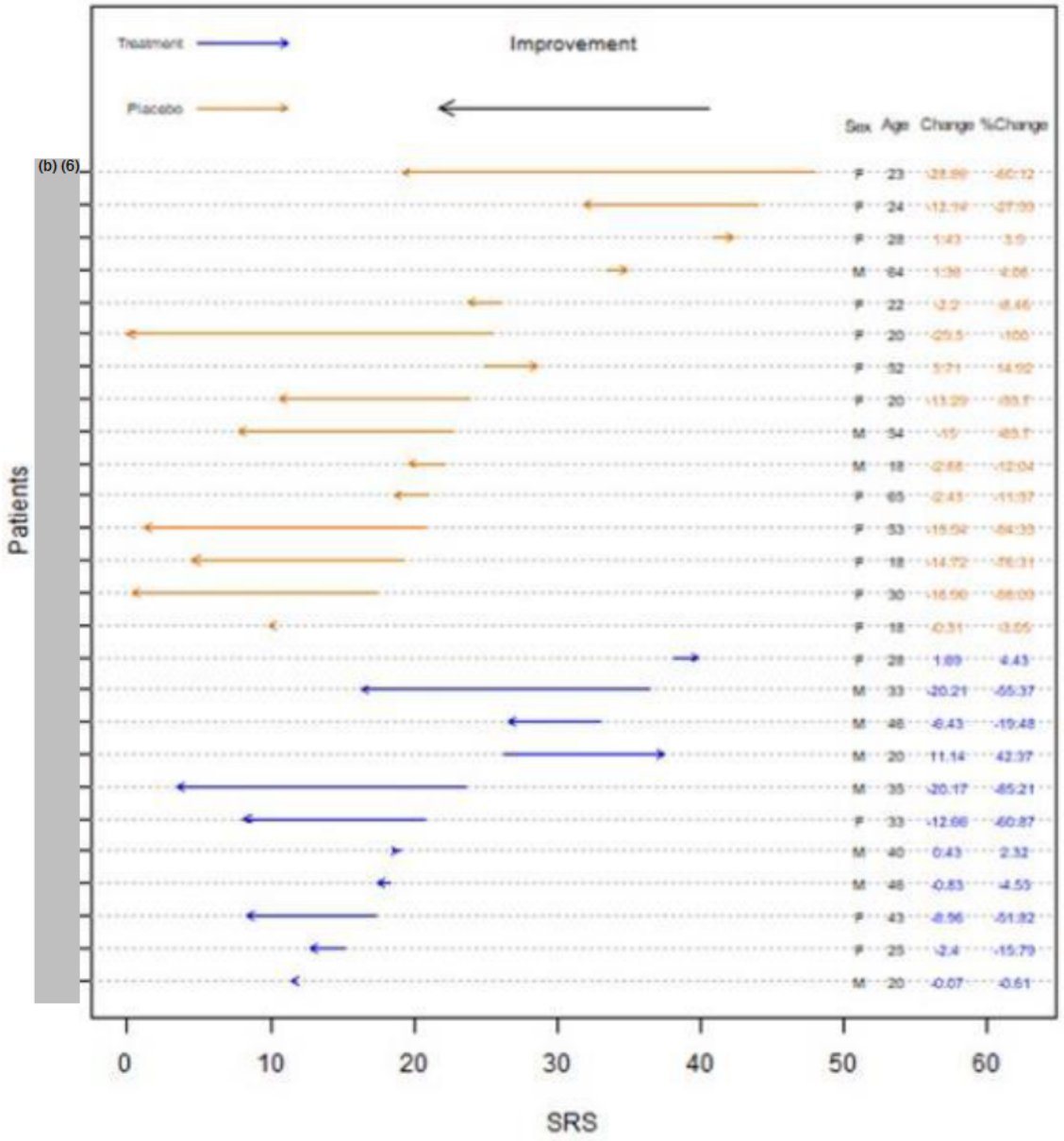
Table 206 provides the crosswalk between the subject number listed above and the trial subject ID.

Figure 119. Individual Changes in Spleen Volume (MN) at Week 52 Among mITT Population, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the admo.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: F, female; M, male; mITT, modified intent to treat; MN, multiples of normal.

Figure 120. Individual Changes in SRS at Week 52 Among mITT Population, DFI12712 (ASCEND)



Source: This figure was produced by the review team based on the adqs.xpt dataset located at \\CDSESUB1\evsprod\BLA761261\0002\m5\datasets\dfi12712\analysis\adam\datasets.
Abbreviations: F, female; M, male; mITT, modified intent to treat; SRS, splenomegaly-related score.

Table 206. Crosswalk Between Subject Number and ID for mITT Population, DFI12712 (ASCEND)

Subject Number	Subject ID
1	012712-(b) (6)
2	012712-
3	012712-
4	012712-
5	012712-
6	012712-
7	012712-
8	012712-
9	012712-
10	012712-
11	012712-
12	012712-
13	012712-
14	012712-
15	012712-
16	012712-
17	012712-
18	012712-
19	012712-
20	012712-
21	012712-
22	012712-
23	012712-
24	012712-
25	012712-
26	012712-
27	012712-
28	012712-
29	012712-
30	012712-
31	012712-

Source: This figure was produced by the review team.
Abbreviations: mITT, modified intent to treat

17. Clinical Safety: Additional Information and Assessment

17.1. Adverse Events of Special Interest

For safety assessment, AEs of special interest included IARs, laboratory values meeting prespecified criteria (i.e., dose limiting toxicities (DLTs)), pregnancy, and symptomatic overdose were evaluated. The Applicant's definitions for IARs and DLTs are described as below.

17.1.1. Infusion-Associated Reactions (IARs)

Protocol-defined IARs: AEs that occurred during the infusion or within up to 24 hours after the start of the infusion that were considered related or possibly related to study treatment, as judged by the Investigator. Subsets of protocol-defined IARs were defined as follows:

