SANOFI GENZYME

AMENDED CLINICAL TRIAL PROTOCOL 04

A phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency

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COMPOUND: Olipudase alfa/GZ402665, recombinant human acid sphingomyelinase

STUDY NUMBER: DFI13803

STUDY NAME: ASCEND-Peds

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CLINICAL TRIAL SUMMARY

COMPOUND: GZ402665 (olipudase alfa)	**STUDY No: DFI13803**
TITLE	A phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of olipudase alfa in pediatric patients aged <18 years with acid sphingomyelinase deficiency
INVESTIGATOR/TRIAL LOCATION	Multi-national and multi-center. More than one region as needed to allow enrollment of sufficient numbers of patients in a reasonable time. Potential countries include but are not limited to United States, United Kingdom, Italy, Brazil, Germany, and France.
PHASE OF DEVELOPMENT	1/2
STUDY OBJECTIVE(S)	**Primary objective:** To evaluate the safety and tolerability of olipudase alfa administered intravenously in pediatric patients every 2 weeks for 64 weeks. **Secondary objective(s):** To characterize the pharmacokinetic profile and evaluate the pharmacodynamics and exploratory efficacy of olipudase alfa administered intravenously in pediatric patients every 2 weeks for up to 64 weeks.
STUDY DESIGN	This is a phase 1/2, multi-national, multi-center, open-label, ascending-dose study designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of olipudase alfa administered once every 2 weeks for 64 weeks in pediatric patients, aged <18 years, with non-neuronopathic acid sphingomyelinase deficiency (ASMD). At least 12 pediatric patients will be enrolled in a staggered fashion into the following 3 age cohorts and dose escalated to 3.0 mg/kg olipudase alfa or the highest tolerated dose (HTD): 1. Adolescent cohort – patients aged 12 to <18 years 2. Child cohort – patients aged 6 to <12 years 3. Infant/early child cohort – patients from birth to <6 years of age. Initiation of dosing will be staggered among the three pediatric age cohorts. The adolescent cohort will begin dosing before the child cohort, and the child cohort will begin dosing before the infant/early child cohort. Patients in the child and infant /early child cohorts will not be dosed until a review of all safety data has occurred from the first 3 patients in the respective adolescent and child cohorts who completed the dose escalation phase. At least 8 additional pediatric patients (<12 years), corresponding to the age range of the child and the infant/early child cohorts, will then be enrolled. These patients will be enrolled and treated without age cohort staggering. After the 64 week-treatment phase, eligible patients may enroll in the long-term study LTS13632 to continue receiving olipudase alfa.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria** I 01. The patient and/or patient's parent(s)/legal guardian(s) must provide written informed assent/consent prior to any protocol-related procedures being performed.

	I 02. The patient is male or female <18 years of age on the date of informed assent/consent. I 03. The patient has documented deficiency of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes. I 04. The patient has a spleen volume ≥5 multiples of normal (MN) measured by magnetic resonance imaging(MRI); patients who have had partial splenectomy will be allowed if the procedure was performed ≥1 year before screening and the residual spleen volume is ≥5 MN. I 05. The patient's height is -1 Z-score or lower. I 06. A negative serum pregnancy test in female patients of childbearing potential. I 07. Female patients of childbearing potential and male patients must be willing to practice true abstinence in line with their preferred and usual lifestyle, or use 2 acceptable effective methods of contraception. **Exclusion criteria** E 01. The patient has received an investigational drug within 30 days before study enrollment. E 02. The patient has any of the following medical conditions: - An active, serious, intercurrent illness; - Active hepatitis B or hepatitis C infection; - Infection with human immunodeficiency virus (HIV); - Cirrhosis (determined by clinical evaluation): - Significant cardiac disease (eg, clinically significant arrhythmia, moderate or severe pulmonary hypertension or valvular dysfunction, or <40% left ventricular ejection fraction by echocardiogram); - Malignancy diagnosed within the previous 5 years (except basal cell carcinoma); - Any other extenuating circumstance that can significantly interfere with study compliance, including all prescribed evaluations and follow-up activities. E 03. The patient has acute or rapidly progressive neurological abnormalities. E 04. The patients is homozygous for *SMPD1* gene mutations R496L, L302P, and fs330 or any combination of these 3 mutations. E 05. The patient has a delay of gross motor skills. E 06. The patient has had a major organ transplant (eg, bone marrow, liver). E 07. The patient requires use of invasive ventilatory support. E 08. The patient requires use of noninvasive ventilatory support while awake and for >12 hours a day. E 09. The patient, in the investigator's opinion, is unable to adhere to the requirements of the study. E 10. The patient has a platelet count <60 × 10^3/μL (based on the average of 2 screening samples obtained greater than 24 hours apart). E 11. The patient has alanine aminotransferase or aspartate

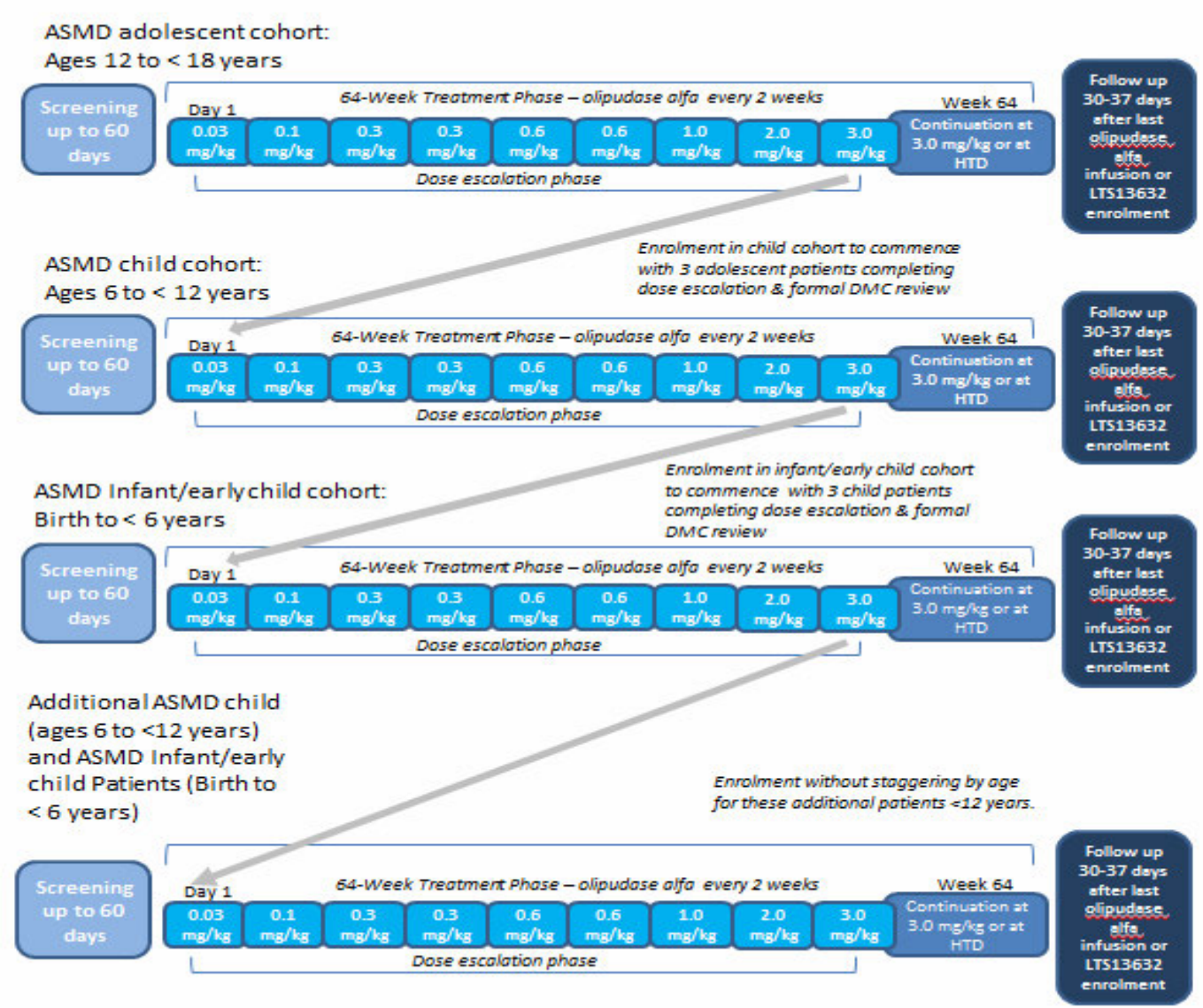
	aminotransferase >250 IU/L or total bilirubin >1.5 mg/dL. E 12. The patient has an international normalized ratio (INR) >1.5. E 13. The patient is unwilling or unable to abstain from ingesting alcohol the day before through 3 days after each infusion of olipudase alfa during the treatment period. Measuring alcohol concentration in blood is not required. E 14. The patient is scheduled during the study for in-patient hospitalization including elective surgery E 15. The patient requires medication(s) that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine; tricyclic antidepressants [eg, imipramine, or desipramine]). E 16. The patient is breast-feeding.
Total expected number of patients	A total of at least 20 patients with ASMD <18 years of age will be enrolled. • At least 12 patients with ASMD who are able to tolerate 2 consecutive doses of 0.3 mg/kg olipudase alfa will be enrolled to 3 age cohorts. A minimum of 3 patients each will be enrolled in the adolescent and child cohorts; a minimum of 2 patients will be enrolled in the infant/early child cohort. • At least 8 additional patients with ASMD will be enrolled in the child and infant/early child cohorts, who are able to tolerate 2 consecutive doses of 0.3mg/kg olipudase alfa. A minimum of 4 patients will be enrolled in the child cohort; a minimum of 2 patients will be enrolled in the infant/early child cohort.
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Olipudase alfa (GZ402665, recombinant human acid sphingomyelinase or rhASM)
Formulation	Sterile, lyophilized cake
Route(s) of administration	Intravenous infusion
Dose regimen	Olipudase alfa will be administered every 2 weeks for 64 weeks. All patients will receive an initial dose of 0.03 mg/kg olipudase alfa, which will then be followed by one dose of 0.1 mg/kg, and two consecutive doses at 0.3 mg/kg. Patients tolerating 2 consecutive doses of 0.3 mg/kg will be dose escalated step-wise to receive 2 consecutive doses at 0.6 mg/kg, which will be followed by infusions at 1.0 mg/kg and 2.0 mg/kg, and to the final target dose of 3.0 mg/kg, which is to be maintained for the remaining duration of the treatment period. Patients unable to tolerate 3.0 mg/kg olipudase alfa will receive the highest tolerable dose every 2 weeks until the end of the treatment period. Patients unable to tolerate 2 consecutive doses of 0.3 mg/kg olipudase alfa will be replaced.
Noninvestigational medicinal product(s) (if applicable)	Not applicable.
ENDPOINT(S)	**Primary endpoint:** Data pertaining to the safety and tolerability of olipudase alfa: • Assessment of adverse events/treatment-emergent adverse events (TEAEs), including infusion-associated reactions • Physical examinations • Neurological examinations

	• Clinical laboratory evaluations • Vital sign measurements • Electrocardiograms (ECGs) • Safety biomarkers • Doppler echocardiography • Liver ultrasound Doppler • Immune response assessments **Secondary endpoint(s):** **Pharmacokinetics:** • Plasma parameters include C_{max}, $AUC_{0\text{-}last}$, AUC, $t_{1/2}$, CL and V_{ss} following the first infusion of olipudase alfa at 0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg and with olipudase alfa infusion at Week 52. **Exploratory efficacy** • Spleen volume and liver volume (in multiples of normal [MN]), as measured by abdominal magnetic resonance imaging (MRI). • Infiltrative lung disease scoring as measured by high resolution computed tomography (HRCT) and by chest x-ray (at selected sites). • Linear patient growth by height Z-score. • Pulmonary function testing endpoints. • Bone age by hand x-ray. • Cycle ergometry endpoints. • Physician's global assessment. • Efficacy biomarkers. • Lipid profile. • Bone biomarkers. • Health outcome questionnaires. • Cognitive and adaptive function testing. **Pharmacodynamics** • Sphingomyelin and sphingomyelin metabolite levels.
ASSESSMENT SCHEDULE	Screening assessments are to be completed within 60 days of Day 1. The timing for safety and tolerability, pharmacokinetic, pharmacodynamic and exploratory efficacy assessments is presented in the Study Flow Chart. Patients who do not enroll into the long-term study, LTS13632, or lag treatment between studies will be followed-up with a telephone call 30 to 37 days after the last olipudase alfa infusion.
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size set for this study was based on empirical considerations; no calculations were performed. **Analysis Population:** The safety analysis set will include all patients who receive at least 1 infusion (partial or total) of olipudase alfa. The pharmacokinetic analysis set includes all patients who receive at least 1 infusion of study medication and have evaluable pharmacokinetic data. The modified intent-to-treat analysis set is the same as the safety set and is

	used as the primary population for the efficacy analysis. The pharmacodynamic population includes all patients who have at least 1 infusion of study medication and have at least 1 evaluable pharmacodynamic data.measurement available post-baseline.
	Safety Analysis: Safety analyses will include a summary of treatment duration, the total number of infusions received, and the total amount of olipudase alfa received. Frequencies (number and percentage) of patients with one or more treatment-emergent adverse events (TEAEs) will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) overall and by age group. All TEAEs, including those potentially related to study drug, those leading to treatment discontinuation and study discontinuation, infusion-associated reactions, serious adverse events (SAEs), and all AEs with fatal outcome (including fatal TEAEs) will be summarized overall and by age group. Other safety variables, including laboratory parameters and vital signs, will be summarized overall and by age group. **Pharmacokinetic Analysis:** The pharmacokinetic analysis will be conducted on the pharmacokinetic analysis set. Plasma concentration-time data will be analyzed by non-compartmental methods, nonlinear mixed effects modeling, or by population-based analysis, based upon patient age and data suitability. Pharmacokinetic parameters will be calculated for each patient and summarized by age group, by dose (0.3, 1.0, 3.0 mg/kg), and by time point, and by manufacturing scale, including the week 52 visit. **Exploratory Efficacy Analysis:** An assessment of exploratory efficacy will be conducted on the modified intent-to-treat analysis set. Efficacy summaries will include descriptive statistics of the observed value and/or change or percentage change (eg, spleen volume, liver volume, platelet count, etc.) from baseline to week 52 or week 64, as appropriate, including 95% confidence intervals. Categorical variables (eg, pulmonary imaging, chest X-ray) will be summarized using frequencies and percentages according to time points collected from screening or baseline to week 52 or week 64, as appropriate. Analysis will be performed overall and by manufacturing scale as appropriate. **Pharmacodynamic Analysis:** The pharmacodynamic analysis will be conducted on the pharmacodynamic analysis set. Concentration of sphingomyelin and its metabolites will be summarized by dose and time point, and manufacturing scale as appropriate, using descriptive statistics. **Pharmacodynamic-Pharmacokinetic Analysis:** Exploratory analyses may be performed to elucidate exposure-response relationships with biomarkers of safety and/or efficacy.
DURATION OF STUDY PERIOD (per patient)	Per patient, the maximum study duration is approximately 18 months: • Screening period: up to 60 days • Treatment period: 64 weeks • Post-treatment period: up to 37 days. Not applicable if patient enrolls in LTS13632.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN


ASMD adolescent cohort:
Ages 12 to < 18 years
Screening up to 60 days
Day 1
64-Week Treatment Phase – olipudase alfa every 2 weeks
Week 64
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
0.3 mg/kg
0.6 mg/kg
0.6 mg/kg
1.0 mg/kg
2.0 mg/kg
3.0 mg/kg
Continuation at 3.0 mg/kg or at HTD
Dose escalation phase
Follow up 30-37 days after last olipudase alfa infusion or LTS13632 enrolment
Enrolment in child cohort to commence with 3 adolescent patients completing dose escalation & formal DMC review
ASMD child cohort:
Ages 6 to < 12 years
Screening up to 60 days
Day 1
64-Week Treatment Phase – olipudase alfa every 2 weeks
Week 64
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
0.3 mg/kg
0.6 mg/kg
0.6 mg/kg
1.0 mg/kg
2.0 mg/kg
3.0 mg/kg
Continuation at 3.0 mg/kg or at HTD
Dose escalation phase
Follow up 30-37 days after last olipudase alfa infusion or LTS13632 enrolment
Enrolment in infant/early child cohort to commence with 3 child patients completing dose escalation & formal DMC review
ASMD Infant/early child cohort:
Birth to < 6 years
Screening up to 60 days
Day 1
64-Week Treatment Phase – olipudase alfa every 2 weeks
Week 64
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
0.3 mg/kg
0.6 mg/kg
0.6 mg/kg
1.0 mg/kg
2.0 mg/kg
3.0 mg/kg
Continuation at 3.0 mg/kg or at HTD
Dose escalation phase
Follow up 30-37 days after last olipudase alfa infusion or LTS13632 enrolment
Additional ASMD child (ages 6 to <12 years) and ASMD Infant/early child Patients (Birth to < 6 years)
Enrolment without staggering by age for these additional patients <12 years.
Screening up to 60 days
Day 1
64-Week Treatment Phase – olipudase alfa every 2 weeks
Week 64
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
0.3 mg/kg
0.6 mg/kg
0.6 mg/kg
1.0 mg/kg
2.0 mg/kg
3.0 mg/kg
Continuation at 3.0 mg/kg or at HTD
Dose escalation phase
Follow up 30-37 days after last olipudase alfa infusion or LTS13632 enrolment