- **Hypersensitivity-Related IARs**: Hypersensitivity using the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries of Hypersensitivity (board and narrow)
- **Anaphylactic reaction IARs**: Anaphylactic reaction events were identified based on the algorithmic approach defined in the Introductory Guide for Standardized MedDRA Queries (1). Specifically, all anaphylactic reactions as per the narrow search preferred terms (PT) terms were included. Any combination of PT terms from Categories B (upper airway/respiratory) and C (angioedema/urticaria/pruritus/flush), Categories B and D (cardiovascular/hypotension), or Categories C and D, that happened within 24 hours of each other, were also included. Maximum combinations were used and symptoms within one combination were counted as one event
- **Acute phase reactions (APRs)**
  - **Investigator identified APRs**: Identified by investigators based on a composite of clinical symptoms (reported as AEs) and laboratory values that occurred within 72 hours to the closest infusion.
  - **Algorithm identified APRs**: Identified by a three-criteria algorithm that was developed to systematically screen for potential APRs independent of investigator determination. All three criteria had to be met at the same visit during the initial dose escalation period. The Applicant defined the initial dose escalation period as the time from the first infusion to when the first 3 mg/kg infusion was received; or if a patient never reached 3 mg/kg, then period was defined as from the first infusion to the first time the patient maintained the maximum tolerated dose consecutively for six visits.
    - At least one of the following clinical symptoms reported as an AE
      - Headache
      - Pyrexia
      - Relevant PTs from GI disorder system organ classes, inflammatory terms of Musculoskeletal and connective tissue disorders system organ classes from the 3 following high level terms: muscle pains, joint related signs and symptoms, and musculoskeletal and connective tissue pain and discomfort.
    - High sensitivity CRP >=3xULN
    - At least one other abnormal laboratory value defined as:
      - Adult: ferritin > ULN and serum iron < lower limit of normal, or calcitonin > ULN, or IL-6>ULN
      - Pediatrics: ferritin > ULN, or calcitonin > ULN, or IL-6>ULN
- **Cytokine release syndrome (CRS)**
  - **Investigator identified CRS**: Identified by investigators based on a composite of clinical symptoms (reported as AEs) and laboratory values that occurred within 72 hours of an infusion.

- **Algorithm identified CRS**: Identified by a two-criteria algorithm that was developed to systemically screen for potential CRS episodes independent of investigator determination. Both criteria had to be met at the same visit during the initial dose escalation period.
  - At least one clinical symptom reported as an AE
    - Pyrexia
    - Relevant PT from GI disorders system organ class
    - Non-cardiogenic pulmonary edema
    - Hypotension
    - Hypertension
    - Inflammatory terms from the three following high level terms: muscle pains, joint related signs and symptoms, and musculoskeletal and connective tissue pain and discomfort
  - Elevations in both biomarkers
    - High-sensitivity CRP >=3 ULN
    - IL-6>ULN

17.1.2. Dose-Limiting Toxicities

The definition of quantifiable DLTs evolved during the clinical development program of olipudase alfa and were identified as described below.

- **DLT 1**: Any increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, or ALP >3x baseline (prior to olipudase alfa therapy) and > ULN
- **DLT 2**: Any increase in total bilirubin or ALP >1.5 x baseline in the presence of AST or ALT >2 ULN.
- **DLT 3**: Any increase in ALT or AST >3 ULN combined with an increase in ALT or AST >2 x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, fever, rash, or eosinophilia.

17.2. Treatment-Emergent Adverse Events

The review team conducted additional safety analyses using narrow FMQ terms using the Safety Population Including Subjects Who Received Only Process C in the adult population and pediatric population.

During ASCEND PAP, TEAEs by FDA MedDRA Query (Narrow) occurring in a higher percentage of adults in the active treatment group than in the placebo group included headache, nasopharyngitis, cough, viral infection, myalgia, urticaria, dyspnea, fracture, fungal infection, constipation, erythema, hypotension, acute kidney injury, alopecia, and cardiac conduction disturbance (Table 207). The acute kidney injury reported in one adult who was randomized to active treatment was considered not related to olipudase alfa; the subject had a history of acute kidney injury and had viral gastritis at the time of the event. TEAEs by FDA MedDRA Query (Narrow) in the pediatric population are summarized in Table 208.

Table 207. Subjects With Adverse Events by FDA Medical Query (Narrow) and Preferred Term, Safety Population, Trials DFI12712 (ASCEND), DFI13412, LTS13632 and Pooled (ISS), Adult Subjects Who Received Only Process C

FMQ (Narrow) Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Headache (FMQ)	7 (53.8)	8 (44.4)	7 (53.8)	9 (52.9)	16 (53.3)
Headache	7 (53.8)	8 (44.4)	7 (53.8)	9 (52.9)	16 (53.3)
Cervicogenic headache	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Migraine	0	2 (11.1)	0	0	0
Abdominal Pain (FMQ)	2 (15.4)	5 (27.8)	5 (38.5)	7 (41.2)	12 (40.0)
Abdominal pain	1 (7.7)	3 (16.7)	2 (15.4)	5 (29.4)	7 (23.3)
Abdominal pain upper	1 (7.7)	3 (16.7)	2 (15.4)	4 (23.5)	6 (20.0)
Abdominal discomfort	0	0	1 (7.7)	1 (5.9)	2 (6.7)
Abdominal pain lower	0	1 (5.6)	0	0	0
Nasopharyngitis (FMQ)	6 (46.2)	7 (38.9)	6 (46.2)	6 (35.3)	12 (40.0)
Nasopharyngitis	6 (46.2)	6 (33.3)	6 (46.2)	4 (23.5)	10 (33.3)
Pharyngitis	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Rhinitis	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Hemorrhage (FMQ)	3 (23.1)	6 (33.3)	4 (30.8)	6 (35.3)	10 (33.3)
Epistaxis	1 (7.7)	1 (5.6)	2 (15.4)	1 (5.9)	3 (10.0)
Contusion	0	2 (11.1)	1 (7.7)	1 (5.9)	2 (6.7)
Hematoma	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Hemorrhage subcutaneous	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Hepatic hemorrhage	1 (7.7)	1 (5.6)	1 (7.7)	0	1 (3.3)
Infusion site hematoma	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Petechiae	0	0	0	1 (5.9)	1 (3.3)
Post procedural hemorrhage	0	0	0	1 (5.9)	1 (3.3)
Vessel puncture site hematoma	0	0	0	1 (5.9)	1 (3.3)
Gingival bleeding	0	1 (5.6)	0	0	0
Menorrhagia	0	1 (5.6)	0	0	0
Shock hemorrhagic	0	1 (5.6)	0	0	0
Nausea (FMQ)	1 (7.7)	8 (44.4)	2 (15.4)	7 (41.2)	9 (30.0)
Nausea	1 (7.7)	8 (44.4)	2 (15.4)	7 (41.2)	9 (30.0)
Procedural nausea	0	0	0	1 (5.9)	1 (3.3)

FMQ (Narrow) Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Bacterial Infection (FMQ)	2 (15.4)	6 (33.3)	3 (23.1)	5 (29.4)	8 (26.7)
Cellulitis	1 (7.7)	0	1 (7.7)	2 (11.8)	3 (10.0)
Urinary tract infection	0	1 (5.6)	0	2 (11.8)	2 (6.7)
Cholecystitis acute	0	0	1 (7.7)	0	1 (3.3)
Eyelid infection	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Furuncle	0	0	0	1 (5.9)	1 (3.3)
Helicobacter gastritis	0	0	0	1 (5.9)	1 (3.3)
Appendicitis	0	1 (5.6)	0	0	0
Ear infection staphylococcal	0	1 (5.6)	0	0	0
Hordeolum	0	1 (5.6)	0	0	0
Periodontitis	0	1 (5.6)	0	0	0
Peritonitis	0	1 (5.6)	0	0	0
Postoperative wound infection	0	1 (5.6)	0	0	0
Subcutaneous abscess	0	1 (5.6)	0	0	0
Tooth abscess	0	1 (5.6)	0	0	0
Dyspepsia (FMQ)	2 (15.4)	3 (16.7)	3 (23.1)	5 (29.4)	8 (26.7)
Abdominal pain upper	1 (7.7)	3 (16.7)	2 (15.4)	4 (23.5)	6 (20.0)
Dyspepsia	2 (15.4)	0	2 (15.4)	1 (5.9)	3 (10.0)
Pruritus (FMQ)	0	3 (16.7)	0	8 (47.1)	8 (26.7)
Pruritus	0	3 (16.7)	0	7 (41.2)	7 (23.3)
Rash pruritic	0	0	0	2 (11.8)	2 (6.7)
Injection site pruritus	0	1 (5.6)	0	0	0
Arthralgia (FMQ)	2 (15.4)	3 (16.7)	3 (23.1)	4 (23.5)	7 (23.3)
Arthralgia	2 (15.4)	3 (16.7)	3 (23.1)	4 (23.5)	7 (23.3)
Cough (FMQ)	4 (30.8)	2 (11.1)	4 (30.8)	3 (17.6)	7 (23.3)
Cough	4 (30.8)	2 (11.1)	4 (30.8)	3 (17.6)	7 (23.3)
Rash (FMQ)	1 (7.7)	2 (11.1)	2 (15.4)	5 (29.4)	7 (23.3)
Urticaria	1 (7.7)	0	2 (15.4)	3 (17.6)	5 (16.7)
Rash pruritic	0	0	0	2 (11.8)	2 (6.7)
Rash	0	2 (11.1)	0	1 (5.9)	1 (3.3)
Rash erythematous	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Rash morbilliform	0	1 (5.6)	0	0	0
Viral Infection (FMQ)	2 (15.4)	1 (5.6)	5 (38.5)	2 (11.8)	7 (23.3)
COVID-19	0	0	2 (15.4)	1 (5.9)	3 (10.0)
Influenza	1 (7.7)	1 (5.6)	2 (15.4)	1 (5.9)	3 (10.0)
Anogenital warts	0	0	1 (7.7)	0	1 (3.3)
Gastritis viral	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Genital herpes	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Oral herpes	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Viral upper respiratory tract infection	0	0	1 (7.7)	0	1 (3.3)
Dizziness (FMQ)	1 (7.7)	2 (11.1)	3 (23.1)	3 (17.6)	6 (20.0)
Dizziness	0	2 (11.1)	1 (7.7)	2 (11.8)	3 (10.0)
Presyncope	1 (7.7)	0	2 (15.4)	0	2 (6.7)
Vertigo	0	0	0	1 (5.9)	1 (3.3)
Pyrexia (FMQ)	2 (15.4)	4 (22.2)	2 (15.4)	4 (23.5)	6 (20.0)
Pyrexia	2 (15.4)	4 (22.2)	2 (15.4)	4 (23.5)	6 (20.0)

FMQ (Narrow) Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Back Pain (FMQ)	0	4 (22.2)	1 (7.7)	4 (23.5)	5 (16.7)
Back pain	0	4 (22.2)	1 (7.7)	4 (23.5)	5 (16.7)
Diarrhea (FMQ)	2 (15.4)	2 (11.1)	2 (15.4)	3 (17.6)	5 (16.7)
Diarrhea	2 (15.4)	2 (11.1)	2 (15.4)	3 (17.6)	5 (16.7)
Fatigue (FMQ)	1 (7.7)	4 (22.2)	3 (23.1)	2 (11.8)	5 (16.7)
Fatigue	0	3 (16.7)	2 (15.4)	2 (11.8)	4 (13.3)
Asthenia	1 (7.7)	1 (5.6)	1 (7.7)	0	1 (3.3)
Myalgia (FMQ)	1 (7.7)	0	2 (15.4)	3 (17.6)	5 (16.7)
Myalgia	1 (7.7)	0	2 (15.4)	3 (17.6)	5 (16.7)
Urticaria (FMQ)	1 (7.7)	1 (5.6)	2 (15.4)	3 (17.6)	5 (16.7)
Urticaria	1 (7.7)	0	2 (15.4)	3 (17.6)	5 (16.7)
Infusion site urticaria	0	1 (5.6)	0	0	0
Vomiting (FMQ)	1 (7.7)	7 (38.9)	1 (7.7)	4 (23.5)	5 (16.7)
Vomiting	1 (7.7)	7 (38.9)	1 (7.7)	4 (23.5)	5 (16.7)
Dyspnea (FMQ)	1 (7.7)	0	3 (23.1)	1 (5.9)	4 (13.3)
Dyspnea	1 (7.7)	0	2 (15.4)	1 (5.9)	3 (10.0)
Dyspnea exertional	0	0	1 (7.7)	0	1 (3.3)
Local Administration Reaction (FMQ)	1 (7.7)	2 (11.1)	3 (23.1)	1 (5.9)	4 (13.3)
Vaccination site pain	0	0	1 (7.7)	1 (5.9)	2 (6.7)
Infusion site extravasation	0	0	1 (7.7)	0	1 (3.3)
Infusion site hematoma	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Infusion site urticaria	0	1 (5.6)	0	0	0
Injection site pain	0	1 (5.6)	0	0	0
Injection site pruritus	0	1 (5.6)	0	0	0
Anxiety (FMQ)	1 (7.7)	3 (16.7)	1 (7.7)	2 (11.8)	3 (10.0)
Anxiety	0	3 (16.7)	0	2 (11.8)	2 (6.7)
Panic attack	1 (7.7)	1 (5.6)	1 (7.7)	0	1 (3.3)
Fracture (FMQ)	2 (15.4)	2 (11.1)	3 (23.1)	0	3 (10.0)
Hand fracture	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Lower limb fracture	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Tooth fracture	0	0	1 (7.7)	0	1 (3.3)
Foot fracture	0	1 (5.6)	0	0	0
Rib fracture	0	1 (5.6)	0	0	0
Fungal Infection (FMQ)	1 (7.7)	0	1 (7.7)	2 (11.8)	3 (10.0)
Fungal infection	1 (7.7)	0	1 (7.7)	1 (5.9)	2 (6.7)
Dermatophytosis of nail	0	0	0	1 (5.9)	1 (3.3)
Oral candidiasis	0	0	0	1 (5.9)	1 (3.3)
Vulvovaginal mycotic infection	0	0	0	1 (5.9)	1 (3.3)
Hepatic Injury (FMQ)	0	1 (5.6)	0	3 (17.6)	3 (10.0)
Alanine aminotransferase increased	0	0	0	3 (17.6)	3 (10.0)
Aspartate aminotransferase increased	0	0	0	3 (17.6)	3 (10.0)
Hepatomegaly	0	1 (5.6)	0	0	0