1.2 STUDY FLOW CHART

	Screening	Treatment Period[a, b]									Post-treatment Observations	
DAY/WEEK (Wk)	Day -60 to Day -1	Day1 /Wk0	Wk 2 to Wk 10	W12 QV	Wk 14 to Wk 24	Wk 26 QV	Wk 28 to Wk 36[c] Wk 40 to Wk 50, Wk 54 to WK 62	Wk 38 QV	Wk 52 QV	Wk 64	Withdrawal	Follow-up
Screening/Demography/Baseline												
Informed consent/Assent	X											
Inclusion and exclusion criteria	X	X										
Patient demography	X											
Medical/Surgical history	X											
Prior medication history	X											
ASM activity in peripheral leukocytes	X[d]											
Genotyping of *SPMD1*, *CHIT1*, and *UGT1A1*	X[d]											
HIV antibody testing	X											
Hepatitis B surface antigen test	X											
Hepatitis C antibody test	X											
Tanner Staging	X			X		X		X	X		X[e]	
CRIM testing[f]	X											
Patient photographs (optional)	X								X		X[e]	
Safety												
Complete physical exam	X	X		X		X		X	X		X[e]	
Abbreviated physical exam		Prior to each infusion when a complete exam is not indicated										
Neurological exam	X	X		X		X		X	X		X	
Weight, height, BMI	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications and therapies	X	Continuous monitoring									X	X
AE /SAE collection	X	Continuous monitoring									X	X

	Screening	Treatment Period[a, b]									Post-treatment Observations	
DAY/WEEK (Wk)	Day -60 to Day -1	Day1 /Wk0	Wk 2 to Wk 10	W12 QV	Wk 14 to Wk 24	Wk 26 QV	Wk 28 to Wk 36[c]Wk 40 to Wk 50, Wk 54 to WK 62	Wk 38 QV	Wk 52 QV	Wk 64	Withdrawal	Follow-up
Vital sign measurements	X	Every visit – Before, halfway through, and after infusion (± 10 minutes): Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (± 10 minutes).									X	
Electrocardiogram [g]	X	X[h]	Each new olipudase alfa dose ≥0.3 mg/kg			X		X	X			
Doppler echocardiogram	X				With the first infusion at 3.0 mg/kg or highest tolerated dose				X			
Liver ultrasound Doppler	X								X			
Clinical laboratory sampling:												
Liver function testing[g]	X	X	X	X	X	X		X	X	X	X	
Clinical chemistry[g], hematology[g], coagulation[g], urinalysis[g]	X	X		X		X		X	X	X		
β-hCG pregnancy test[i]	X	X	Every 4 weeks from Day 1: Wk4, Wk8, Wk12, Wk16, Wk20, Wk24, Wk28, Wk32, Wk36, Wk40, Wk44, Wk48, Wk 52, Wk 56, Wk 60, Wk 64								X	
Safety biomarkers [g]		X	X	X	X	X		X	X	X	X	
Anti-olipudase alfa IgG and neutralizing antibodies in IgG positive patients		X	Every 2 weeks from Day 1 through Wk16, then at quarterly visits (Wk26, Wk38, Wk52) and Wk 64								X	
Anti-olipudase alfa IgE antibody test		In the event of a moderate/severe or recurrent-infusion associated reaction suggestive of hypersensitivity, a sample will be collected ≥3 days after event or prior to next infusion.										
Serum tryptase and complement activation		In the event of a moderate/severe or recurrent-infusion associated reaction suggestive of hypersensitivity, a sample will be collected within 1 to 3 hours of event onset.										
Skin testing		As necessary for assessing hypersensitivity reactions. See study manual.										
Exploratory efficacy												
Spleen volume by abdominal	X					X			X		X[e]	

	Screening	Treatment Period[a, b]									Post-treatment Observations	
DAY/WEEK (Wk)	Day -60 to Day -1	Day1 /Wk0	Wk 2 to Wk 10	W12 QV	Wk 14 to Wk 24	Wk 26 QV	Wk 28 to Wk 36[c] Wk 40 to Wk 50, Wk 54 to WK 62	Wk 38 QV	Wk 52 QV	Wk 64	Withdrawal	Follow-up
MRI[j]												
Liver volume by abdominal MRI[j]	X					X			X		X[e]	
Pulmonary imaging with HRCT	X								X		X[e]	
Pulmonary function test[k]	X					X			X		X[e]	
Chest X-ray[l]	X								X		X[e]	
Bone age by hand X-ray	X								X		X[e]	
Cycle ergometry[m]	X					X			X		X[e]	
Physician's global assessment	X					X			X		X	
Efficacy biomarkers		X				X			X	X	X	
Lipid profile	X	X[n]		X[n]		X		X	X	X	X	
Serum bone-specific ALP and C-telopeptide[n]		X				X			X	X	X	
Health outcome questionnaires	X					X			X		X[e]	
Cognitive and adaptive function testing[o]	X					X			X		X[e]	
Pharmacodynamics												
Plasma and/or DBS sphingomyelin and metabolite concentrations[g]		X	X	X	X	X		X	X	X	X	
Treatment and pharmacokinetics												
Olipudase alfa infusion		X	X	X	X	X	X	X	X	X		
Olipudase alfa pharmacokinetics[p]		First 0.3 mg/kg dose; first 1.0 mg/kg dose; first 3.0 mg/kg dose; and Wk 52										

a During the Treatment Period, patients are infused with olipudase alfa every 2 weeks (±3 days). In-patient hospitalization will be required before and, for at least 24 hours after infusion for all doses during the dose escalation process through the second infusion at the highest tolerated dose. Patients may be required to stay in the hospital for additional time for safety purposes at the investigator's discretion. During the study,

	Screening	Treatment Period[a, b]									Post-treatment Observations	
DAY/WEEK (Wk)	**Day -60 to Day -1**	**Day1 /Wk0**	**Wk 2 to Wk 10**	**W12 QV**	**Wk 14 to Wk 24**	**Wk 26 QV**	**Wk 28 to Wk 36[c] Wk 40 to Wk 50, Wk 54 to WK 62**	**Wk 38 QV**	**Wk 52 QV**	**Wk 64**	**Withdrawal**	**Follow-up**

if released from the hospital, patients will be required to return as needed for evaluation and collection of samples at 48h and 96h. After the second infusion at the highest tolerable dose, patients will be observed for a minimum of 3 hours following infusion completion, and discharged at the investigator's discretion.

b Unless specified otherwise, assessments are completed before starting the olipudase alfa infusion. See Flow Chart 1.3 and protocol Section 10 for sample collection windows. When multiple assessments are required, the order should be vital signs before ECG before PK or blood draw.

c If dose escalation is extended beyond Week 26, visit assessments should match the Week 14 to Week 24 column content.

d Assessment not required if historical results available.

e Not required if assessment previously collected within 12 weeks prior to the post-treatment withdrawal follow-up visit.

f Assessment not required in patients >2 years of age.

g See Flow Chart Section 1.3 and Section 1.4 for sample collection details per each age cohort.

h Pre-infusion ECG in triplicate.

i Females achieving menarche will have serum test for pregnancy at Screening, a urine β-hCG test up to 24 hours before day 1/week 0 infusion and every 4 weeks thereafter.

j Patients are required to fast from solid foods (liquids such as water, milk, juice allowed) for 6 hours before an abdominal MRI to reduce the effect of a meal on MRI data.

k Assessment not required in patients <5 years of age at day 1/week 0.

l Chest x-ray to be performed at selected sites.

m Assessment not required in patients ≤ 6 years of age or < 120 cm in height at day 1/week 0.

n Assessment not required in patients ≤ 2 years of age.

o Assessment not required in patients ≥ 6 years of age at day 1/week 0.

p See Flow Chart Section 1.5 for sample collection details.

Abbreviations: AE = adverse event; ASM = acid sphingomyelinase; β-hCG = beta-human chorionic gonadotropin; BMI = body mass index; DBS = dried blood spot; CRIM = cross reactive immune material; ECG = electrocardiography; HRCT = high resolution computed tomography; Ig = immunoglobulin; MRI = magnetic resonance imaging; PK = pharmacokinetics; QV = Quarterly Visit; ; SAE = serious adverse event; TEAE = treatment-emergent AE; UGT1A1 = uridine diphospho-glucuronosyltransferase 1 family, polypeptide A1; Wk = week.

1.3 SUPPLEMENTAL FLOWCHART - DOSE ESCALATION VISITS, SECOND INFUSION AT THE HIGHEST TOLERATED DOSE, QUARTERLY VISIT AND WEEK 64 ASSESSMENTS: PATIENTS IN THE ADOLESCENT COHORT, CHILD COHORT AND PATIENTS AGED 3 TO < 6 YEARS

	Dose escalation visits & 2nd infusion at highest tolerated dose				Quarterly visits (day 1/wk0, wk12, wk26, wk38, wk52)				Week 64
	Pre-infusion	End of infusion	24 hr	48 hr	Pre-infusion	End of infusion	24 hr	48 hr	Pre-infusion
Electrocardiogram	X[a]	X[a]	X[a]	X[a]	X[b]	X	X[c]	X	
Liver function testing	X		X[c]	X	X		X[c]	X	X
Clinical chemistry & coagulation					X		X[c]	X	X
Urinalysis					X				X
Hematology					X[d]		X[c]	X	
Safety biomarkers:									
Ceramide	X		X[c]	X	X		X[c]	X	X
Cardiac troponin-1	X		X[c]	X	X		X[c]	X	X
hsCRP	X		X[c]	X	X		X[c]	X	X
Calcitonin	X		X[c]	X	X		X[c]	X	X
Iron and ferritin	X		X[c]	X	X		X[c]	X	X
IL6 and IL8[e]	X		X[c]	X	X[f]		X[c, f]	X[f]	
Plasma and/or DBS sphingomyelin and metabolite concentrations[g]	X		X[c]	X	X		X[c]	X	X

Note: When multiple assessments are required, the order should be vital signs before ECG before PK or blood draws. Preinfusion assessments are to be completed within 24 hours prior to olipudase alfa infusion. End of infusion assessments are to be completed with 10 minutes following the end of olipudase alfa infusion. Twenty four (24) hour and 48 hour post infusion assessments to be completed within ± 3 hours of scheduled time.

a At each new dose of ≥ 0.3 mg/kg only.

b ECG in triplicate on day 1/week 0

c Sample/assessment is not required in patients in the child cohort (patients aged 6 to <12 years) or in patients aged 3 to < 6 years.

d Two samples to be collected within 24 hours of olipudase alfa at week 52. See Section 10.3.5 for details.

e Sample not required in patients aged 3 to < 6 years.

f Sample not required at week 26, week 38 or week 52.

g DBS collection not required in patients aged 3 to < 6 years.

Abbreviations: hr = hour; hsCRP = high sensitivity C reactive protein; IL = interleukin; wk = week.

1.4 SUPPLEMENTAL FLOWCHART - DAY 1/WEEK 0, DOSE ESCALATION VISITS, SECOND INFUSION AT THE HIGHEST TOLERATED DOSE, QUARTERLY VISIT AND WEEK 64 ASSESSMENTS IN PATIENTS ≤ 2 YEARS OLD

	Day 1/Week 0			Dose escalation visits & 2nd infusion at highest tolerated dose			Quarterly visits (wk12, wk26, wk38, wk52)			Week 64
	Pre-infusion	End of infusion	48 hr	Pre-infusion	End of infusion	48 hr	Pre-infusion	End of infusion	48 hr	Pre-infusion
Electrocardiogram	X[a]			X[b]	X[b]	X[b]	X	X	X	
Liver function testing			X	X		X	X		X	X
Clinical chemistry & coagulation			X				X[c]		X[c]	X
Urinalysis	X						X			X
Hematology			X				X[d]		X	
Safety biomarkers:										
Ceramide	X		X	X		X	X		X	X
hsCRP			X	X		X	X		X	X
Calcitonin	X		X	X		X	X		X	X
Ferritin	X		X	X		X	X		X	X
Plasma sphingomyelin and/or metabolite concentrations	X		X	X		X	X		X	X

Note: When multiple assessments are required, the order should be vital signs before ECG before PK or blood draws. Preinfusion assessments are to be completed within 24 hours prior to olipudase alfa infusion. End of infusion assessments are to be completed with 10 minutes following the end of olipudase alfa infusion. Twenty four (24) hour and 48 hour post infusion assessments to be completed within ± 3 hours of scheduled time.

a In triplicate

b At each new dose of ≥ 0.3 mg/kg only.

c Assessment not required at week 12 quarterly visit.

d Two samples to be collected within 24 hours of olipudase alfa at week 52. See Section 10.3.5 for details.

Abbreviations: wk, week; hr, hour; hsCRP, high sensitivity C reactive protein.

1.5 SUPPLEMENTAL FLOWCHART - PHARMACOKINETIC SAMPLES FOR FIRST INFUSIONS AT 0.3MG/KG, 1.0 MG/KG, 3.0 MG/KG AND AT WEEK 52 BY AGE COHORT

	Time from end of infusion						
Age cohort	**Pre-infusion[a]**	**End of infusion**	**2 hr**	**6 hr**	**24 hr**	**48 hr**	**96 hr**
Adolescent cohort[b]	X	X	X	X	X	X	X
	Pre-infusion[a]	**End of infusion**	**0-30 min**	**2 — 4 hr**	**6-12 hr**	**24-36 hr**	**84—96 hr**
Child cohort	X		X	X	X	X	X
Infant/early child cohort	X		X		X	X	X

a Pre-infusion sample to be collected with 24 hours prior to infusion start.

b Sample collections are to be within ± 10 minutes for those < 8 hours from infusion end and ± 3 hour for those ≥ 8 hours after infusion end.

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3 LIST OF ABBREVIATIONS

ABAS: Adaptive Behavior Assessment System
ACE: angiotensin-converting enzyme
AE: adverse event
ALT: alanine aminotransferase
AP: alkaline phosphatase
APR: acute phase reaction
ASM: acid sphingomyelinase
ASMD: acid sphingomyelinase deficiency
ASMKO: acid sphingomyelinase knock out
AST: aspartate aminotransferase
CCL18: chemokine (CC-motif) ligand 18
CRIM: cross-reactive immunological material
CRS: cytokine release syndrome
CS: clinically significant
DBS: dried blood spots
DLT: dose limiting toxicity
DMC: Data Monitoring Committee
DP-3: Development Profile-3
ECG: electrocardiogram
e-CRF: electronic case report form
EOS: end of study
FDA: Food and Drug Administration
FVC: forced vital capacity
HIV: immunodeficiency virus
HR: heart rate
HRCT: high resolution computed tomography
hsCRP: high sensitivity C reactive protein
HTD: highest tolerated dose
IAR: infusion-associated reaction
ICH: International Conference on Harmonisation
IgE: immunoglobulin E
IgG: immunoglobulin G
IL: interleukin
IMP: investigational medicinal product
INR: international normalized ratio
IRB/IEC: Institutional Review Board/Independent Ethics Committee
MedDRA: Medical Dictionary for Regulatory Activities
MN: multiples of normal
MRI: magnetic resonance imaging
NCS: not clinically significant
NOAEL: no observable adverse effect level

NPD:	Niemann Pick disease
NPD A:	Niemann Pick disease type A
NPD B:	Niemann Pick disease type B
PCSA:	potentially clinically significant abnormality
PedsQL:	Pediatric Quality of Life Inventory
PFT:	pulmonary function testing
Protime:	prothrombin time
PT:	preferred term
PTT:	partial thromboplastin time
rhASM:	recombinant human acid sphingomyelinase
SAE:	serious adverse event
SAP:	statistical analysis plan
SMPD1:	acid sphingomyelinase gene
SOC:	system organ class
TEAEs:	treatment-emergent adverse events
ULN:	upper limit of normal
β-HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Human acid sphingomyelinase deficiency (ASMD) is a serious, rare, and life-threatening lysosomal storage disorder for which only palliative treatment exists. Patients with ASMD are unable to metabolize sphingomyelin properly due to mutations in *SMPD1*, the gene encoding acid sphingomyelinase, whose transcription and translation results in a defective acid sphingomyelinase (ASM) enzyme. Inactivity of ASM leads to the lysosomal accumulation of sphingomyelin and, secondarily, increases in cholesterol and other related lipids, mostly in the organs spleen, liver, lung, and bone marrow.