FMQ (Narrow) Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Systemic Hypertension (FMQ)	0	1 (5.6)	2 (15.4)	1 (5.9)	3 (10.0)
Hypertension	0	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Blood pressure increased	0	0	1 (7.7)	0	1 (3.3)
Arrhythmia (FMQ)	0	0	1 (7.7)	1 (5.9)	2 (6.7)
Bradycardia	0	0	1 (7.7)	0	1 (3.3)
Extrasystoles	0	0	0	1 (5.9)	1 (3.3)
Arthritis (FMQ)	0	0	1 (7.7)	1 (5.9)	2 (6.7)
Arthritis	0	0	1 (7.7)	0	1 (3.3)
Osteoarthritis	0	0	0	1 (5.9)	1 (3.3)
Synovitis	0	0	0	1 (5.9)	1 (3.3)
Constipation (FMQ)	1 (7.7)	0	1 (7.7)	1 (5.9)	2 (6.7)
Constipation	1 (7.7)	0	1 (7.7)	1 (5.9)	2 (6.7)
Erythema (FMQ)	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Erythema	1 (7.7)	1 (5.6)	1 (7.7)	1 (5.9)	2 (6.7)
Rash erythematous	0	1 (5.6)	0	1 (5.9)	1 (3.3)
Application site erythema	0	1 (5.6)	0	0	0
Fall (FMQ)	0	3 (16.7)	1 (7.7)	1 (5.9)	2 (6.7)
Fall	0	3 (16.7)	1 (7.7)	1 (5.9)	2 (6.7)
Hyperglycemia (FMQ)	0	0	0	2 (11.8)	2 (6.7)
Blood glucose increased	0	0	0	1 (5.9)	1 (3.3)
Hyperglycemia	0	0	0	1 (5.9)	1 (3.3)
Hypotension (FMQ)	2 (15.4)	2 (11.1)	2 (15.4)	0	2 (6.7)
Hypotension	2 (15.4)	2 (11.1)	2 (15.4)	0	2 (6.7)
Insomnia (FMQ)	1 (7.7)	3 (16.7)	1 (7.7)	1 (5.9)	2 (6.7)
Insomnia	1 (7.7)	3 (16.7)	1 (7.7)	1 (5.9)	2 (6.7)
Paresthesia (FMQ)	0	2 (11.1)	0	2 (11.8)	2 (6.7)
Hypoesthesia	0	1 (5.6)	0	2 (11.8)	2 (6.7)
Paraesthesia	0	1 (5.6)	0	0	0
Renal and Urinary Tract Infection (FMQ)	0	1 (5.6)	0	2 (11.8)	2 (6.7)
Urinary tract infection	0	1 (5.6)	0	2 (11.8)	2 (6.7)
Abnormal Uterine Bleeding (FMQ)	0	2 (11.1)	1 (7.7)	0	1 (3.3)
Menstruation delayed	0	0	1 (7.7)	0	1 (3.3)
Menorrhagia	0	1 (5.6)	0	0	0
Polymenorrhea	0	1 (5.6)	0	0	0
Acute Kidney Injury (FMQ)	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Acute kidney injury	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Alopecia (FMQ)	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Alopecia	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Anemia (FMQ)	0	3 (16.7)	1 (7.7)	0	1 (3.3)
Anemia	0	3 (16.7)	1 (7.7)	0	1 (3.3)
Angioedema (FMQ)	0	0	0	1 (5.9)	1 (3.3)
Angioedema	0	0	0	1 (5.9)	1 (3.3)

FMQ (Narrow) Preferred Term	DFI12712 (Adult) PAP OA N=13 n (%)	DFI12712 (Adult) PAP PLB N=18 n (%)	DFI12712 (Adult) PAP+ETP OA/OA N=13 n (%)	DFI12712 (Adult) PAP+ETP PLB/OA N=17 n (%)	Pooled Adult (DFI12712/ DFI13412/ LTS13632) N=30 n (%)
Cardiac Conduction Disturbance (FMQ)	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Electrocardiogram repolarization abnormality	1 (7.7)	0	1 (7.7)	0	1 (3.3)
Cholecystitis (FMQ)	0	0	1 (7.7)	0	1 (3.3)
Cholecystitis acute	0	0	1 (7.7)	0	1 (3.3)
Irritability (FMQ)	0	0	0	1 (5.9)	1 (3.3)
Agitation	0	0	0	1 (5.9)	1 (3.3)
Malignancy (FMQ)	0	0	0	1 (5.9)	1 (3.3)
Hepatocellular carcinoma	0	0	0	1 (5.9)	1 (3.3)
Peripheral Edema (FMQ)	0	0	1 (7.7)	0	1 (3.3)
Oedema peripheral	0	0	1 (7.7)	0	1 (3.3)
Purulent Material (FMQ)	0	3 (16.7)	0	1 (5.9)	1 (3.3)
Furuncle	0	0	0	1 (5.9)	1 (3.3)
Liver abscess	0	1 (5.6)	0	0	0
Subcutaneous abscess	0	1 (5.6)	0	0	0
Tooth abscess	0	1 (5.6)	0	0	0
Syncope (FMQ)	0	1 (5.6)	1 (7.7)	0	1 (3.3)
Syncope	0	1 (5.6)	1 (7.7)	0	1 (3.3)
Tendinopathy (FMQ)	0	0	0	1 (5.9)	1 (3.3)
Tendon rupture	0	0	0	1 (5.9)	1 (3.3)
Vertigo (FMQ)	0	0	0	1 (5.9)	1 (3.3)
Vertigo	0	0	0	1 (5.9)	1 (3.3)
Excessive Menstrual Bleeding (FMQ)	0	2 (11.1)	0	0	0
Menorrhagia	0	1 (5.6)	0	0	0
Polymenorrhea	0	1 (5.6)	0	0	0
Lipid Disorder (FMQ)	0	1 (5.6)	0	0	0
Hypercholesterolemia	0	1 (5.6)	0	0	0

Source: adae.xpt; Software: R
Note: Adult subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Note: Duration is up to the data cutoff dates.
Note: Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: AE, adverse event; ETP, extended treatment; FMQ, FDA medical query; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OA, olipudase alfa; PAP, primary analysis period; PLB, placebo; SOC, system organ class

Table 208. Subjects With Adverse Events by FDA Medical Query (Narrow) and Preferred Term, Safety Population, Trials DFI13803 (ASCEND-Peds), LTS13632 and Pooled (ISS), Pediatric Subjects Who Received Only Process C

FMQ (Narrow) Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Nasopharyngitis (FMQ)	7 (100)	1 (100)	8 (100)
Nasopharyngitis	6 (85.7)	1 (100)	7 (87.5)
Rhinitis	6 (85.7)	0	6 (75.0)
Pharyngitis	2 (28.6)	0	2 (25.0)
Pyrexia (FMQ)	7 (100)	1 (100)	8 (100)
Pyrexia	7 (100)	1 (100)	8 (100)
Cough (FMQ)	5 (71.4)	1 (100)	6 (75.0)
Cough	5 (71.4)	1 (100)	6 (75.0)
Diarrhea (FMQ)	5 (71.4)	1 (100)	6 (75.0)
Diarrhea	5 (71.4)	1 (100)	6 (75.0)
Viral Infection (FMQ)	5 (71.4)	1 (100)	6 (75.0)
Influenza	2 (28.6)	0	2 (25.0)
Oral herpes	2 (28.6)	0	2 (25.0)
Epstein-Barr virus infection	0	1 (100)	1 (12.5)
Hand-foot-and-mouth disease	1 (14.3)	0	1 (12.5)
Herpes virus infection	1 (14.3)	0	1 (12.5)
Varicella	1 (14.3)	0	1 (12.5)
Viral infection	1 (14.3)	0	1 (12.5)
Abdominal Pain (FMQ)	4 (57.1)	1 (100)	5 (62.5)
Abdominal pain	4 (57.1)	0	4 (50.0)
Abdominal pain upper	1 (14.3)	1 (100)	2 (25.0)
Headache (FMQ)	4 (57.1)	0	4 (50.0)
Headache	4 (57.1)	0	4 (50.0)
Hemorrhage (FMQ)	3 (42.9)	1 (100)	4 (50.0)
Contusion	2 (28.6)	1 (100)	3 (37.5)
Epistaxis	2 (28.6)	0	2 (25.0)
Petechiae	0	1 (100)	1 (12.5)
Rash (FMQ)	3 (42.9)	1 (100)	4 (50.0)
Urticaria	3 (42.9)	1 (100)	4 (50.0)
Rash	1 (14.3)	1 (100)	2 (25.0)
Dermatitis contact	1 (14.3)	0	1 (12.5)
Skin exfoliation	1 (14.3)	0	1 (12.5)
Urticaria (FMQ)	3 (42.9)	1 (100)	4 (50.0)
Urticaria	3 (42.9)	1 (100)	4 (50.0)
Vomiting (FMQ)	3 (42.9)	1 (100)	4 (50.0)
Vomiting	3 (42.9)	1 (100)	4 (50.0)
Arthralgia (FMQ)	2 (28.6)	1 (100)	3 (37.5)
Arthralgia	2 (28.6)	1 (100)	3 (37.5)
Nausea (FMQ)	3 (42.9)	0	3 (37.5)
Nausea	3 (42.9)	0	3 (37.5)
Back Pain (FMQ)	2 (28.6)	0	2 (25.0)
Back pain	1 (14.3)	0	1 (12.5)
Flank pain	1 (14.3)	0	1 (12.5)

FMQ (Narrow) Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Bacterial Infection (FMQ)	2 (28.6)	0	2 (25.0)
Cystitis	1 (14.3)	0	1 (12.5)
Pneumonia mycoplasmal	1 (14.3)	0	1 (12.5)
Dyspepsia (FMQ)	1 (14.3)	1 (100)	2 (25.0)
Abdominal pain upper	1 (14.3)	1 (100)	2 (25.0)
Erythema (FMQ)	2 (28.6)	0	2 (25.0)
Erythema	2 (28.6)	0	2 (25.0)
Fatigue (FMQ)	1 (14.3)	1 (100)	2 (25.0)
Asthenia	1 (14.3)	0	1 (12.5)
Fatigue	0	1 (100)	1 (12.5)
Pruritus (FMQ)	2 (28.6)	0	2 (25.0)
Pruritus	2 (28.6)	0	2 (25.0)
Anaphylactic Reaction (FMQ)	0	1 (100)	1 (12.5)
Anaphylactic reaction	0	1 (100)	1 (12.5)
Arrhythmia (FMQ)	1 (14.3)	0	1 (12.5)
Tachycardia	1 (14.3)	0	1 (12.5)
Constipation (FMQ)	0	1 (100)	1 (12.5)
Constipation	0	1 (100)	1 (12.5)
Dizziness (FMQ)	1 (14.3)	0	1 (12.5)
Dizziness	1 (14.3)	0	1 (12.5)
Fall (FMQ)	1 (14.3)	0	1 (12.5)
Fall	1 (14.3)	0	1 (12.5)
Fracture (FMQ)	1 (14.3)	0	1 (12.5)
Femur fracture	1 (14.3)	0	1 (12.5)
Hypersensitivity (FMQ)	0	1 (100)	1 (12.5)
Anaphylactic reaction	0	1 (100)	1 (12.5)
Hypotension (FMQ)	1 (14.3)	0	1 (12.5)
Hypotension	1 (14.3)	0	1 (12.5)
Local Administration Reaction (FMQ)	1 (14.3)	0	1 (12.5)
Infusion site swelling	1 (14.3)	0	1 (12.5)
Vaccination site pain	1 (14.3)	0	1 (12.5)
Peripheral Edema (FMQ)	1 (14.3)	0	1 (12.5)
Peripheral swelling	1 (14.3)	0	1 (12.5)
Pneumonia (FMQ)	1 (14.3)	0	1 (12.5)
Pneumonia mycoplasmal	1 (14.3)	0	1 (12.5)
Renal and Urinary Tract Infection (FMQ)	1 (14.3)	0	1 (12.5)
Cystitis	1 (14.3)	0	1 (12.5)

FMQ (Narrow) Preferred Term	Child OA LTS13632/ DFI13803 N=7 n (%)	Infant/early child OA LTS13632/ DFI13803 N=1 n (%)	Pooled Pediatric OA LTS13632/ DFI13803 N=8 n (%)
Respiratory Failure (FMQ)	1 (14.3)	0	1 (12.5)
Respiratory failure	1 (14.3)	0	1 (12.5)
Tachycardia (FMQ)	1 (14.3)	0	1 (12.5)
Tachycardia	1 (14.3)	0	1 (12.5)
Thrombocytopenia (FMQ)	1 (14.3)	0	1 (12.5)
Thrombocytopenia	1 (14.3)	0	1 (12.5)

Source: adae.xpt; Software: R.
Note: Pediatric subjects who ever received Process B were excluded.
Note: Treatment-emergent adverse events defined as AEs that started or worsened after the first administration of olipudase alfa during the olipudase alfa exposure period.
Note: Duration is up to the data cutoff dates.
Note: Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: AE, adverse event; FMQ, FDA medical query; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OA, olipudase alfa; SOC, system organ class

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not Applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

Not Applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

20.1. Clinical Site Inspections

In support of BLA 761261, clinical investigators Dr. Melissa Wasserstein, Renata Gallagher, George Diaz, and Laila Arach-Kaps were inspected, covering Protocols DFI12712 and DFI13803. Refer to Clinical Inspection Summary dated May 20, 2022 for more information.