Historically, ASMD has been diagnosed as Niemann-Pick Disease (NPD) and of either types A or B disease. Type A (NPD A) is characterized as the early-onset and acute neuronopathic form of Niemann-Pick disease and results in failure to thrive, hepatosplenomegaly, rapidly progressive neurological degeneration, and death usually before the age of 3 years (1). Niemann-Pick disease type B (NPD B) is a much milder disease with no or little neurological involvement and is also a childhood disease. The most common disease manifestation is hepatosplenomegaly; other, more variable features include liver dysfunction, pulmonary disease, retinal stigmata, and growth retardation. NPD B is usually diagnosed in childhood after organomegaly is observed, typically after the age of 2 years. The majority of patients diagnosed with type B disease live into adulthood. Being an autosomal recessive single gene disease, ASMD is acknowledged to generate a spectrum of phenotypes. Accordingly, cases classified as intermediate to the A and B extremes, have been reported. Patients with this intermediate form (NPD A/B) may develop neurologic symptoms during childhood and have a chronic neurodegenerative disease course.

Genzyme is developing a potential enzyme therapy for ASMD with recombinant human acid sphingomyelinase (rhASM; olipudase alfa) for the treatment of the non-neurological manifestations of ASMD. This recombinantly-derived enzyme is expressed in Chinese hamster ovarian cells transfected with olipudase alfa complementary DNA that encodes a 627-residue peptide chain. The resulting gene-product retains the enzymatic activity and lysosomal targeting of the native protein.

Proof of concept for olipudase alfa enzyme replacement therapy has been demonstrated in the acid sphingomyelinase knock out (ASMKO) mouse model of ASMD (2), which exhibits both systemic and neurological features of ASMD. Repeat intravenous bolus administration of olipudase alfa to ASMKO mice led to dose-dependent reductions of sphingomyelin in visceral organs and in the lungs, to a lesser extent, but was unable to prevent neurologic decline and prolong survival (3, 4). Although chronic dosing in the ASMKO animal model is limited as the animal succumbs to the neurologic disease resulting from the natural progression of complete ASMD and subsequent shortened lifespan of approximately 6 to 8 months.

Pharmacodynamic, pharmacokinetic, and toxicological studies conducted in the ASMKO mouse found significant reductions of sphingomyelin in the liver, lung, kidney, and spleen at olipudase alfa doses ranging from 0.1 to 5.0 mg/kg in a time dependent manner; however, toxicity was observed in ASMKO mice given single high bolus doses of olipudase alfa (≥10 mg/kg). The same

single high doses did not cause toxic effects in normal mice, Sprague Dawley rats, or cynomolgus monkeys, which suggested that catabolites of sphingomyelin, and not olipudase alfa itself, were the cause of the toxic effects. Subsequent "debulking" studies in ASMKO mice demonstrated that a slow reduction in the sphingomyelin load over time using multiple low doses of olipudase alfa (4 doses of 3.0 mg/kg olipudase alfa administered over 8 days) followed by a high dose (20 mg/kg 3 days later) prevented the toxicity associated with the single initial high doses. These findings suggest that the observed toxicity is related to the rate of substrate degradation and that step-wise removal of substrate likely mitigates toxicity. Furthermore, repeat, high doses of olipudase alfa (30 mg/kg every 2 weeks for 7 doses) administered after a 7-day debulking period (3 mg/kg on Days 1, 3, 5, and 7), also did not cause toxicity.

In the completed Phase 1 study (5), the safety, pharmacokinetic, and pharmacodynamic profiles of single, ascending doses of olipudase alfa were evaluated (5). Single doses of 0.03, 0.1, 0.3, 0.6, and 1.0 mg/kg olipudase alfa were infused sequentially by dose cohort in 11 adult patients with ASMD. Study results found dose-related increases in ceramide, bilirubin, high sensitivity C-reactive protein (hsCRP), and other acute phase reactants in patients that peaked 24 to 48 hours post-dose and resolved by Day 14. Reported adverse events (AEs) involving constitutional symptoms (pain, fever, nausea, and vomiting) were consistent with first dose-related toxicity and occurred in a dose dependent fashion, as was previously observed in the ASMKO mouse. Serious AEs (SAEs) related to olipudase alfa treatment were not reported. The sponsor terminated the study subsequent to the single patient dosed at 1.0 mg/kg olipudase alfa presenting with hyperbilirubinemia and an acute-phase reaction with clinical symptoms. Of note, this patient was subsequently confirmed to have Gilbert's syndrome. Because there were no other signs of liver toxicity or hemolysis, the observed hyperbilirubinemia may have been secondary to specific inhibition of bilirubin uptake into hepatocytes and/or glucuronide conjugation of bilirubin within hepatocytes.

In a Phase 1b, open-label, multi-center, ascending dose study (DFI13412) in 5 adult patients with ASMD, the safety and tolerability of olipudase alfa was evaluated during a 26-week treatment period (6). Patients received an initial intravenous dose of 0.1 mg/kg olipudase alfa and then dose-escalated in a step wise manner to a final target intravenous dose of 3.0 mg/kg. All patients remained 3.0 mg/kg for the remainder of the treatment period. Upon completion of the study, all patients enrolled into an open-label, long term treatment study (LTS13632) (7).

Results from this trial demonstrated that the progressive, within-patient olipudase alfa dose escalation regimen was well tolerated in adult ASMD patients. No serious or severe AEs or deaths were reported in the study. Related AEs consisted predominantly of infusion-associated reactions (IARs), the majority of which were mild in severity with all patients recovering without sequelae. At the end of the 6 month treatment period, a positive response to treatment with olipudase alfa was observed in several individual efficacy parameters. This included mean decreases in spleen and liver volumes by 25.3% and 17.1%, respectively; decreased interstitial lung disease scores; increased percent predicted DL_{CO}; reduction in serum chitotriosidase, chemokine (CC-motif) ligand 18 (CCL18) and angiotensin-converting enzyme (ACE); a positive trend towards a less pro-atherogenic lipid profile; and trends for improvement in quality of life assessments for fatigue and pain.

A complete summary of nonclinical and clinical experience with olipudase alfa can be found in the Investigator's brochure.

4.2 STUDY RATIONALE

The sponsor believes that cumulative data from the single-dose Phase 1 study (5) and repeat-dose Phase 1b study (6) demonstrate both the safety and tolerability of the olipudase alfa dose escalation regimen and repeat dosing at 3.0 mg/kg; such data support the conduction of this repeat, ascending dose study of olipudase alfa in pediatric patients with ASMD.

This Phase 1/2, open-label, multi-center, multi-national study is designed to evaluate the safety and tolerability of olipudase alfa in pediatric patients less than 18 years of age with non-neuronopathic ASMD. Olipudase alfa will be administered every 2 weeks using a progressive, within-patient dose escalation regimen, with dose escalation starting at 0.03 mg/kg and ending at 3.0 mg/kg. This study was also designed to characterize olipudase alfa pharmacokinetics, pharmacodynamics and exploratory efficacy throughout a 64-week treatment period.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to evaluate the safety and tolerability of olipudase alfa administered intravenously in pediatric patients every 2 weeks for 64 weeks.

5.2 SECONDARY

The secondary objectives of this study are to characterize the pharmacokinetic profile and evaluate the pharmacodynamics and exploratory efficacy of olipudase alfa administered intravenously in pediatric patients every 2 weeks for up to 64 weeks.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

DFI13803 is a Phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of olipudase alfa administered once every 2 weeks for 64 weeks in pediatric patients less than 18 years of age with non-neuronopathic ASMD. At least 12 patients will be enrolled in a staggered fashion into 3 age cohorts, with a minimum of 3 patients aged from 12 to <18 years (adolescent cohort), 3 patients aged from 6 to <12 years (child cohort), and 2 patients with ages ranging from birth to <6 years (infant/early child cohort).

In this study, intravenous infusions of olipudase alfa will be administered every 2 weeks for 64 weeks. Patients will begin with a dose of 0.03 mg/kg olipudase alfa, which will be followed with dose escalation to 0.1mg/kg and then to 0.3 mg/kg olipudase alfa. Patients able to tolerate 2 consecutive doses of 0.3 mg/kg olipudase alfa will continue to dose escalate step-wise as indicated in Section 1.1 to 0.6 mg/kg, 1.0 mg/kg, 2.0 mg/kg, and the final target dose of 3.0 mg/kg olipudase alfa. Patients unable to tolerate 2 consecutive doses of 0.3 mg/kg olipudase alfa will be replaced. Patients unable to tolerate the target 3.0 mg/kg dose will receive the highest dose tolerable every 2 weeks for the remainder of the 64-week treatment period.

Patient enrollment and initiation of dosing will be staggered among the three pediatric age cohorts for the first 12 patients. The study will begin with the enrollment of patients from the adolescent cohort (ages 12 to less than 18 years). Subsequently, a Data Monitoring Committee (DMC) and the sponsor will review all safety data collected from the first 3 patients in the adolescent cohort who have completed the dose escalation phase, reflecting the most critical point in olipudase alfa safety. Pending the outcome of the DMC and sponsor review, patients from the child cohort (6 to less than 12 years) will be enrolled. When the first 3 patients in the child cohort complete the dose escalation phase, another DMC and sponsor review will be conducted. Pending the outcome of the DMC and sponsor review of safety data from the child cohort, the study will be opened for enrollment of the infant/early child cohort (patients younger than 6 years of age).

To open enrollment in younger age cohorts, the sponsor and DMC will review at a minimum the following safety data: AEs/treatment emergent AEs (TEAEs) including IARs, clinical laboratory results including but not limited to hematology and clinical chemistry, electrocardiograms (ECGs), vitals, and any available immunology results as applicable.

Following enrollment in the youngest age cohort, an additional group of at least 8 patients <12 years will be enrolled. These patients will be included in the appropriate age cohort (at least 4 patients in the child cohort and at least 2 patients in the infant/early child cohort) without staggering of enrollment/ treatment.

Eligible patients may enroll in a long-term study (LTS13632) following completion the 64-week treatment period to continue receiving olipudase alfa. Patients not enrolling in the long-term study, or those with a treatment gap between the end of the 64-week treatment period of DFI13803 and enrollment in the long-term study, will undergo a final safety follow-up assessment by telephone 30 to 37 days after the last infusion in this study.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Per patient, the maximum study duration is approximately 18 months:

- Screening period: up to 60 days
- Treatment period: 64 weeks
- Post-treatment period: up to 37 days, which is not applicable if patient enrolls in LTS13632

6.2.2 Determination of end of clinical study (all patients)

The end of the clinical study is defined as the day that the last patient completes his/her last visit at the end of the treatment period as planned in the protocol.

6.3 STUDY COMMITTEES

An independent DMC appointed by the sponsor will review the protocol and will thereafter provide medical and ethical guidance related to the conduct of this study. The DMC will review safety information as outlined in the DMC Charter, which is maintained separately from the study protocol.

A formal safety review will be performed by the DMC:

- When 3 patients in the adolescent cohort complete the dose escalation phase.
- Approximately every 12 weeks after the first DMC meeting until study end. Frequency can be adapted based on availability of patient data and key visits.
- When 3 patients in the child cohort complete the dose escalation phase.
- With all relevant data at the end of the study.

Relevant data for DMC reviews will be, at a minimum, AEs including IARs, clinical laboratory results including, but not limited to, hematology and clinical chemistry, ECG, vitals, and any available immunology results as applicable.

The DMC will also review data on an ad hoc basis to assist in determining if AEs should preclude continued treatment with olipudase alfa and if stopping rules apply. The report of a potential dose limiting toxicity (DLT) to the sponsor or the occurrence of any safety related issues identified by

the DLT sponsor's medical monitor or global safety officer that pose a medical concern, for example a fatal event, will result in the DMC holding an ad hoc review of the safety data and providing its recommendations to the sponsor regarding further patient treatment. Should any major safety issues arise, final decisions regarding the study will be made by the sponsor, taking into consideration the DMC opinion (as applicable).

6.4 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

The following points were taken into consideration in the design of the study:

Rationale for dose selection and escalation: The starting dose of 0.03 mg/kg in this pediatric clinical trial is 10 times below the no observable adverse effect level (NOAEL) in single dose studies in ASMKO mice, and 1000 times below the NOAEL in repeat dose studies in ASMKO mice following a sphingomyelin debulking regimen. In addition, the starting dose of 0.03 mg/kg is 3 times lower than the highest dose that was not associated with any related AEs in the Phase 1 single-dose study, 0.1 mg/kg (5).

The target dose of 3.0 mg/kg olipudase alfa was selected to evaluate a dose effect for olipudase alfa to clear sphingomyelin from the lungs in patients with ASMD. In nonclinical studies, treatment of ASMKO mice with olipudase alfa led to dose dependent reductions of sphingomyelin in tissues, with the liver and spleen clearing substantially more substrate than the lung, suggesting the need for a higher dose and/or longer treatment duration to effectively treat the lung. As noted previously, chronic dosing in the ASMKO animal model is limited by the animal's shortened lifespan of approximately 6 to 8 months, a direct consequence of complete ASMD.

The highest repeat-dose for this study, 3.0 mg/kg, is supported by nonclinical repeat-dose toxicology data and experience from the adult Phase 1b trial. This dose is 10 times less than the 30 mg/kg repeat dose NOAEL in ASMKO mice after a debulking regimen, and is 3.3 times less than the 10 mg/kg single dose, at which significant toxicity and deaths were observed in ASMKO mice without prior debulking. In the Phase 1b study, the safety and tolerability of within-patient dose escalation of olipudase alfa administered intravenously every two weeks for 26 weeks was studied. In this trial, 5 adult patients with NPD B were given ascending doses of olipudase alfa administered intravenously every two weeks, as tolerated, according to the following dose escalation schedule: 0.1, 0.3, 0.3, 0.6, 1.0, 2.0, and 3.0 mg/kg. The olipudase alfa dose was increased if the patient experienced no or only mild AEs at the lower dose. Patients were monitored in-hospital prior to and for at least 72 hours after olipudase alfa infusion during the dose escalation period, and during the first 2 doses at the maximum tolerable dose; thereafter patients were maintained at their maximum tolerable dose until the end of the 26-week treatment period and discharged after dosing and a 3-hour minimum observational period. Study assessments included continuous AE reporting and periodic evaluations of safety, pharmacokinetics, pharmacodynamics, and efficacy parameters.

All 5 patients completed the dose escalation regimen, receiving 3.0 mg/kg olipudase alfa, the highest dose allowed per protocol, and remained at that dose for the remainder of the study. Three patients completed the dose escalation regimen without a dose reduction or repeat. One patient had a dose reduction following a moderate IAR with the first olipudase alfa dose at 1.0 mg/kg;

subsequently, this patient continued dose escalation to 2.0 and 3.0 mg/kg olipudase alfa. One patient repeated the 2.0 mg/kg olipudase alfa dose following a moderate IAR and subsequently dose escalated to 3.0 mg/kg. Adverse events were mild or moderate with those considered related to olipudase alfa administration generally occurring between 12 and 48 hours post-dose. The most commonly reported of these events were headache, arthralgia, abdominal pain, and nausea. Plasma ceramide levels typically peaked 48 hours post-dose and attenuated with repeat dosing.

The dose of 3.0 mg/kg will only be administered once a patient has safely escalated through the lower doses following the progressive dose escalation regimen. By comparison, the same dose of olipudase alfa that caused toxic effects in ASMKO mice (ie, 10 mg/kg), did not cause toxic effects in normal mice, Sprague Dawley rats, or cynomolgus monkeys, suggesting that a sphingomyelin catabolite (eg, ceramide, sphingosine, sphingosine-1-phosphate, or phosphocholine) was responsible for the toxic effects, and not olipudase alfa itself.