21. Labeling Summary of Considerations and Key Additional Information

Full Prescribing Information Sections[1]	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
All Sections	Required Applicant to revise labeling to include only data from Process C (the to be marketed form) as data from Process B is considered an analytically different product and therefore discussion of evidence from process B would be considered misleading to the public and should not be included in labeling. Noted to Applicant that the safety and efficacy information between process B and process C is similar in our analysis at this time and therefore the public will still have adequate information to make an informed decision.
BOXED WARNING	Added a Boxed Warning for severe hypersensitivity reactions including anaphylaxis due to class effect of ERT therapy. Concern existed about an elevated risk for anaphylaxis in patients with ASMD type A and patients <2 years of age as both developed anaphylaxis with the product in the clinical development program.
1 INDICATIONS AND USAGE	• Removed (b) (4) from Applicant's proposed indication. This section should only describe (b) (4) (b) (4) • Removed (b) (4) (b) (4) as not necessary to include.
2 DOSAGE AND ADMINISTRATION	2.1 Important Recommendations Prior to Treatment Initiation • Added important recommendations prior to treatment initiation which included liver and pregnancy testing and pre-treatments. 2.4 Missed Doses • Created a table to incorporate the steps for addressing a missed dose. 2.5 Dosage and Administration Modifications & Monitoring • Moved information pertaining to dosage and administration modifications due to hypersensitivity and/or infusion-associated reactions to this subsection. 2.6 Preparation Instructions & 2.7 Administration Instructions • Re-organized information and text for clarity on preparation and administration instructions for XENPOZYME along with

	streamlining steps to calculate and prepare total volume of infusion for patients.
4 CONTRAINDICATIONS	No contraindications listed.
5 WARNINGS AND PRECAUTIONS	5.1 Hypersensitivity Reactions Including Anaphylaxis • Moved Heading for Hypersensitivity Reactions Including Anaphylaxis to this subsection. • Included the ASMD type A patient treated outside of clinical study program. • Removed (b) (4) (b) (4) 5.3 Elevated Transaminases Levels • Added steps to mitigate elevated transaminase levels. 5.4 Risk of Fetal Malformations During Dosage Initiation or Escalation in Pregnancy • Created sub-section to describe the potential risk to the developing fetus based on findings of exencephaly in animal studies (See 3.1.2.1 & 7.7.1).
6 ADVERSE REACTIONS	• The review team based the safety evaluation on 60 patients with non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) and included patients enrolled in studies DFI13412, DFI12712/ASCEND, DFI13803/ASCEND-Peds, and LTS13632 (See 7.5). • Adverse reactions reported in these patients were hypersensitivity or infusion-associated in nature. • Applicant proposed (b) (4) (b) (4) • Added adverse reaction data for elevated transaminase levels under separate heading. • Moved immunogenicity information to subsection 12.6 consistent with *Guidance for Industry-Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling*. • Added subheading Immunogenicity: Antidrug Antibody-Associated Adverse Reactions under subsection 6.1 as recommended in the draft Immunogenicity Labeling Guidance.

	• Included the ASMD type A patient treated outside of clinical study program.
[redacted] (b) (4)	
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy • Re-wrote Applicant proposed language to align with Pregnancy and Lactation Labeling Rule. • Included statement highlighting scientific literature to add perspective and biological plausibility to the finding of exencephaly. • Revised calculation for margins of exencephaly as it is not correct to use [redacted] (b) (4) (b) (4) 8.2 Lactation • Re-wrote Applicant proposed language to align with Pregnancy and Lactation Labeling Rule. 8.3 Females and Males of Reproductive Potential <u>Pregnancy Testing</u> Added heading to verify pregnancy status for females of reproductive potential prior to initiating XENPOZYME. <u>Contraception</u> Added heading to advise female patients of reproductive potential to use effective contraception during treatment and for 14 days if XENPOZYME is discontinued. 8.4 Pediatric Use • Revised Applicant proposed language to align with the *Guidance for Industry- Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling*. • Included a high level summary of the pediatric trials and their efficacy findings serving as the basis for the finding of efficacy of olipudase in pediatric patients after the Pediatric Use (e.g. indication) statement. • Removed statement [redacted] (b) (4) (b) (4) • Included language pertaining to pediatric patient that developed a potentially life-threatening anaphylactic reaction with olipudase therapy.

	• Included language about the pediatric patient with ASMD Type A that developed anaphylaxis with XENPOZYME treatment outside of the clinical trial program. 8.5 Geriatric Use • Revised Applicant proposed language to align with the *Guidance for Industry-Content and Format for Geriatric Labeling.*
[redacted] (b) (4)	
12 CLINICAL PHARMACOLOGY	12.1 Mechanism of Action • Removed Applicant proposed language describing detailed information (b) (4) 12.3 Pharmacokinetics • Replaced (b) (4) with standard deviation (SD) for PK parameters in adult patients to harmonize with the presentation of PK parameters in pediatric patients and pharmacodynamic results. • Pooled the pediatric PK data as there were limited number of patients and no significant PK differences among the subgroups. • Removed (b) (4) as not relevant (b) (4) (b) (4) 12.6 Immunogenicity • Created subsection as recommended in Guidance for Industry-*Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling* to contain immunogenicity information.
13 NONCLINICAL TOXICOLOGY	13.2 Animal Toxicology and/or Pharmacology • Removed information (b) (4) (b) (4) as is inappropriate.
14 CLINICAL STUDIES	• Included 8 digit National Clinical Trial (NCT) number(s) the first time the study/studies are discussed. • Added demographic information (proportion of males/females). • Moved p-values (b) (4) to footnote only as (b) (4)

	(b) (4) Presented observed mean and SD for all tables and text in this section. • Modified title of tables to conform with Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. • Removed (b) (4) (b) (4) • Removed (b) (4) and included any p-values as a footnote only. (b) (4) (b) (4) • Combined Tables 9 and 10 and removed (b) (4) (b) (4) • Provided the specific n for each endpoint in each table. • Removed terms (b) (4) from labeling as these are not accepted terms in labeling and not used consistently (b) (4) (b) (4). Recommend retaining the age ranges for the cohorts alone to describe the pediatric study population. • Removed information (b) (4) (b) (4) • Revised information to state that continued improvement in height Z-score occurred through 24 months and bone age through 30 months due to low numbers of patients with measured data past 24 and 30 months respectively.
17 PATIENT COUNSELING INFORMATION	Revised this section for consistency with the revisions to the Full Prescribing Information focusing on major risks of the drug (e.g., W&P), and when appropriate, how the patient may mitigate or manage these risks.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	11 Description • Revised the inactive ingredient names to their compendial names and adjusted their quantity on anhydrous basis if needed to fulfill FDCA section 502(e). • Added established name and dosage form • Added pH of reconstituted solution. • Added molecular weight. • Added route of administration. 16 How Supplied/Storage & Handling • Added proper name and dosage form. • Added additional recommendations for the storage conditions.

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

22. Postmarketing Requirements and Commitments

PMR #1

Conduct a five-year observational study to evaluate the long-term safety of olipudase alfa-rpcp including severe hypersensitivity reactions, infusion-associated reactions, and laboratory abnormalities in pediatric patients less than two years of age with ASMD and patients with ASMD Type A. Assess antibody response (b) (4) (b) (4) and evaluate the relationship between anti-drug antibodies and (b) (4)

- Draft Protocol Submission: 02 /2023
- Final Protocol Submission: 08 /2024
- Study Completion: 08 /2029
- Interim Report: 02 /2027
- Final Report Submission: 02 /2030

PMC #2

To establish a working reference standard (WRS) using a (b) (4) batch and qualify this WRS against the current olipudase alfa primary reference standard (b) (4) Once the WRS is established, the qualification data for the first WRS together with a WRS requalification protocol specifying how subsequent working reference standards will be qualified will be submitted.

The WRS will be created from a representative DS batch which has passed all release specifications. The WRS will be qualified according to a predefined protocol using a statistically derived replication strategy for key attributes in addition to a panel of extended characterization methods.

- Final Report Submission: 03/2024

PMC #3

To develop an endotoxin method for the drug product which mitigates the low endotoxin recovery effect, to submit method qualification results with three lots of drug product, and to provide results of an low endotoxin recovery study performed with the updated method with three lots of drug product. The rabbit pyrogen test will be replaced by a suitable in vitro endotoxin method upon approval of the supplement.

- Final Report Submission: 6/2026

PMC #4

To repeat the performance qualification study for the container closure integrity on the (b) (4) (b) (4) utilizing the current container closure integrity testing method which is capable of detecting breach sizes down to 5 µm.

- Final Report Submission: 10/2023

PMC #5

To perform the qualification of the bioburden method using a test volume of 100 mL with 3 batches of drug product.

- Final Report Submission: 10/2023

23. Financial Disclosure

Table 209. Covered Clinical Studies: DFI12712 (ASCEND)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 150		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: Genzyme Corporation		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 144		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviations: CFR, Code of Federal Regulations.

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Table 210. Covered Clinical Studies: DFI13803 (ASCEND-Peds)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 37		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: Genzyme Corporation		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 34		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviations: CFR, Code of Federal Regulations.

Table 211. Covered Clinical Studies: LTS13632

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 42		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: Genzyme Corporation		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 37		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviations: CFR, Code of Federal Regulations.

Table 212. Covered Clinical Studies: DFI13412

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 15		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: Genzyme Corporation		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 15		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviations: CFR, Code of Federal Regulations.

24. References

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25. Review Team

Table 213. Reviewers of Integrated Assessment

Role	Names
Regulatory Project Manager	CAPTAIN Jenny Doan, MSN, BSN
Chief Project Management Staff	Michael G. White, PhD
Nonclinical Reviewer	Mary Ellen McNerney, PhD
Nonclinical Team Leader	Laurie McLeod-Flynn, PhD
Office of Clinical Pharmacology Reviewers	Nayeem Hossain, PhD, Clinical Pharmacology Reviewer Hongshan Li, PhD, Pharmacometrics Reviewer Guansheng Liu, PhD, PBPK Reviewer
Office of Clinical Pharmacology Team Leaders	Jie (Jack) Wang, PhD, Clinical Pharmacology Team Lead Jiang Liu, PhD, Pharmacometrics Team Lead Yang Yuching, PhD, PBPK Team Lead Hao Zhu, PhD, PBPK Team Lead
Clinical Reviewer	Christine Hon, PhD, PharmD, Clinical Analyst
Clinical Team Leader	Anita Zaidi, MD
Statistical Reviewer	Andrew Giffin, PhD
Statistical Team Leader	Yan Wang, PhD
Cross-Disciplinary Team Leader	Anita Zaidi, MD
Division Director (pharm/tox)	Mukesh Summan, PhD
Division Director (OCP)	Michael Pacanowski, PharmD, MPH
Deputy Division Director (OB)	Nie Lei, PhD
Division Director (ORO)	Pamela Lucarelli
Division Director (clinical)	Kathleen M. Donohue, MD, MSc
Office Deputy Director	Christine Nguyen, MD, MHS

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; ORO, Office of Regulatory.

Table 214. Additional Reviewers of Application

Office or Discipline	Names
Division of Cardiology and Nephrology/ Interdisciplinary Review Team (IRT) for Cardiac Safety Studies	Eliford Kitabi, PharmD, Clinical Analyst Girish Bende, PharmD, Team Lead Devi Kozeli, MSc, Senior Regulatory Project Manager
Division of Pediatric and Maternal Health (DPMH) Team Leaders	Tamara Johnson, MD, Maternal Health Mona Khurana, MD
DPMH/Maternal Health Reviewer	Jane Liedtka, MD
DPMH/Pediatrics Reviewer	Shamir Tuchman, MD, MPH
DPMH/Regulatory Project Manager	Denise Pica-Branco, PharmD, RPM Rosemary Addy, PharmD, Chief Project Management Staff