Open label, no placebo control: Given that the primary purpose of the study is to understand the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of repeat olipudase alfa dosing in pediatric patients with ASMD, the study is designed as an open-label, no comparator group trial.

Inclusion of infant/early child ASMD patients: Given the rarity of ASMD and that patients with the non-neuronopathic form of the disease can be diagnosed as early as birth, the age for the study includes patients from birth to <18 years of age.

Sixty-four week treatment period: The 64-week treatment period will allow for a broader understanding of olipudase alfa safety and tolerability in a patient population rapidly changing physiologically relative to shorter studies. Depending on the assessment, change from baseline in exploratory efficacy parameters will be evaluated through 52 weeks or 64 weeks of olipudase alfa administration. In addition, long term olipudase alfa safety and tolerability will also be further explored via the extension study LTS13632.

Patient enrollment between age cohorts: Enrollment of patients in DFI13803 for the first 12 patients will begin with adolescent patients (ages 12 to less than 18 years), followed by enrollment of child patients (6 to less than 12 years) and ending with the enrollment of infant/early child patients (patients below 6 years of age) as described in Section 6.1. The most critical phase for olipudase alfa safety is the dose escalation phase as indicated by Phase 1b study data (6). For this reason, enrollment of child cohort patients will commence once 3 patients in the adolescent cohort complete the dose escalation phase, and resulting safety data reviewed by the DMC and sponsor. The same process will occur with the enrollment of infant/early child patients based upon complete dose escalation safety data from 3 child cohort patients. Following enrollment in the youngest age cohort, an additional group of at least 8 patients <12 years will be enrolled. These patients will be included in the appropriate age cohort without staggering of enrollment/ treatment.

Number of patients: A sample size power calculation was not performed for this study. The sample size approximation of 20 pediatric patients is based upon empirical considerations.
At least 12 patients will be enrolled in a staggered fashion to 3 age cohorts with a minimum of 3 patients aged from 12 to <18 years, 3 patients aged from 6 to <12 years, and 2 patients with ages

ranging from birth to <6 years; followed by at least 8 additional patients <12 years enrolled without staggering. Out of the 8 additional patients, at least 4 patients in the child cohort and at least 2 patients in the infant/early child cohort will be enrolled.

Number of investigator sites: In order to fully enroll the study, this will be a multi-center, multi-national trial. ASMD is an orphan disease with a limited number of patients available to participate in clinical trials. Multiple sites will allow for the inclusion of patients from multiple regions.

6.4.1 Specific parameters rationale

6.4.1.1 Safety

Data collected in the phase 1 single ascending dose study with olipudase alfa in ASMD adult patients demonstrated dose-related increases in ceramide, bilirubin, hsCRP, and other acute phase reactants that peaked 24 to 48 hours post-dose and resolved by Day 14 (5). With the use of a progressive dose escalation regimen in the Phase 1b adult ASMD, such increases in ceramide, bilirubin, hsCPR and other acute phase reactants were attenuated, with the majority of AEs being mild (6).

As a result, safety biomarkers for the monitoring of olipudase alfa in pediatric patients include, but are not limited to, hsCRP, ceramide, iron, ferritin, cardiac-specific troponin I, calcitonin, interleukin (IL)-6 and IL-8.

An immune reaction against an exogenously administered recombinant protein plays a critical role in the safety of such compounds. Therefore, safety assessments will also include blood samples for anti-olipudase alfa immunoglobulin G (IgG) antibodies and neutralizing antibody formation in patients testing positive for IgG.

In the event that a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions, additional blood samples will be collected for the evaluation of:

- circulating immune complex detection; and
- immunoglobulin E (IgE), serum tryptase, and complement activation.

Additionally, skin testing may be performed, as appropriate, in patients who experience an IAR that meets the following criteria:

- Infusion associated reaction is suggestive of IgE-mediated hypersensitivity reaction, with persistent symptoms of bronchospasm, hypotension and/or urticaria requiring intervention;
- or any other signs or symptoms at the discretion of the investigator or the sponsor.

Skin testing may be another predictor of IgE-mediated reaction and may be suggested for confirmation of the IgE results.

6.4.1.2 Exploratory efficacy

Exploratory efficacy of olipudase alfa in pediatric patients will be assessed by evaluating changes in organomegaly, lung function and pulmonary imaging parameters, exercise testing, lipid profile, bone biomarkers, linear growth, and biomarkers known to be elevated in ASMD. Such biomarkers include chitotriosidase, CCL18, and ACE (8). Several of the above assessments have been identified as potential indicators of clinical outcome in ASMD (9).

Levels of the olipudase alfa enzymatic substrate sphingomyelin and sphingomyelin metabolites will also be evaluated throughout the treatment period in plasma and/or dried blood spots.

Changes in quality of life, fatigue and pain levels will be evaluated using age- appropriate scales, including the Pediatric Quality of Life Inventory (PedsQL), the PedsQL Multidimensional Fatigue Scale and the PedsQL Pediatric Pain Questionnaire. Changes in cognitive function will be evaluated in ASMD patients younger than 6 years with the Development Profile-3 (DP-3) assessment tool. Changes in adaptive function will be evaluated in ASMD patients less than 6 years using the Adaptive Behavior Assessment System (ABAS).

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

To enter this study, patients must fulfill the following criteria:

I 01. The patient and/or patient's parent(s)/legal guardian(s) must provide written informed assent/consent prior to any protocol-related procedures being performed.

I 02. The patient is male or female <18 years of age on the date of signed informed assent/consent.

I 03. The patient has documented deficiency of ASM consistent with NPD, as measured in peripheral leukocytes, cultured fibroblasts, and/or lymphocytes.

I 04. The patient has a spleen volume ≥5 multiples of normal (MN) measured by magnetic resonance imaging (MRI); patients who have had partial splenectomies will be allowed if the procedure was performed ≥1 year before screening and the residual spleen volume is ≥5 MN.

I 05. The patient's height is -1 Z-score or lower.

I 06. Female patients of childbearing potential must have a negative serum pregnancy test for beta-human chorionic gonadotropin (β-hCG).

I 07. Female patients of childbearing potential and male patients are required to practice true abstinence in line with their preferred and usual lifestyle or use two acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device or intrauterine system for the duration of the study.

7.2 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria:

E 01. The patient has received an investigational drug within the 30 days before study enrollment.

E 02. The patient has any of the following medical conditions:

a) An active, serious, intercurrent illness;

b) Active hepatitis B or hepatitis C infection;

c) Infection with human immunodeficiency virus (HIV);

d) Cirrhosis (determined by clinical evaluation);

e) Significant cardiac disease (eg, clinically significant arrhythmia, moderate or severe pulmonary hypertension or valvular dysfunction, or <40% left ventricular ejection fraction by echocardiogram);

f) Malignancy diagnosed within the previous 5 years (except basal cell carcinoma);

g) Any other extenuating circumstance that can significantly interfere with study compliance, including all prescribed evaluations and follow-up activities.

E 03. The patient has acute or rapidly progressive neurological abnormalities.

E 04. The patient is homozygous for *SMPD1* gene mutations R496L, L302P, and fs330 or any combination of these 3 mutations.

E 05. The patient has delayed gross motor skills.

E 06. The patient has had a major organ transplant (eg, bone marrow, liver).

E 07. The patient requires use of invasive ventilatory support.

E 08. The patient requires use of noninvasive ventilatory support while awake and for >12 hours a day.

E 09. The patient, in the investigator's opinion, is unable to adhere to the requirements of the study.

E 10. The patient has a platelet count $<60 \times 10^3/\mu L$ (based on the average of 2 screening samples obtained greater than 24 hours apart).

E 11. The patient has alanine aminotransferase or aspartate aminotransferase >250 IU/L or total bilirubin >1.5 mg/dL.

E 12. The patient has an international normalized ratio (INR) >1.5.

E 13. The patient is unwilling or unable to abstain from ingesting alcohol the day before through 3 days after each infusion of olipudase alfa during the treatment period. Measuring alcohol concentration in blood is not required.

E 14. The patient is scheduled during the study for in-patient hospitalization including elective surgery.

E 15. The patient requires medication(s) that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine; tricyclic antidepressants [eg, imipramine, or desipramine]).

E 16. The patient is breast-feeding.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

The study drug, olipudase alfa, is a sterile, non-pyrogenic white to off-white lyophilized cake supplied in single-use, 20 cc Type 1 glass vials. Each vial contains 20 mg of extractable olipudase alfa.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

Not applicable.

8.3 PREPARATION AND ADMINISTRATION OF TREATMENTS

8.3.1 Investigational medicinal product preparation

Detailed information on preparation and administration of olipudase alfa is provided in the pharmacy manual.

Study drug or investigational medicinal product (IMP) infusions must be prepared by a qualified, authorized pharmacist (or designee) using aseptic technique. The pharmacist or designee will determine the quantity of vials required based on the patient's weight and dose. Olipudase alfa doses should be adjusted every 4 weeks to account for patient growth.

The study drug will be reconstituted with 5.1 mL of Sterile Water for Injection to yield a concentration of 4.0 mg/mL olipudase alfa. The study drug will be further diluted in 0.9% sodium chloride for injection solution to a specific volume based on dose.

All infusions will be prepared based on patient weight (kg) and dose (ranging from 0.03 mg/kg to 3.0 mg/kg). Therefore, the total volume of the infusion will be dependent on the patient's weight and total dose, as recommended in the pharmacy manual.

The diluted solution should be filtered through a 0.2 – 0.22 micron, low protein-binding, in-line filter during administration to remove any visible particles.

Olipudase alfa should not be infused in the same intravenous line with other products.

8.3.2 Investigational medicinal product administration

For all dose levels, dosing with olipudase alfa is by intravenous infusion every 2 weeks (±3 days). The dose escalation phase and the 64-week treatment period begin with the first intravenous infusion of 0.03 mg/kg olipudase alfa on Day 1/Week 0 (Section 1.1). All subsequent olipudase alfa administrations are to be scheduled relative to the Day 1/Week 0 visit. The dose escalation phase ends with the first infusion at 3.0 mg/kg or with the identification of a patient-specific highest tolerated dose.

Patients who tolerate the 0.03 mg/kg dose at Day 1/Week 0 (one re-challenge of the 0.03 mg/kg dose is allowed) will receive a dose of 0.1 mg/kg 2 weeks later. Patients who tolerate the 0.1 mg/kg dose (one re-challenge of the first 0.1 mg/kg dose is allowed) will receive a dose of 0.3 mg/kg dose 2 weeks later. Patients tolerating 2 consecutive doses of 0.3 mg/kg will be dose escalated step-wise to receive 2 consecutive doses at 0.6 mg/kg, followed by infusions at 1.0 mg/kg and 2.0 mg/kg, and to the final target dose of 3.0 mg/kg, which is maintained for the remaining duration of the treatment period. Patients unable to tolerate 3.0 mg/kg olipudase alfa will receive the highest tolerable dose every 2 weeks until the end of the treatment period. (Refer to Section 8.3.4.2.1 for patient stopping criteria.)

Decisions regarding dose escalations may be made by discussion between the investigator and the sponsor upon review on an individual patient basis. See Section 8.3.4 for dose escalation criteria.

All infusions will take place in a monitored setting with ready access to emergency resuscitation equipment and medications.

Patients will receive intravenous olipudase alfa over a period of approximately 20 minutes to 4.5 hours, depending on the dose. The length of the infusion time may be adjusted based on the patient's tolerance of the infusion.

Infusions should be administered at approximately the same time of the day. There are no restrictions on the infusion timing with respect to meals.

8.3.3 Infusion delays or missed infusions

During the treatment period, patients are infused with olipudase alfa every 2 weeks (±3 days) with all olipudase alfa infusions scheduled relative to the first study infusion on Day 1/Week 0. If any olipudase alfa infusion is delayed by more than 3 days, the infusion is considered a missed infusion. Missed infusions should not be administered. The patient should return to the clinic for their next scheduled visit and receive their last previously tolerated dose level of olipudase alfa. If more than 1 infusion is missed during dose escalation, the next dose will be decreased by 1 level. If more than 1 infusion is missed after the patient has completed dose escalation, the last previously tolerated dose level of olipudase alfa may be administered or the dose may be decreased by 1 level at the investigator's discretion.

8.3.4 Escalation schema including dose-limiting toxicity criteria and maximally tolerated dose determination

8.3.4.1 Dose escalation schema

During dose escalation, patients will undergo in-patient hospitalization as indicated in Section 10.3.1. The following criteria will determine the next dose of olipudase alfa to be administered, provided the patient does not experience an AE that meets the patient stopping criteria (see Section 8.3.4.2.1). Only AEs not related to the patient's underlying condition will affect dose escalation. These criteria apply to AEs considered related to study treatment.

1. If the patient experiences no AE or a mild AE, escalate to the next dose.
2. If the patient experiences a moderate AE, repeat the same dose. Note: Re-challenge for patients with a moderate AE at a dose of 0.03 or 0.1 mg/kg olipudase alfa is permitted only once before the patient is discontinued from the study and replaced.
3. If the patient experiences a severe AE, decrease to the prior dose. Note: Patients with a severe AE at a dose of 0.03 mg/kg or 0.1 mg/kg olipudase alfa will be discontinued from the study and replaced. Re- challenge for patients with a severe AE at a dose of 0.3 mg/kg olipudase alfa is permitted only once (at the lower dose of 0.1 mg/kg) before the patient is discontinued and replaced.

If a patient presents on the day of infusion either with an unresolved AE or an acute illness, neither of which meets the patient stopping criteria (Section 8.3.4.2.1), the olipudase alfa infusion may be withheld or administered at the discretion of the investigator. If it is not possible to administer a regularly scheduled infusion within the 3-day window allowed per protocol, see Section 8.3.3.

8.3.4.2 Dose-limiting toxicity criteria

For the purpose of this study, the events listed under patient stopping criteria (see Section 8.3.4.2.1) are considered indicative of a potential DLT for olipudase alfa at a given dose. If a potential DLT is observed, dosing will be temporarily stopped in an individual patient or in the entire study, and the DMC will review the safety data. The DMC will then provide recommendation(s) to the sponsor regarding further patient treatment (Section 6.3). Screening for eligible patients may continue during DMC review of patient or study stopping events.

When olipudase alfa dosing is temporarily halted for a particular patient, safety monitoring of the patient will continue. If the AE(s) is/are reversible and the clinical laboratory tests (including liver function tests) have reached pre-event levels, the patient will resume dosing and receive the previously-tolerated lower dose. Depending on the patient's response, dose escalation will either continue (as described in Section 8.3.4.1) or the patient will remain at the previously tolerated dose (ie, the patient's highest tolerated dose [HTD]).

The investigator is responsible for notifying his/her Institutional Review Board/Independent Ethics Committee (IRB/IEC) in writing when a potential DLT is being evaluated at his/her investigative site.

8.3.4.2.1 Dose limiting toxicity patient stopping criteria

If any of the following AEs occur, dosing will be temporarily stopped for the specific patient who experienced the AE:

- Any SAE, not related to the patient's underlying condition and considered related to the study treatment.
- Any increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, or alkaline phosphatase (AP) >3x baseline (prior to olipudase alfa therapy) and > the upper limit of normal (ULN).
- Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT >2x ULN.
- Any increase in ALT or AST >3x the ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, fever, rash, or eosinophilia (>ULN).
- Any AE that, in the opinion of the investigator or sponsor, raises significant concern regarding the safety of olipudase alfa at the administered dose.

8.3.4.2.2 Study stopping criteria

If either of these criteria are met:

- Two patients develop the same severe AE that is not related to their underlying condition, or
- A death occurs that is assessed as related or possibly related to olipudase alfa,

an ad hoc DMC meeting will be held to review the safety data and provide its recommendations to the sponsor regarding further patient treatment.

After consideration of DMC recommendations, final decisions regarding discontinuation of study drug for all or selected clinical trial patients will be made by the Sponsor.

In the event a significant safety concern arises, the Sponsor may immediately decide to discontinue study drug dosing in all clinical trial patients prior to receipt of DMC recommendation.

If the study is temporarily or permanently halted, the Sponsor will notify the health authorities of the halt by a substantial amendment in regions where this applies.

8.4 BLINDING PROCEDURES

Not applicable. This is an open-label study design.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

This is a single-arm treatment study whereby patients who comply with all inclusion/exclusion eligibility criteria will be enrolled. Investigator sites will access an interactive response system to confirm patient enrollment.

8.6 PACKAGING AND LABELING

Olipudase alfa is packaged and labeled according to good manufacturing practices and local regulatory specifications and requirements. Refer to the pharmacy manual for additional details.