Office or Discipline	Names
Division of Pulmonology, Allergy, and Critical Care	Robert Lim, MD, Clinical Team Leader Khalid Puthawala, MD, Clinical Reviewer
Division of Rare Diseases and Medical Genetics (DRDMG)	Mona Patel, PharmD, RAC, Associate Director Labeling Yuliya Yasinskaya, MD, Deputy Director for Safety Cheronda Cherry-France, RN, MHA, BSN, Safety Regulatory Project Manager
New Drug Transition Team	Rhonda Hearns-Stewart, MD Adam Horin, Clinical Data Scientist Pamela Hsieh, PharmD, Medical Editor James Ebersole, Medical Editor Joseph Dorn, Medical Editor Katherine Bradley, Medical Editor, Team Leader
Office of Pharmaceutical Quality	Brian Roelofs, PhD, Application Team Leader Yongmin Liu, PhD, CMC Reviewer Michael Shanks, PhD, Primary Drug Substance Microbiology and Facility Reviewer Yarery Smith, PhD, Primary Drug Product Microbiology and Facility Reviewer Virginia Carroll, PhD, Microbiologist and Facilities Team Lead Faruk Sheikh, PhD, Immunogenicity Reviewer Harold Dickensheets, PhD, Immunogenicity Team Lead Jennifer Kim, PharmD, Labeling Reviewer Nowrin Kakon, PharmD, Regulatory Business Project Manger
Office of Prescription Drug Promotion	Carrie Newcomer, Regulatory Reviewer Elvy Varghese, Regulatory Reviewer James Dvorksy, Team Leader
Office of Scientific Investigations	Tina Suyoung Chang, PharmD, Clinical Analyst Phillip Kronstein, MD, Team Lead
Office of Surveillance & Epidemiology (OSE)/ Division of Epidemiology (DEPI)	Sally Peprah, PharmD, Reviewer Benjamin Booth, PhD, Team Leader
OSE/ Division of Medication Error Prevention and Analysis (DMEPA)	Sali Mahmoud, PharmD, BCPS, Safety Evaluator Ashleigh Lowery, PharmD, PharmD, Team Leader
OSE/Division of Pharmacovigilance (DPV)	Mohamed A. Mohamoud, PharmD, MPH, BCPS, Safety Evaluator Ivone Kim, MD, Medical Reviewer Carmen Cheng, MD, Team Leader
OSE/Division of Risk Management (DRM)	Laura Zendel, PharmD, Team Leader Theresa Ng, PharmD, Reviewer
OSE/ Safety Regulatory Project Manager (SRPM)	Aleksander Winiarski, PharmD, RPh, Team Leader Commander Su-Lin Sun, RPh, PharmD, GWCPM, SRPM

Table 215. Signatures of Reviewers

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Tertiary Reviewer	**Signature:** Kathleen Donohue -S Digitally signed by Kathleen Donohue -S Date: 2022.08.29 11:06:21 -04'00'		
Clinical	Kathleen M. Donohue, MD, MSc Director	OND/Division of Rare Diseases and Medical Genetics (DRDMG)	All ☐ Authored ☒ Contributed ☒ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Anita Zaidi, MD	OND/DRDMG	All ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Anita A. Bailey Zaidi -S Digitally signed by Anita A. Bailey Zaidi -S Date: 2022.08.29 10:40:10 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Christine Hon, PharmD, PhD	OND/DRDMG	1,2,3,4,6,7,8,10,11,12,15,16,17, 20, 21,22,23,24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Yuen-yi Hon -S Digitally signed by Yuen-yi Hon -S Date: 2022.08.29 11:33:03 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Mona Patel, PharmD, RAC	OND/DRDMG	21 ☒ Authored ☐ Contributed ☒ Approved
Associate Director for Labeling	**Signature:** Mona Patel -S Digitally signed by Mona Patel -S Date: 2022.08.29 14:14:50 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Michael G. White, PhD Chief Program Management Staff	OND/DRO-RPURM	12, 25 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Michael White -S Digitally signed by Michael White -S Date: 2022.08.26 17:10:05 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Jenny Doan, MSN, BSN	OND/DRO-RPURM	12, 25 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** Jenny Doan -S Digitally signed by Jenny Doan -S Date: 2022.08.30 09:06:36 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Mukesh Summan, PhD Director	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine/Specialty Medicine (DPT-ORPURM/SM)	5.1, 7.1, 7.7, 8.4, 13.1, 13.2 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Mukesh Summan -S Digitally signed by Mukesh Summan -S Date: 2022.08.30 11:18:17 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Laurie McLeod-Flynn, PhD Team Leader	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine/Specialty Medicine (DPT-ORPURM/SM)	5.1, 7.1, 7.7, 8.4, 13.1, 13.2 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Laurie L. Mcleod-flynn -S Digitally signed by Laurie L. Mcleod-flynn -S Date: 2022.08.26 15:50:52 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Mary Ellen McNerney, PhD	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine (DPT-ORPURM)	5.1, 7.1, 7.7, 8.4, 13.1, 13.2 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Mary Ellen Mcnerney -S Digitally signed by Mary Ellen Mcnerney -S Date: 2022.08.29 10:52:16 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Michael Pacanowski, PharmD, MPH Director	OTS/OCP/ Division of Translational and Precision Medicine (DTPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Michael Pacanowski -S Digitally signed by Michael Pacanowski -S Date: 2022.08.30 09:32:39 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jie (Jack) Wang, PhD Team Leader	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Jie Wang -S Digitally signed by Jie Wang -S Date: 2022.08.29 15:10:55 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Nayeem Hossain, PhD	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Md Nayeem Hossain -S Digitally signed by Md Nayeem Hossain -S Date: 2022.08.29 18:23:53 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jiang Liu, PhD Team Leader	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.08.28 18:35:59 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Hongshan Li, PhD	OTS/OCP/DPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Hongshan Li -S Digitally signed by Hongshan Li -S Date: 2022.08.30 09:02:57 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Lei Nie, PhD Director	OB/Division of Biometrics IV (DBIV)	6.2, 6.3, and 16 ☐ Authored ☒ Contributed ☒ Approved
Tertiary Reviewer	**Signature:** Lei Nie -S Digitally signed by Lei Nie -S Date: 2022.08.27 21:16:07 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Yan Wang, PhD Team Leader	OB/DBIV	6.2, 6.3, and 16 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Yan Wang -S Digitally signed by Yan Wang -S Date: 2022.08.26 22:48:19 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Andrew Giffin, PhD	OB/DBVII	6.2, 6.3, and 16 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Andrew B. Giffin -S Digitally signed by Andrew B. Giffin -S Date: 2022.08.29 11:44:54 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Brian Roelofs, PhD Application Team Leader	OPQ/Office of Biotechnology	9 ☒ Authored ☐ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Brian Roelofs -S Digitally signed by Brian Roelofs -S Date: 2022.08.29 09:49:23 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics (QSP)	Hao Zhu, PhD Deputy Director	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** Hao Zhu -S Digitally signed by Hao Zhu -S Date: 2022.08 30 13:37:20 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics (QSP)	Yuching Yang, PhD Team Leader	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	**Signature:** (Dr. Zhu signed on behalf) Hao Zhu -S Digitally signed by Hao Zhu -S Date: 2022.08.30 13:39:14 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics (QSP)	Guansheng Liu, PhD	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Guansheng Liu -S Digitally signed by Guansheng Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guansheng Liu -S, 0.9.2342.19200300.100.1.1=2003130570 Date: 2022.08.30 13:29:50 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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