8.7 STORAGE CONDITIONS AND SHELF LIFE

All clinical trial material must be kept in a secure area with restricted access, and stored under adequate refrigerated temperature conditions, 2 to 8°C (36 to 46°F). Temperature excursions will be handled as described in the pharmacy manual.

It is recommended that the reconstituted product be used immediately after reconstitution. Additional stability data are provided in the pharmacy manual.

8.8 RESPONSIBILITIES

The investigator, the hospital pharmacist, or other personnel allowed to store and dispense the study drug will be responsible for ensuring that the study drug used in the clinical trial is securely maintained as specified by the sponsor and in accordance with applicable regulatory requirements.

All study drug will be dispensed in accordance with the investigator's prescription and it is the investigator’s responsibility to ensure that an accurate record of study drug issued and returned is maintained.

Any quality issue noticed with the receipt or use of study drug (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of study drug may be subject to initiation of a recall procedure by the sponsor. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor, in order to recall study drug and eliminate potential hazards.

Under no circumstances will the investigator supply study drug to a third party, allow the study drug to be used other than as directed by this clinical trial protocol, or dispose of study drug in any other manner.

8.8.1 Treatment accountability and compliance

Compliance to the treatment regimen will be monitored in terms of the percentage of scheduled infusions the patient receives through the treatment period. No infusions should be missed. Noncompliance is defined as missing 2 consecutive infusions (not for cause, such as when the missed infusions are required by the protocol due to a DLT) or 4 total infusions per the 64-week treatment period. As they are identified, the investigator should discuss noncompliant patients on a case by case basis with the sponsor.

The investigator or designee will keep an accurate record of all study drug received, dispensed, and returned on a per patient basis using a study drug or IMP accountability log.

8.8.2 Return and/or destruction of treatments

Reconciliation of all used, partially-used or unused treatments must be performed at the site by the investigator and the monitoring team using treatment log forms.

Authorization for destruction will be given by the sponsor once the reconciliation has been completed. This destruction can be performed at the site depending on local regulations and site specific capabilities; alternatively, study drug may be returned to the sponsor or designee for destruction.

8.9 CONCOMITANT MEDICATION

Medications and therapeutic procedures received by the patient in the 30 days prior to their first infusion until the final visit will be recorded on the Prior and Concomitant Medication electronic case report form (e-CRF) as appropriate.

Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary.

- Prior medications will be defined as medications that are taken 30 days prior to the first infusion of olipudase alfa in this study.
- Concomitant medications will be defined as medications that are taken after the first infusion of olipudase alfa in this study.

During the study, prohibited medications include those that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine; tricyclic antidepressants [eg, imipramine, or desipramine]). See the study manual for a list of concomitant medications that may decrease olipudase alfa activity.

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

Pretreatment in general is not recommended for prophylactic management of IARs. For patients who experience moderate to severe or recurrent IARs suggestive of hypersensitivity (as defined in

Section 10.6.1.3.2.1), pre-treatment regimens (eg, antihistamines, antipyretics, glucocorticoids) may be prescribed by the investigator as per clinical judgment. In particular, the need for cationic amphiphilic antihistamines administered orally or IV should be carefully considered given the potential risk for functional inhibition of olipudase alfa activity by such drugs.

8.9.1 Treatment of infusion-associated reactions

For management of mild IARs, infusion rate reductions (eg, reduced to half the rate) or temporary interruptions may mitigate the reaction. For moderate to severe or recurrent IARs, the investigator may consider the use of pre-treatment medications (eg, antihistamines, antipyretics, and/or glucocorticoids), if the symptoms are suggestive of hypersensitivity reaction, in addition to infusion rate reductions, interruptions, or discontinuation. In particular, the need for cationic amphiphilic antihistamines administered orally or IV should be carefully considered given the potential risk for functional inhibition of olipudase alfa activity by such drugs.

Patients experiencing symptoms suggestive of hypersensitivity reactions, including anaphylactic or anaphylactoid reactions, during olipudase alfa infusion should be managed according to the general standards of care consistent with the treatment of such reactions. If anaphylaxis or other severe allergic reactions occur, immediate discontinuation of the infusion should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe IARs, appropriate medical personnel and equipment to perform resuscitation must be readily available in the event of a hypersensitivity reaction.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT - SAFETY

Primary safety endpoints include data pertaining to the safety and tolerability of olipudase alfa: assessment of AEs/TEAEs, including IARs; physical examinations; neurological examinations; clinical laboratory evaluations; vital sign measurements; ECGs; safety biomarkers; Doppler echocardiography and liver ultrasound Doppler; and immune response assessments.

A site physician will assess safety findings as normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). Any abnormal findings that meet the definition of an AE per Section 10.6 will be recorded on the AE e-CRF.

9.1.1 Physical examination

Complete physical examinations will be completed as indicated in Section 1.2 and will include the following observations/measurements: general appearance, examination of the skin; head, eyes, ears, nose, and throat; lymph nodes; heart, lungs, and abdomen; extremities and joints and body mass index. The patient's weight will be measured without shoes and wearing the lightest possible clothing. At visits where height is measured, the patient will be measured without shoes. While patient height is included as part of the physical examination, z-score for height will be evaluated as an exploratory efficacy parameter.

An abbreviated physical examination will assess only the general appearance of the patient and is only required when a complete exam is not indicated.

Whenever possible, the same physician should perform the physical examination at all study visits.

9.1.2 Neurological Examination

Neurological examinations will be performed as specified in Section 1.2. Assessments include, but are not limited to the patient's mental status, posture, cranial nerves, motor system including muscle atrophy, tone and power, reflexes, sensory system, coordination, gait, and age-appropriate responses. The examination should be performed by the same neurologist throughout the study, if possible.

9.1.3 Adverse events

See Section 10.6 for details.

9.1.3.1 Infusion associated reactions

For a moderate/severe or recurrent IAR that is suggestive of a hypersensitivity reaction (as defined in Section 10.6.1.3.2.1), additional blood samples will be collected and sent to the sponsor for anti olipudase alfa antibody (IgG and IgE), tryptase activity, and complement activation testing as described below. Skin testing may also be performed if clinically indicated.

- For IgE anti-olipudase alfa antibody testing the same pre-infusion serum sample drawn for anti-olipudase alfa IgG testing (every 4 weeks) may be used if the IAR occurs at that study visit. If a pre-infusion sample was not drawn on that day, the patient should return to the study site or local laboratory at least 3 days after the event for a serum sample to be drawn. Testing is conducted for research purposes to gain additional information as to individual patients' responses to study treatment and for aiding in the clinical management of patient safety.
- Blood samples will be drawn within 1 to 3 hours of an IAR for serum tryptase activity testing (serum) and complement activation testing (plasma), when clinically indicated.
- Refer to the study manual for guidelines on the collection and shipping of samples.
- Skin testing may be performed if necessary following consultation between the investigator and the sponsor in patients who experience an IAR that meet the following criteria:
  - Assessed as moderate or severe in intensity, or recurrent, by the investigator AND.
  - Suggestive of an IgE-mediated hypersensitivity reaction (ie, persistent and intractable symptoms of hypersensitivity [as described in Section 10.6.1.3.2.1] as assessed by the investigator).

Refer to the study manual for skin testing procedures.

9.1.4 Vital signs

Vital signs will be evaluated as indicated in Section 1.2. More specifically, vitals are to be measured at every visit before, halfway through, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes). Vital signs will include heart rate (HR, beats/minute), systolic and diastolic blood pressure (mmHg), and body temperature (°F or °C).

9.1.5 Electrocardiograms

Standard 12-lead ECGs will be recorded using an electrocardiographic device at the visits and timepoints specified in Section 1.2 and Section 1.3 after at least 5 minutes in supine position, and prior to any blood collections.

For Day 1/Week 0, triplicate ECG (3 ECGs) will be recorded within 5 minutes with at least 1 minute between 2 replicates prior to IMP administration.

Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to:

- A single 12-lead ECG (25 mm/s, 10 mm/mV) printout with heart rate, PR, QRS, QT, QTc automatic correction evaluation, including date, time, initials, and patient number (ie, 9 digits) , signature of the research physician, and at least 3 complexes for each lead. This printout will be retained at the site.
- A digital storage that enables eventual further reading by an ECG reading center: each digital file will be identified by theoretical day and time, real date and real time (recorder time), sponsor study code, patient number (ie, 3 digits), date of birth, and site and country numbers, if relevant. The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory requirements (ie, FDA 21 CFR, part 11).

The study site cardiologist should review the ECGs in a timely manner to determine if there are any safety concerns and for clinical management of the patient. In the event of any CS or NCS abnormal findings that meet the definition of an AE (see Section 10.6 for definitions and reporting), the investigator will continue to monitor the patient with additional ECGs until the ECG returns to baseline or the investigator determines that follow-up is no longer necessary. The investigator's or cardiologist's assessments are to be captured in the e-CRF.

All ECGs will also be collected and read centrally by a third party independent reviewer.

9.1.6 Doppler echocardiogram

A 2-dimensional and M-mode echocardiograph with Doppler will be performed at the visits specified in Section 1.2.

Examination will include but not be limited to: left ventricular cavity size, left ventricular mass, valve characterization, ejection fraction, ventricular wall thickness, regional wall motion, systolic and diastolic functions, pericardium characterization and congenital abnormalities. Pulmonary artery pressure will be determined by Doppler ultrasound.

The review of these assessments will be performed locally by a certified cardiologist. Whenever possible, the same cardiologist will perform all evaluations per patient.

Wherever possible, the same physician should review all echocardiographs for a given patient.

9.1.7 Liver ultrasound Doppler

Liver ultrasound Doppler will be performed as specified in Section 1.2 to document hepatic blood flow characteristics, principally portal vein pressure, and blood flow direction. The structures to be examined include hepatic portal vein, the main hepatic artery and the main hepatic vein. Additional structures that may be examined include the network of intrahepatic portal veins, the main and intrahepatic arteries, the hepatic veins, the main and intrahepatic portal veins, the intrahepatic portion of the inferior vena cava, collateral venous pathways, and transjugular intrahepatic portosystemic shunts. Liver ultrasound Doppler will be performed using methods that are compatible with the standard institutional procedures of the investigational site.

9.1.8 Clinical laboratory evaluations

The following hematology, chemistry, serology and urine analyses will be evaluated as indicated in Section 1.2, Section 1.3 and Section 1.4.

- Hematology: complete blood count including white blood cell count, platelet count, hemoglobin, and hematocrit with absolute and percentage differential cell counts of lymphocytes, monocytes, neutrophils, basophils, eosinophils, and (if applicable) abnormal cells.
- Clinical chemistry: sodium, potassium, chloride, blood urea nitrogen, glucose, uric acid, calcium, phosphorus, magnesium, albumin, total protein, creatinine, AST, ALT, total bilirubin, direct bilirubin, AP.
- Coagulation: prothrombin time (Protime), partial thromboplastin time (PTT), INR, and D-dimer.
- Serology tests: hepatitis B antigen, hepatitis C antibodies, anti-human immunodeficiency virus-1 and anti-human immunodeficiency virus-2 antibodies.
- Urinalysis: dipstick for pH, ketones, glucose, bilirubin, protein and blood.
- If female of child bearing potential, β-hCG serum or urine test as appropriate per Section 1.2 and Section 10.3.

Analysis of all safety laboratory parameters will be conducted by a central laboratory. Procedures for handling and shipment of all central laboratory samples will be included in the information provided by the central laboratory. Specimens will be processed appropriately by the central laboratory facility and laboratory reports will be made available to the study investigator in a timely manner to assure appropriate clinical review.

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

The study investigator must score all abnormal laboratory values as either CS or NCS. Because some laboratory values may be outside of the normal value range due to the underlying disease, the study investigators should use clinical judgment when considering clinical significance. Clinical significance is defined as any change in laboratory parameters from baseline, which has medical relevance. If CS worsening of laboratory values from screening levels is noted, the changes will be documented as an AE and scored per Section 10.6.1.4.3. The study investigator will continue to monitor the patient with additional laboratory assessments until (1) values have reached normal range and/or screening levels, or, (2) in the judgment of the study investigator, abnormal values are not related to the administration of IMP or other protocol-specific procedures.

9.1.9 Safety biomarkers

Biomarkers for monitoring the safety of olipudase alfa include, but are not limited to hsCRP, ceramide, iron, ferritin, cardiac-specific troponin I, calcitonin, IL-6 and IL-8. Samples will be collected as specified in Section 1.2 and Section 1.3 study flow charts.

9.1.10 Immune response assessments

Samples will be collected as specified in Section 1.2 for the evaluation of anti-olipudase alfa IgG antibodies. IgG seropositive patient serum will be subsequently assessed for neutralizing IgG antibodies to olipudase alfa.

9.2 SECONDARY ENDPOINTS

9.2.1 Pharmacokinetics

9.2.1.1 Sampling time

Pharmacokinetic sampling will occur with the first infusion at 0.3, 1.0 and 3.0 mg/kg olipudase alfa and at Week 52. Specific time points and collection time windows are detailed in Section 1.5 for each age cohort. To minimize the amount of blood drawn, post-dose time points have been selected for sparse sampling of pharmacokinetic parameters and microsampling methods (volumes ≤0.5 mL) may be used.

If a patient receives only a partial infusion (eg, due to a safety concern), pharmacokinetic sampling will be repeated the next time the patient receives that dose.

Depending on patient age, blood samples will be drawn for pharmacokinetic assessments using an indwelling catheter from an arm that is not used for olipudase alfa infusions. The exact time of olipudase alfa infusions (start and stop times of infusion), rate of infusion, time of infusion rate changes, and dose will be recorded along with exact sampling times.

9.2.1.2 Number of pharmacokinetic samples

Table 1 - Approximate number of plasma samples by age cohort

	Adolescent cohort	Child cohort	Infant/early child cohort
By patient 0.3 mg/kg	7	6	5
By patient 1.0 mg/kg	7	6	5
By patient 3.0 mg/kg	7	6	5
By patient Week 52	7	6	5
Total by patient	28	24	20

9.2.1.3 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipment are provided in the study manual.

9.2.1.4 Bioanalytical method

Plasma olipudase alfa concentrations will be determined using a validated enzyme-linked immunosorbent assay (ELISA) method.

9.2.1.5 Pharmacokinetics parameters

Plasma concentration-time data will be analyzed by noncompartmental methods, nonlinear mixed effects modeling or by population-based analysis, based upon patient age and data suitability. Pharmacokinetic parameters listed in Table 2 will be calculated using noncompartmental methods from plasma olipudase alfa concentrations.

Table 2 - List of pharmacokinetic parameters and definitions

Parameters	*Drug/Analyte*	*Matrix*	*Definition/Calculation*
C_{eio}	*olipudase alfa*	*Plasma*	*Concentration at end of infusion*
C_{max}	*olipudase alfa*	*Plasma*	*Maximum plasma concentration observed*
t_{max}	*olipudase alfa*	*Plasma*	*Time to reach* C_{max}
AUC_{last}	*olipudase alfa*	*Plasma*	*Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time*
AUC	*olipudase alfa*	*Plasma*	*Area under the plasma concentration versus time curve extrapolated to infinity according to the following equation:* $AUC = AUC_{last} + \frac{C_{last}}{3_Z}$ *Values with a percentage of extrapolation >20% will not be taken into account in the descriptive statistics*
$t_{1/2z}$	*olipudase alfa*	*Plasma*	*Terminal half-life associated with the terminal slope (λz) determined according to the following equation:* $t_{1/2Z} = \frac{0.693}{\lambda_z}$ *where λz is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semi-logarithmic scale. Half-life is calculated by taking the regression of at least 3 points.*

Parameters	Drug/Analyte	Matrix	Definition/Calculation
CL	*olipudase alfa*	*Plasma*	Total body clearance of a drug from the plasma calculated using equations below: CL = Dose / AUC after the first dose or CL_{ss} = Dose / AUC_{0-T} after repeated dose; where CL_{ss} is the clearance estimated for steady state after repeated doses.
Vss	*olipudase alfa*	*Plasma*	Volume of distribution at steady state after the first dose calculated using the equation: Where, MRT is the mean residence time a molecule resides in body calculated using the equation: $MRT = \frac{AUMC}{AUC} - Tinf/2$ where, T_{inf} is the duration of infusion and AUMC is the area under the curve of moments calculated with the trapezoidal method according to the equation: $AUMC = \sum_{i=1}^{n} (t_i - t_{i-1}) \cdot \frac{(C_i \cdot t_i + C_{i-1} \cdot t_{i-1})}{2} + \frac{C_{last}}{\lambda_z^2} + \frac{C_{last} \cdot t_{last}}{\lambda_z}$ After repeated doses, $V_{ss} = CL_{ss} \cdot MRT$

9.2.2 Exploratory efficacy

For MRI, high resolution computed tomography (HRCT), and chest x-ray, a site physician will review and assess as normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). Any abnormal findings that meet the definition of an AE per Section 10.6 will be recorded on the AE.

9.2.2.1 Abdominal magnetic resonance imaging

Spleen and liver volumes will be assessed by abdominal MRI to quantitate the degree of splenomegaly and hepatomegaly at the time points specified in Section 1.2. Patients are required to fast from solid foods (liquids such as water, milk, juice allowed) for 6 hour prior to the MRI to reduce the effect of a meal.

Magnetic resonance imaging data will be collected and read centrally by a third party blinded to patient number and study visit. Procedures for abdominal MRI are detailed in the study manual.

9.2.2.2 Pulmonary imaging by high resolution computed tomography

High resolution computed tomography scans of the chest will be obtained as specified in Section 1.2 to quantitate the degree of possible infiltrative lung disease.

High resolution computed tomography will be performed using methods that are compatible with the standard institutional procedures of the investigational site. Images will be collected centrally by a medical imaging core laboratory where they will be digitized and coded, and read by a third party blinded to patient number and study visit. The mean density will be calculated at each lung level using standard HRCT software. The lung fields will be assessed by a central reader and scored subjectively for the degree of interstitial lung disease (0 = normal, 1 = mild, 2 = moderate, or 3 = severe) (10).

The bilateral lung boundaries are determined from the following 4 pre-defined levels on the HRCT images (10).

- Level 1 includes the aortic arch
- Level 2 includes the carina
- Level 3 is midway between the carina and 1 cm above the hemidiaphragm
- Level 4 is 1 cm above the hemidiaphragm

A qualitative assessment will be made of the interstitial, reticular, nodular and pleura areas of the right and left lungs based on the following criteria:

- 0 = No disease
- 1 = Mild (affecting 1 to 25% of the lung volume)
- 2 = Moderate (affecting 26 to 50% of the lung volume)
- 3 = Severe (affecting 51 to 100% of the lung volume)
- NE = Not evaluable

Procedures for HRCT are detailed in the study manual.

9.2.2.3 Pulmonary function testing

Pulmonary function testing (PFT) will be performed at the time points specified in Section 1.2 in patients ≥5 years old on day 1/week 0. Completion of PFT may also depend upon patient age and/or cooperation.

The PFT administration protocol is standardized across sites in accordance with American Thoracic Society/European Respiratory Society guidelines. Pulmonary function testing will include but will not be limited to the assessment of forced vital capacity (FVC), forced expiratory volume in the 1st second of the FVC maneuver and total lung capacity. Diffusing capacity of carbon monoxide will be used to measure gas exchange across the alveolocapillary membrane. Pulmonary function testing should occur at the same time of day across study visits (±2 hour of the screening assessment).

A trained physician should review the PFTs in a timely manner for clinical management of the patient. The investigator will continue to monitor the patient until the parameter returns to

baseline or until the investigator determines that follow-up is no longer medically necessary. Procedures for PFTs are detailed in the study manual.

9.2.2.4 Chest X-ray

A chest X-ray (posterior-anterior and lateral views) will be performed as indicated in Section 1.2 at selected sites.

A study site physician, such as the investigator, a pneumologist or a radiologist should review the chest X-ray in a timely manner to determine if there are any safety concerns, and for clinical management of the patient. Chest X-rays will be collected at the site and sent to a medical imaging core laboratory where they will be digitized (if not already done at the site), coded, and read by a third party reader blinded to patient number and study visit. The lung fields will be scored subjectively for the degree of infiltrative lung disease (10):

- 0 = No infiltrative lung disease
- 1 = Mild (affecting 1 to 25% of the lung volume)
- 2 = Moderate (affecting 26 to 50% of the lung volume)
- 3 = Severe (affecting 51 to 100% of the lung volume)

Procedures for chest x-ray scoring are detailed in the study manual.

9.2.2.5 Hand x-ray

Patients will have an x-ray performed on their left hand, fingers and wrist as indicated in Section 1.2.

X-rays will be collected at the site and sent to a medical imaging core laboratory where they will be digitized (if not already done at the site), coded, and read by a third party blinded to patient number and study visit. Bone age will be calculated using the Greulich & Pyle Atlas.

9.2.2.6 Cycle ergometry

Cycle ergometry will be performed within 1 week after infusion at the time points specified in Section 1.2. This assessment is not required in patients that are ≤6 years of age or <120 cm in height on day 1/week 0. Completion of the assessment may depend upon patient cooperation.

Cardiopulmonary status will be assessed using a stationary one-wheeled cycle used as an ergometer to measure a person's work output under controlled conditions. Patients will be asked to ride the cycle at increasing workload levels until they can no longer proceed. Patients will breathe through a tube connected to a one-way valve for continuous measurements of oxygen (O_2) uptake, carbon dioxide (CO_2) output, and tidal volume throughout the test. Heart rate, respiratory rate, and digital O_2 saturation will also be continuously monitored. Steady state levels for each workload will be calculated for O_2 uptake, CO_2 output, tidal volume, ventilation, and respiratory exchange ratio. Maximum workload achieved will be recorded and expressed as percent predicted. In addition, percent predicted maximum will be calculated for O_2 uptake and heart rate. Note that

cycle ergometry assessments must occur at the same time for each assessment (ie, ±2 hours of the screening assessment).

Procedures for cycle ergometry assessments are detailed in the study manual.

9.2.2.7 Physician's global assessment of change

The physician's global assessment of the patient's progress will be evaluated prior to infusion at the time points specified in Section 1.2.

At Week 26 and Week 52, the investigator will also evaluate the patient's current clinical status compared with screening (baseline) by marking 1 of the following 7 categories: marked improvement, moderate improvement, mild improvement, no change, mild worsening, moderate worsening, or marked worsening.

9.2.2.8 Efficacy biomarkers

Chitotriosidase, CCL18, and ACE levels will be evaluated as indicated in Section 1.2.

9.2.2.9 Lipid profile

A lipid profile will be assessed as an efficacy parameter as specified in Section 1.2.

Blood will be collected prior to infusion for lipids including total cholesterol, low density lipoprotein, high density lipoprotein, very low density lipoprotein, triglycerides, apolipoprotein B, apolipoprotein A1, and lipoprotein [a].

9.2.2.10 Bone biomarkers

Serum bone-specific alkaline phosphatase and C-telopeptide levels will be evaluated as indicated in Section 1.2.

9.2.2.11 Health outcome questionnaires

Health outcome measures will be evaluated as specified in Section 1.2 using the assessment tools summarized by age range in Table 3. Completion of questionnaires may depend upon patient age and/or cooperation.

Table 3 - Quality of life assessments

Assessment	Scale
Quality of life – general	**PedsQL Core Scales:** Young Child (5-7 years of age), Child (8-12 years of age), Teen (13-18 years of age) **Parent report for:** Infants (1-12 months of age), Infants (13-24 months of age), Toddlers (2-4 years of age), Young Child (5-7 years of age), Child (8-12 years of age), Teen (13-18 years of age)
Fatigue	**PedsQL Multidimensional Fatigue Scale, Standard version for:** Young Child (5-7 years of age), Child (8-12 years of age), Teen (13-18 years of age) **Parent report for:** Toddlers (2-4 years of age), Young Child (5-7 years of age), Child (8-12 years of age), Teen (13-18 years of age)
Pain	**PedsQL Pediatric Pain Questionnaire:** Young Child (5-7 years of age), Child (8-12 years of age), Teen (13-18 years of age) **Parent report for:** Young Child (5-7 years of age), Child (8-12 years of age), Teen (13-18 years of age)

PedsQL, Pediatric Quality of Life.

The Pediatric Quality of Life (PedsQL) scale is a brief, standardized, generic assessment instrument that systematically assesses patients' and parents' perceptions of health-related quality of life in pediatric patients with chronic health conditions (11). The PedsQL consists of a 23-item core measure including a child self-report for patients aged 5 to 18 years and a report for parents of patients from birth to 18 years of age.

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

The PedsQL Pediatric Pain Questionnaire consists of 3 questions and includes a child self-report (ages 5-18) and a proxy report for parents of patients aged 5 to 18 years. Refer to the study manual for further details.

9.2.2.12 Cognitive and adaptive function

Cognitive function will be evaluated using the DP-3 assessment tool as specified in Section 1.2. Patients that are ≥ 6 years of age on day 1/week 0 are not required to complete this assessment.

Adaptive function will be evaluated as specified in Section 1.2 using the ABAS. Patients that are ≥6 years on day 1/week 0 are not required to complete this assessment.

Refer to the study manual for further details. Completion of the above assessments may depend upon patient age and/or cooperation.

9.2.3 Pharmacodynamics

Sphingomyelin and sphingomyelin metabolites including but not limited to ceramide, lyso-sphingomyelin, and sphingosine-1-phosphate will be quantified in plasma and/or dried blood spots (DBS) as appropriate using samples collected as detailed in Section 1.2 and Section 1.3. Procedures, preparation, and sample shipment guidelines for plasma and DBS sampling are provided in the study manual.

9.2.4 Pharmacogenetic assessments

9.2.4.1 Genotyping of SMPD1, CHIT1, UGT1A1 and genes

The acid sphingomyelinase gene (*SMPD1*), the chitotriosidase gene (*CHIT1*) and the uridine diphosphoglucuronosyltransferase 1 family, polypeptide A1 gene (*UGT1A1*) will be sequenced if historical results are not available.

A blood sample will be sent to a centralized laboratory where it will be extracted to yield DNA. The DNA will be amplified by polymerase chain reaction using gene specific primers and the resulting PCR products will be sequenced for the identification of mutations and genetic variation (polymorphisms and associated haplotypes) within the genes. The chitotriosidase gene will be analyzed for the presence or absence of the 24-base pair duplication mutation. *SMPD1* mutations of patients participating in this study will be summarized and may be compared to those previously identified in ASDM patients from historical data outside of this study. Mutations will be annotated according to the guidelines of the Human Genome Variation Society (12).

9.3 OTHER ASSESSMENTS

9.3.1 Demographic information and medical/surgical history

During patient screening, demographic information including gender, date of birth, and ethnicity will be collected from each patient. Additionally, patients will provide a complete medical history. Specific information relating to any relevant prior or existing medical conditions/surgical procedures will be recorded on the patient's e-CRF. The patient's diagnosis of ASMD and first symptom date will also be collected and recorded, if available. Additional data to be collected include ASMD family history and smoking and alcohol drinking history.

9.3.2 Acid sphingomyelinase enzyme activity

Acid sphingomyelinase activity will be measured as specified in Section 1.2 in peripheral leukocytes in patients for whom these results are not available. A central laboratory may conduct the analysis of the samples and will provide reports. Sample processing, storage, and shipment guidelines are provided in the study manual.

9.3.3 Tanner staging

Patient puberty stage will be evaluated according to Tanner staging (13, 14). Tanner stage for genitals (male, stage I though V), breasts (females, stage I though V) and pubic hair (both genders, stage I through V) will be documented at times specified in Section 1.2.

9.3.4 Cross-reacting immunological material

A Western blot assay will be developed to evaluate cross-reactive immunological material (CRIM) on peripheral blood mononuclear cells to determine each patient's CRIM status. An alternative method may be considered pending sufficient cell counts in patient blood samples. This assessment is to be performed as specified in Section 1.2 and is not required in patients that are >2 years of age.

Sample processing, storage, and shipment guidelines are provided the study manual.

9.3.5 Patient photographs

Photographs (eg, abdominal) will be taken as specified in Section 1.2 of patients who volunteer to provide visual context of the disease.

9.4 FUTURE USE OF SAMPLES

For patients who have consented to it, left over samples following testing may be used for other research purposes (excluding genetic analysis) related to ASMD.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labeled with the same identifiers than the one used during the study (ie, subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.5 SAMPLED BLOOD VOLUME

No more than 7 ml/kg of blood will be collected during any 8-week period of the 64-week treatment period in all patients, regardless of age cohort. Additional blood samples may be collected at the investigator's discretion for patient safety monitoring.

Table 4 - Approximate sampled blood volume in ASMD patients ages 12 to <18 years (adolescent cohort).

		Screening period		64-week treatment period	
Assessment	**Volume per sample (mL)**	**Number of samples**	**Total (mL)**	**Number of samples**	**Total (mL)**
SMPD1 genotyping	3	1	3		
UGT1A1 genotyping	3	1	3		
CHIT1 genotyping	3	1	3		
ASM activity in leukocytes	6	1	6		
Serology tests: HIV, Hep C, Hep B	7	1	7		
Liver function	3	1	3	43	129
Clinical chemistry	4	1	4	16	64
Hematology	4	2	8	16	64
Coagulation	5	1	5	16	80
β—hCG	2	1	2	0	
Safety biomarkers	8			43	344
Anti-olipudase alfa IgG and neutralizing antibodies in IgG positive patients	3.5			13	45.5
Efficacy biomarkers	5			4	20
Lipid profile	8	1	8	6	48
Serum bone-specific ALP and C-telopeptide	4			4	16
Sphingomyelin and metabolites in plasma and/or DBS	3			43	129
Olipudase alfa pharmacokinetics	2			28	56
Total for screening (mL)			**52**		
Total for 64-week treatment period (mL)					**995.5**
Total for study (mL)				**1047.5**	

Table 5 - Approximate sampled blood volume in ASMD patients in the child cohort (6 to <12 years) and in patients aged 3 to <6 years.

		Screening period		64-week treatment period	
Type	Volume per sample (mL)	Number of samples	Total (mL)	Number of samples	Total (mL)
SMPD1 genotyping	3	1	3		
UGT1A1 genotyping	3	1	3		
CHIT1 genotyping	3	1	3		
ASM activity in leukocytes	3	1	3		
Serology tests: HIV, Hep C, Hep B	2.2	1	2.2		
Liver function	3	1	3	30	90
Clinical chemistry	4	1	4	11	44
Hematology	2	2	4	11	22
Coagulation	2.8	1	2.8	11	30.8
Safety biomarkers	6			30	180
Anti-olipudase alfa IgG and neutralizing antibodies in IgG positive patients	2.2			13	28.6
Efficacy biomarkers	3.8			4	15.2
Lipid profile	1.1	1	1.1	6	6.6
Serum bone-specific ALP and C-telopeptide	1			4	4
Sphingomyelin and metabolites in plasma and/or DBS	1.5			43	64.5
Olipudase alfa pharmacokinetics	1.5			24	36
Total for screening (mL)			**29.1**		
Total for 64-week treatment period (mL)					**521.7**
Total for study (mL)				**550.8**	

See Section 1.3 for additional information on sample collections based upon patient age.

Table 6 - Approximate sampled blood volume in adolescent ASMD patients from birth to ≤2 years of age (infant/early child cohort).

		Screening period		64-week treatment period	
Type	Volume per sample (mL)	Number of samples	Total (mL)	Number of samples	Total (mL)
SMPD1 genotyping	3	1	3		
UGT1A1 genotyping	3	1	3		
CHIT1 genotyping	3	1	3		
ASM activity in leukocytes	3	1	3		
CRIM testing	5	1	5.0		
Serology tests: HIV, Hep C, Hep B	2.2	1	2.2		
Liver function	1.1	1	1.1	29	31.9
Clinical chemistry	1.1	1	1.1	8	8.8
Hematology	1.2	2	2.4	10	12
Coagulation	1.4	1	1.4	11	15.4
Safety biomarkers	4.4			30	132
Anti-olipudase alfa IgG and neutralizing antibodies in IgG positive patients	1.1			13	14.3
Efficacy biomarkers	3.8			4	15.2
Lipid profile	1.1	1	1.1	6	6.6
Sphingomyelin and metabolites in plasma	1.5			29	43.5
Olipudase alfa pharmacokinetics	1.5			20	30
Total for screening (mL)			**26.3**		
Total for 64-week treatment period (mL)					**309.7**
Total for study (mL)				**336**	

Additional blood samples may be required for circulating immune complex detection, IgE, serum tryptase, and complement activation following moderate, severe, or recurrent mild IARs suggestive of hypersensitivity reactions. Additional blood volumes are provided in Table 7.

Table 7 - Approximate sampled blood volume per infusion following moderate, severe, or recurrent infusion associated reactions suggestive of hypersensitivity reactions

Type	Volume per sample (mL)
Circulating immune complex	3.5 mL
IgE antibodies	3.5 mL
Serum tryptase	3.5 mL
Complement	2 mL
Total per infusion	12.5 mL

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

Section 1.2 summarizes the schedule of study events for all patients enrolled in the study, with specific requirements based upon patient age and gender. Details on the timing of study assessments are provided below and in Section 1.3, Section 1.4, Section 1.5 and in Section 10.3.2 through Section 10.3.7. Individual evaluations are also described in Section 9.

10.2 SCREENING AND INCLUSION PROCEDURES

During screening, the patient or a patient representative will receive information on the study objective(s) and procedures from the investigator. The patient and/or patient representative (parent or legal guardian) will have to sign the informed assent/consent prior to any action related to the study. Screening assessments as specified in Section 1.2 may need several out-patient visits to the site or in-patient hospitalization may be required to proceed with all screening or baseline assessments. Two samples are to be collected greater than 24 hours apart during the screening period for platelet count assessments. The mean platelet count is to be used for determining patient eligibility.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible for inclusion into the study.

Retesting of any screening parameter is limited to a maximum of 3 times and with a minimum of 14 days in between reassessments. Unless indicated otherwise, the last retest value will be considered as the baseline value and reported in the e-CRF.

Screening procedures will be carried out within 60 days prior to the start of 64-week treatment period of DFI13803.

If a patient does not meet all inclusion criteria or meets one or more exclusion criterion within 60 days prior to the start of the treatment period, the patient may rescreen for the study once. For screening failures, the following data obtained during screening will be transferred to the e-CRF and entered into the database: patient's demographic data, inclusion and exclusion criteria, relevant medical history and surgical history (if available), previous and concomitant medications (if available), AE data (if available) and reason for failure.

10.3 TREATMENT PERIOD PROCEDURES

Final inclusion in the study will be performed just before study drug infusion at Day 1/Week 0 of the treatment period.

Retesting of parameters during the treatment period is limited to one time, except for when the measurement has not been obtained in accurate conditions.

The dose escalation phase and the 64-week treatment period begins with the first intravenous infusion of 0.03 mg/kg olipudase alfa on Day 1/Week 0.The dose escalation phase ends with the first infusion at 3.0 mg/kg or with the identification of a patient-specific highest tolerated dose.

Day 1/Week 0 and Week 12 assessments and samples are to be collected per quarterly visit specifications, even though patients are actively dose escalating at these clinical visits. Samples are not to be collected in duplicate (ie, Week 12 quarterly visit and dose escalation visit) under such circumstances.

10.3.1 Hospitalization

In-patient hospitalization will be required before and for at least 24 hours after infusion for all infusions during the dose escalation process through the second infusion at the highest tolerated dose. Patients may be required to stay in the hospital for additional time for safety purposes at the investigator's discretion. If discharged 24 hours after infusion, patients are required to return to the clinical site for assessments at 48 hours post infusion, and at 96 hours post infusion if necessary for pharmacokinetic samples.

After the second infusion at the highest tolerable dose, patients will be observed for a minimum of 3 hours following infusion completion, and may be discharged at the investigator's discretion. For quarterly visits at Week 26, Week 38 and Week 52 patients will be observed for a minimum of 3 hours following infusion completion, and may be discharged at the investigator's discretion. However, patients are required to return to the clinical site for assessments at 24 hours and 48 hours post infusion, and at 96 hours if necessary for pharmacokinetic samples.

10.3.2 Day 1/Week 0 procedures (Quarterly visit schedule)

After a patient (or parent or guardian) has provided informed consent, met all inclusion and none of the exclusion criteria, the following assessments are to be completed at Day 1/Week 0 as follows:

- Complete physical exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Neurological exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Body weight, height, BMI: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Vital signs: Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).

- ECG: in triplicate within 24 hours prior to olipudase alfa infusion (pre-infusion); in single analysis at the end of infusion (within 10 minutes following end of infusion), 24 and 48 hours following end of infusion (±3 hours).
- Clinical laboratory samples for liver function testing, clinical chemistry, hematology, and coagulation: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
  - Urinalysis: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Urine β-hCG pregnancy test: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Safety biomarkers: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
- Immunogenicity samples: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Efficacy biomarkers: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Lipid profile: as indicated by age cohort in Section 1.2. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion.
- Bone biomarkers: as indicated by age cohort in Section 1.2, within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Plasma and/or DBS sphingomyelin and metabolites: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.

10.3.3 Dose escalation visits and 2nd infusion at 3.0 mg/kg or highest tolerated dose procedures

The following assessments are to be completed for each dose escalation visit:

- Abbreviated physical exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Doppler echocardiogram: within 24 hours prior to the first infusion of 3.0 mg/kg olipudase alfa or highest tolerated dose (pre-infusion).
- Body weight, height, BMI: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- ECG: with each new dose ≥0.3 mg/kg; within 24 hours prior to olipudase alfa infusion (pre-infusion), at the end of infusion (within 10 minutes following end of infusion), 24 hours and 48 hours following end of infusion (±3 hours).
- Vital signs: Every visit. Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).

- Liver function testing: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
- Urine β-hCG pregnancy test: within 24 hours prior to olipudase alfa infusion (pre-infusion, every 4 weeks).
- Safety biomarkers: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
- Plasma and/or DBS sphingomyelin and metabolites: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
- Immunogenicity samples: within 24 hours prior to olipudase alfa infusion (pre-infusion) every 2 weeks from Day 1/Week 0 through Week 16.
- Pharmacokinetics: with the first infusion at 0.3, 1.0 and 3.0 mg/kg. See Section 1.5 for sample collection times per age cohort.

10.3.4 Quarterly visit procedures at Week 12 and Week 38

The following assessments are to be completed for the Week 12 and Week 38 visit:

- Tanner staging: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Complete physical exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Neurological exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Body weight, height, BMI: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Vital signs: Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).
- ECG: within 24 hours prior to olipudase alfa infusion (pre-infusion), at the end of infusion (within 10 minutes following end of infusion), 24 hours and 48 hours following end of infusion (±3 hours).
- Clinical laboratory samples for liver function testing, clinical chemistry, hematology, and coagulation: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
  - Urinalysis: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Urine β-hCG pregnancy test: within 24 hours prior to olipudase alfa infusion (Week 12 only, pre-infusion).

- Safety biomarkers: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
- Immunogenicity samples: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Lipid profile: as indicated by age cohort in Section 1.2. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion.
- Pharmacokinetics: if applicable at Week 12 with the first infusion at 1.0 mg/kg. See Section 1.5 for sample collection times per age cohort.
- Plasma and/or DBS sphingomyelin and metabolites: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.

10.3.5 Quarterly visit procedures at Week 26 and Week 52

The following assessments are to be completed for Week 26 and Week 52 visits:

- Tanner staging: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Complete physical exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Neurological exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Body weight, height, BMI: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Patient photos: within 24 hours prior to olipudase alfa infusion (Week 52, pre-infusion, optional).
- Doppler echocardiogram: within 24 hours prior to olipudase alfa infusion (Week 52 only, pre-infusion).Vital signs: Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).
- Vital signs: Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).
- ECG: within 24 hours prior to olipudase alfa infusion (pre-infusion), at the end of infusion (within 10 minutes following end of infusion), 24 hours and 48 hours following end of infusion (±3 hours).
- Clinical laboratory samples:
  - Liver function testing, clinical chemistry and coagulation: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
  - Hematology

a) Week 26: within 24 hours prior to olipudase alfa infusion (pre-infusion), 24 hours (adolescent cohort only) and 48 hours following end of infusion (±3 hours).

b) Week 52:

- Pre-infusion: Two (2) samples to be collected greater than 12 hours but less than 24 hours apart. The first sample can be collected up to 24 hours prior to olipudase alfa administration at Week 52. If necessary, the second sample may be collected following olipudase alfa infusion at Week 52.
- 24 hours following end of infusion (adolescent cohort only, ±3 hours).
- 48 hours following end of infusion (±3 hours).

c) Urinalysis: within 24 hours prior to olipudase alfa infusion (pre-infusion).

- Urine β-hCG pregnancy test: within 24 hours prior to olipudase alfa infusion (Week 52 only, pre-infusion).
- Safety biomarkers: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.
- Immunogenicity samples: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Spleen and liver volume by MRI: within 7 days after Week 26 or Week 52 olipudase alfa infusion.
- Pulmonary imaging by HRCT (Week 52 only): within 7 days after Week 52 olipudase alfa infusion.
- Pulmonary function testing: within 7 days after Week 26 or Week 52 olipudase alfa infusion.
- Chest X-ray (at selected sites, Week 52 only): within 7 days after Week 52 olipudase alfa infusion.
- Hand X-ray (Week 52 only): within 7 days after Week 52 olipudase alfa infusion.
- Cycle ergometry: within 7 days after Week 26 or Week 52 olipudase alfa infusion.
- Liver ultrasound Doppler: within 7 days after Week 52 olipudase alfa infusion.
- Physician global assessment: within 24 hours prior to Week 26 or Week 52 olipudase alfa infusion.
- Efficacy biomarkers: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Lipid profile: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Bone biomarkers: as indicated by age cohort in Section 1.2, within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Plasma and/or DBS sphingomyelin and metabolites: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion. Post infusion samples to be collected ±3 hours from scheduled time.

- Health outcome questionnaires: within 7 days after Week 26 and Week 52 olipudase alfa infusion.
- Cognitive and adaptive function testing: within 7 days after Week 26 and Week 52 olipudase alfa infusion.
- Pharmacokinetics (Week 52 only): See Section 1.5 for sample collection times per age cohort.

10.3.6 Non-dose escalation, non-quarterly visits occurring before Week 26

The following assessments are to be completed:

- Abbreviated physical exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Body weight, height, BMI: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Vital signs: Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).
- Liver function testing: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Urine β-hCG pregnancy test: within 24 hours prior to olipudase alfa infusion (pre-infusion), every 4 weeks.
- Safety biomarkers: as indicated by age cohort in Section 1.3 and Section 1.4, within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Plasma and/or DBS sphingomyelin and metabolites: as indicated by age cohort in Section 1.3 and Section 1.4, within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Immunogenicity samples: every 2 weeks from Day 1/Week 0 through Week 16 (pre-infusion).

10.3.7 Non-dose escalation, non-quarterly visit occurring after Week 26

The following assessments are to be completed:

- Abbreviated physical exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Body weight, height, BMI: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Vital signs: Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 hours postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).
- Urine β-hCG pregnancy test: within 24 hours prior to olipudase alfa infusion (pre-infusion), every 4 weeks.

10.3.8 Visit procedures at Week 64

The following assessments are to be completed:

- Abbreviated physical exam: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Body weight, height, BMI: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Vital signs: Before (within 30 minutes prior) infusion, halfway through infusion, and after infusion (±10 minutes). Postinfusion vital signs are measured every 30 minutes for the first 2 hours, hourly for 2 to 6 postinfusion, and then once every 8 hours until the patient is discharged (±10 minutes).
- Clinical laboratory samples:
  - Liver function testing, clinical chemistry and coagulation: as indicated by age cohort in Section 1.3 and Section 1.4. Preinfusion samples to be collected within 24 hours prior to olipudase alfa infusion.
  - Urinalysis: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Urine β-hCG pregnancy test: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Safety biomarkers: as indicated by age cohort in Section 1.3 and Section 1.4, within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Plasma and/or DBS sphingomyelin and metabolites: as indicated by age cohort in Section 1.3 and Section 1.4, within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Immunogenicity samples: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Efficacy biomarkers: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Lipid profile: within 24 hours prior to olipudase alfa infusion (pre-infusion).
- Bone biomarkers: as indicated by age cohort in Section 1.2, within 24 hours prior to olipudase alfa infusion (pre-infusion).

10.3.9 Alcohol consumption

Patients must be willing to abstain from the use of alcohol for 1 day before and 3 days after each olipudase alfa infusion for the duration of the treatment period. Note: blood alcohol levels are not required.

Patients should be counseled to limit alcohol consumption for the entire duration of the study: male patients to a maximum of 30 g alcohol per day; female patients to a maximum of 15 g alcohol per day. Per the investigator's discretion, patients who fail to limit alcohol may be discontinued from the study.

10.3.10 Pregnancy

Pregnancy will lead to permanent treatment discontinuation in all cases. No studies of olipudase alfa have been conducted in pregnant women. To ensure patient safety for this study, all female patients of childbearing potential must have a negative serum β-hCG pregnancy test at screening and before undergoing any further assessments and procedures. In addition, these patients are required to have a negative urine β-hCG pregnancy test every 4 weeks before undergoing visit specific assessments and receiving olipudase alfa.

Every effort should be made to prevent pregnancy during this study. Female patients of childbearing potential and male patients are required to practice true abstinence in line with their preferred and usual lifestyle or use two acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device or intrauterine system for the duration of the study.

10.4 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records (eg, hospital records, clinical and office charts, laboratory reports and notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided in the e-CRF.

10.5 HANDLING OF TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the source and e-CRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to treatment discontinuation in all cases.

10.5.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation decided by the investigator corresponds to more than 1 infusion not administered to the patient.

Temporary treatment discontinuation (also referred to as treatment interruption) may be considered by the investigator because of suspected AEs.

Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the investigator has considered to his/her best medical judgment that the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2). Before re-initiation of treatment, the sponsor must be consulted to determine the starting dose and if dose escalation is required (see Section 8.3.3 and Section 8.3.4).

For all temporary treatment discontinuations, the duration should be recorded by the investigator in the appropriate screens of the e-CRF.

10.5.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the investigator or the patient not to re-expose the patient to the IMP at any time.

10.5.3 List of criteria for permanent treatment discontinuation

The patient may withdraw from treatment with the IMP if he/she decides to do so, at any time and irrespective of the reason, or this may be the investigator's or sponsor's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients should discontinue the IMP for the following reasons:

- Unacceptable toxicity (see Section 8.3.4.2).
- The need for intervention or therapy precluded by protocol, and determination by the investigator that it is medically necessary to do so.
- Patient noncompliance with treatment or if the patient wishes to be withdrawn from treatment.
- The patient is no longer deriving clinical benefit, in the opinion of the investigator.
- Pregnancy

In addition, the sponsor may decide to discontinue the trial prematurely for any other reason.

Any abnormal laboratory value or ECG parameter relevant to the situation will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.5.4 Handling of patients after permanent treatment discontinuation

If a patient or parent/legal guardian decides to discontinue participation in the study, he should be contacted by the study investigator in order to obtain information about the reason(s) for discontinuation and collection of any potential AEs.

When possible, all tests and evaluations listed in Section 1.2 for the post treatment withdrawal visit should be carried out within 2 weeks of the last olipudase alfa infusion. If a patient fails to return for the necessary visits, every effort must be made to contact the patient and determine the reason(s) and recorded on the e-CRF.

In all cases, the sponsor must be notified of all study terminations as soon as possible and the reason for and date of withdrawal from the study must be recorded in the e-CRF and in the patient's medical record.

10.5.5 Procedure and consequence for patient withdrawal from study

If possible, the patients are assessed using the procedure indicated for study withdrawal in Section 1.2.

For patients who fail to return to the site, the investigator should make the best effort to contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

10.5.6 Replacement of patients

The minimum number of patients to be evaluated by age cohort is specified in Section 6.1. Once these are met, if a patient prematurely discontinues the study after tolerating 2 consecutive doses of olipudase alfa at 0.3 mg/kg, an additional patient may be enrolled.

10.6 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.6.1 Definitions of adverse events

10.6.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.6.1.2 Serious adverse event

An SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:

a) Allergic bronchospasm,

b) Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),

c) Convulsions (seizures, epilepsy, epileptic fit, absence, etc).

- Development of drug dependence or drug abuse
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the investigators).

10.6.1.3 Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

AESIs include the following:

10.6.1.3.1 Pregnancy

Pregnancy of a female patient entered in the study as well as pregnancy occurring in female partner of a male patient enrolled in this study. See Section 10.7 for additional details.

10.6.1.3.2 Infusion-associated reactions

Some AEs may be manifestations of IARs, including hypersensitivity reaction, acute phase reactions (APR), and cytokine release syndrome (CRS), as described in Section 10.6.1.3.2.1, Section 10.6.1.3.2.2, and Section 10.6.1.3.2.3, respectively. However, original signs and symptoms must be reported as AEs. In the e-CRF, investigators are asked to identify whether a specific AE represents a clinical manifestation of the IAR.

Infusion-associated reactions are defined as AEs that occur during the infusion or within up to 24 hours after the start of infusion and are considered as related or possibly related to the study treatment by the investigator or the sponsor. An event occurring ≥24 hours after the start of an infusion may be judged an IAR at the discretion of the investigator or sponsor. For this study of olipudase alfa, IARs may present as different types of reactions, such as hypersensitivity reactions, APRs, and CRS.

10.6.1.3.2.1 Hypersensitivity reactions

Infusion-associated hypersensitivity reactions seen with other enzyme replacement therapies are typically immunoglobulin-mediated (IgG/IgE) and occur after sensitization. After subsequent exposure to the antigen typically early into or shortly after the infusion, a "sensitized" patient may experience a broad range of allergic reactions that can be mild to severe or life threatening. Anaphylaxis (or anaphylactic reaction) is a serious, IgE mediated allergic reaction that is rapid in onset, and may cause death (15). Anaphylactoid, or non-immunologic anaphylaxis, reactions may present with similar serious clinical manifestations as anaphylaxis, but without prior exposure to the drug and are due to nonimmunologic-mediated mast cell degranulation. Although mechanistically different, anaphylactic and anaphylactoid reactions are treated similarly.

Common symptoms of hypersensitivity reactions seen with other enzyme replacement therapy include urticaria, rash, dyspnea, and less frequently, angioedema. Other symptoms of hypersensitivity IARs, APRs and CRS include fever, hypotension, tachycardia, nausea, vomiting, pain, and headache.

There were no IAR suggestive of hypersensitivity in the Phase 1b trial (6).

10.6.1.3.2.2 Acute phase reactions

Acute phase reactions observed in the phase 1 and phase 1b studies are considered as one type of IAR, specific to the infused olipudase alfa therapy (5, 6). From observations in both studies the APR reactions typically occurred within 12-72 hours following an infusion of olipudase alfa and were indicative of an inflammatory response. APRs were associated with elevations in hsCRP and changes acute phase reactants including, but not limited to, neutrophils, iron, ferritin, fibrinogen, D-dimer, transferrin, albumin, protime, and partial thromboplastin time. Patient AEs associated with the APR included (but are not limited to) pyrexia, nausea, vomiting, fatigue, and pain. Acute phase reaction is determined based on combined significant laboratory findings and clinical symptoms.

10.6.1.3.2.3 Cytokine release syndrome

Cytokine release syndrome is another type of IAR, attributed to the release of excessive amounts of cytokines shortly after the intravenous administration of certain therapeutic agents. The severe form of CRS is a cytokine storm, which may be life threatening. Nonclinical studies of high-dose olipudase alfa have suggested the possibility of cytokine release syndrome. The Phase 1 single dose study (5) demonstrated increases in IL-8 and IL-6; macrophage inflammatory protein 1, alpha component; macrophage inflammatory protein 1, beta component; and other cytokines and biomarkers (based Myriad Rules-Based Medicine Human Multi-Analyte Profile® antigen panel) after a single dose of ≥0.3 mg/kg olipudase alfa. In the Phase 1b trial, increases in mean IL-6 and IL-8 values were associated with the first administrations of olipudase alfa at doses 0.6 mg/kg through 2.0 mg/kg and tended to be concurrent with acute phase responses (6). Unlike immunoglobulin-mediated hypersensitivity reactions, no prior antigen exposure is required for the development of CRS. Symptoms of CRS develop soon after exposure, and range from mild to severe. Although CRS shares some symptoms with other IARs (ie, hypersensitivity reactions and APRs), symptoms typical of CRS include pyrexia, nausea, vomiting, fatigue, pain, myalgia, and in severe cases, multi-organ system dysfunction or failure, severe headache, and pulmonary edema. Cytokine release syndrome is determined based on combined significant laboratory findings and clinical symptoms.

10.6.1.4 Definitions for criteria of adverse events

10.6.1.4.1 Definition of a protocol-related adverse event

A protocol-related AE is an AE occurring during a clinical study that is not product related (either investigational or control), but is considered by the investigator or the Medical Monitor to be related to the research conditions (ie, related to the fact that a patient is participating in the study). For example, a protocol-related AE may be an untoward event occurring during a washout period of a treatment other than the investigational product or an event related to a medical procedure required by the protocol.

10.6.1.4.2 Relationship to study treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. This assessment is to be made in blinded studies and also for known comparators. For each AE/SAE the investigator is to determine whether there is a reasonable possibility demonstrated by evidence which suggests a causal relationship between the study treatment and the AE according to the categories below:

- Not Related: There is no suspicion of a causal relationship between exposure and the AE.
- Unlikely Related: There is no evidence for a causal relationship between exposure and the AE; however, such a relationship cannot be ruled out.
- Possibly Related: There is some evidence supporting the possibility of a causal relationship between exposure and the AE.
- Related: There is strong evidence that there is a causal relationship between exposure and the AE.

A relationship to the investigational product must be assigned for each AE/SAE recorded, even if there is only limited information at the time. The investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

10.6.1.4.3 Severity of adverse event scoring

Note that "severity" is not the same as "seriousness", which is defined in Section 10.6.1.2.

Intensity:

- Mild = no modification of daily activities and does not require mandatory corrective/symptomatic treatment
- Moderate = hinders normal daily activities and/or requires mandatory corrective/symptomatic treatment
- Severe = prevents daily activities and requires mandatory corrective/symptomatic treatment

10.6.1.4.4 Outcome

Outcome describes the status of the AE. The investigator will provide information regarding the patient outcome of each AE. Definitions for possible results of an AE include:

- Fatal: The termination of life as a result of an AE.
- Not recovered/not resolved: The patient has not recuperated or the AE has not improved.
- Recovering/resolving: The patient is recuperating or the AE is improving.
- Recovered/Resolved: The patient has recuperated or the AE has resolved.
- Recovered with sequelae/resolved with sequelae: The AE has resolved, but the patient has been left with symptoms or pathology.
- Unknown: Not known, not observed, not recorded, or refused.

10.6.1.4.5 Action taken regarding the investigational product

The investigator will be required to provide the action taken regarding investigational product (eg, active, comparator) in response to the AE. Options include:

- Dose increased: Increase in the frequency, strength or amount of investigational product administered.
- Dose not changed: No change in administration of the investigational product.
- Dose reduced: Reduction in the frequency, strength or amount of investigational product administered.
- Drug (investigational product) interrupted: Temporary interruption in administration of the investigational product.
- Drug (investigational product) withdrawn: Administration of the investigational product terminated (no further dosing).
- Not applicable: Determination of a value is not relevant in the current context.
- Unknown: Not known, not observed, not recorded, or refused.

10.6.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- Except for IARs, whenever possible, diagnosis or single syndrome should be reported instead of symptoms. For IARs, all symptoms must be separately recorded.
- The investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.
- The investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI (see Section 10.6.1.3)

10.6.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.6.4 Guidelines for reporting adverse events of special interest

10.6.4.1 Reporting of adverse events of special interest with immediate notification

For AESIs the sponsor will be informed within 24 hours as per the SAE notification instructions described in Section 10.6.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

- Pregnancy
  - Pregnancy occurring in a female patient included in the clinical trial as well as pregnancy occurring in a female partner of a male patient enrolled in the study. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
  - In the event of pregnancy, study drug should be discontinued.
  - Follow-up of the pregnancy is mandatory until the outcome has been determined.

- Infusion-associated reaction (see Section 10.6.1.3.2), which include:
  - Hypersensitivity reactions (see Section 10.6.1.3.2.1)
  - Acute-phase reaction (see Section 10.6.1.3.2.2)
  - Cytokine release syndrome (see Section 10.6.1.3.2.3)
- Symptomatic overdose with IMP

  Note: An overdose (accidental or intentional) of study drug is defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration. The circumstances (ie, accidental or intentional) will be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
- The following laboratory values and symptoms (see also Patient Stopping Criteria in Section 8.3.4.2), as follows:
  - Any increase in AST, ALT, total bilirubin, or AP >3x baseline (before olipudase alfa therapy) and > ULN;
  - Any increase in total bilirubin or AP >1.5x baseline, in the presence of AST or ALT > 2x ULN;
  - Any increase in ALT or AST >3x ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy), with symptoms of fatigue, nausea, vomiting, fever, rash, or eosinophilia (>ULN).
- Any AE that, in the opinion of the investigator or sponsor, raises significant concern regarding the safety of olipudase alfa at the administered dose.

10.6.4.2 Reporting of adverse events of special interest without immediate notification

- Asymptomatic overdose with IMP (see Section 10.6.4.1 for definition of an overdose).

10.6.5 Guidelines for management of specific laboratory abnormalities

Not applicable.

Table 8 - Summary of adverse event reporting instructions

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.6.1.2	Yes	Yes	No
		ALT ≥ 3 ULN	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Symptomatic overdose	Yes	Yes	No
		Infusion associated reactions (IAR)/Hypersensitivity reactions	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes

AE: adverse event; AESI: adverse event of special interest; SAE: serious adverse event; ULN: upper limit of normal

10.7 PREGNANCY REPORTING

Female patients will be instructed to notify the investigator immediately if they discover they are pregnant. Pregnant female patients will be discontinued from the study.

Male patients will be instructed to notify the investigator immediately if they discover that their sexual partner is pregnant.

If the investigator learns of a report of pregnancy at any time after signing the informed consent, the investigator should follow the instructions in Section 10.6.4.1 to contact the sponsor within 24 hours. The investigator is to complete the AE form, the Safety Complementary form and the Pregnancy forms. The patient will be followed until the outcome of the pregnancy is known (eg, live birth or stillbirth). The investigator will be responsible for this follow-up.

If not otherwise established, the investigator will inform the patient that the sponsor is required to gather information regarding the course and outcome of the pregnancy after exposure to a study product. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional time points. All study related visits/contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

Please note that pregnancy in and of itself is not an AE or an SAE. Pregnancy should not be entered into the e-CRF as an AE unless the investigator suspects an interaction between the study treatment and the contraceptive method. Additionally all information received will be assessed for any AEs and SAEs and processed per study guidelines. If the patient is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths are reported as SAEs.

10.8 OBLIGATIONS OF THE SPONSOR

During the course of the study, the sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction), to the health authorities, IECs/IRBs as appropriate and to the investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the health authorities, according to local regulations.

The sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.9 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

A SAP will be written and finalized prior to database lock to give guidance to the statistical analysis. It will be in compliance with the International Conference on Harmonisation (ICH) and Food and Drug Administration's (FDA) Guidance for Industry: Statistical Principles for Clinical Trials.

The sponsor or its designee will perform the statistical analysis of the data from this study. The analysis will be performed using the SAS® statistical software system Version 9.1 2 or higher.

11.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations have been performed. Sample size for this study was based upon empirical considerations.

A total of at least 20 patients with ASMD < 18 years of age will be enrolled.

At least 12 patients will be enrolled in a staggered fashion to 3 age cohorts with a minimum of 3 patients aged from 12 to <18 years (adolescent cohort), 3 patients aged from 6 to <12 years (child cohort), and 2 patients with ages ranging from birth to <6 years (infant/early child cohort); followed by at least 8 additional patients <12 years enrolled without staggering. Out of the 8 additional patients, at least 4 patients in the child cohort and at least 2 patients in the infant/early child cohort will be enrolled.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who signed the informed consent, signed informed assent or whose parent or guardian signed informed consent.

Enrolled patients are defined as those who meet the inclusion criteria and none of the exclusion criteria.

All patients who receive an infusion of olipudase alfa (total or partial) will be included in the summary of patient disposition.

The number of patients screened, enrolled, treated, completing the study, and not completing study along with primary reason for discontinuation will be presented. The number of screen failures, and the reason for screen failure, will also be presented. Patient disposition data will also be listed.

11.3 ANALYSIS POPULATIONS

11.3.1 Safety population

All patients who were exposed to IMP, regardless of the amount of treatment administered (partial or total).

11.3.2 Pharmacokinetic population

The pharmacokinetic population includes all patients who receive at least 1 infusion of study medication and have evaluable pharmacokinetic data.

11.3.3 Modified intent-to-treat population

The modified intent-to-treat population is the same as the safety population, and is used as the primary population for the efficacy analysis.

11.3.4 Pharmacodynamic population

The pharmacodynamic population includes all patients who have at least 1 infusion of study medication and have at least one evaluable pharmacodynamics measurement available post-baseline.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure will be assessed and descriptive statistics will be presented for all patients who receive an infusion of olipudase alfa (total or partial) as detailed in the SAP.

11.4.1.1 Compliance

A given administration will be considered noncompliant if the patient did not take/complete the planned infusions as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (n, mean, standard deviation [SD], median, minimum, and maximum). The percentage of patients with compliance is <80% will be summarized.

11.4.2 Analyses of safety endpoints

Olipudase alfa safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, graphics). Safety analyses will be performed using the safety population. Since the safety population includes patients who are

withdrawn due to intolerance of 0.1 or 0.3 mg/kg olipudase alfa, their safety data will be reported up to and including the time of withdrawal, and follow-up for AEs, where applicable.

The baseline value is defined generally as the last available value before study drug administration.

Selected safety data may be presented by manufacturing scale.

For all safety data, the observation period will be divided into three segments:

- The pre-treatment period is defined as the time between when the patient gives informed consent and the start of the first IMP administration (excluded);
- The on-treatment period will be defined as the time from the start of IMP administration (included) and till end of Week 64, or end of study (EOS);
- The post-treatment period is defined as the time after the EOS visit (excluded).

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, vital signs, and ECG.
- Potentially clinically significant abnormality criteria will determine which patients had at least 1 PCSA during the treatment emergent period, taking into account all evaluations performed during the treatment emergent period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment emergent PCSA percentage.
- Treatment period: the treatment period used for quantitative analysis is defined as the time from first infusion to the last study drug infusion + 14 Days.

11.4.2.1 Adverse events

The definitions in Section 10.6.1 will be used for AEs. Pre-treatment AEs will be listed and presented separately from treatment-emergent AEs.

Adverse events will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event incidence tables will be presented by MedDRA system organ class (SOC) (sorted by internationally agreed order) and preferred term (PT) sorted in decreasing number of patients within SOCs and further alphabetical order within the same number of patients over different PTs for each age group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is the safety population for the entire study and each age group cohort.

Adverse events will be classified into pre-defined standard categories according to chronological criteria:

- Pre-treatment AEs: AEs that occurred or worsened during the pre-treatment period;
- Treatment-emergent AEs (TEAEs): AEs that occurred or worsened during the on-treatment period);
- Post-treatment AEs: AEs that occurred or worsened during the post-treatment period.

If the start date of an AE is incomplete or missing, then the AE will be considered as a TEAE unless a partial date shows it as a pre- or post-treatment event.

All AEs reported in the study will be listed, sorted by patient, and onset date.

11.4.2.1.1 Treatment-emergent adverse events

Patients presenting TEAEs will be listed sorted by age group, SOC and PT.

The number and the percentage of patients with at least one TEAE, severe TEAE, serious TEAE and TEAE leading to treatment discontinuation will be summarized by age group.

Treatment-emergent AEs will be summarized, tabulating:

- The number and percent of patients with at least one TEAE within each and overall SOC(s);
- The number and percent of patients experiencing each PT in each SOC;
- The number of occurrences of all PTs within each and overall SOC(s);
- The number of occurrences of each PT in each SOC.

11.4.2.1.2 Deaths, serious, and other significant adverse events

Any deaths and SAEs will be listed.

11.4.2.1.3 Adverse events leading to treatment discontinuation

Any AEs leading to treatment discontinuation will be listed.

11.4.2.1.4 Adverse events of special interest (AESI)

Adverse events of special interest will be listed, including IAR, APR and CRS.

11.4.2.2 Clinical laboratory tests

The values to be used as baselines will be the values collected on Day 1/Week 0 (D1) pre-infusion assessment with the exception of white blood cell count, platelet count, and hemoglobin. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be considered as baseline, provided they were done pre- infusion.

Baseline white blood cell count, platelet count, and hemoglobin values will be calculated using the mean of 2 samples collected greater than 24 hours apart during the screening period.

Abnormalities analyses

For parameters with laboratory ranges and/or abnormality criteria, an on-treatment analysis will be performed using all post-baseline assessments done during the on-treatment period, including rechecked values. Counts of patients with PCSAs will be provided in summary tables showing shifts from normal and abnormal baselines to post-baseline abnormalities, presented by age group the PCSA occurred in. The same type of summary tables will be provided for out-of-normal laboratory range values.

A listing of liver function data for patients who experienced at least one occurrence of ALT ≥3 ULN and at least one occurrence of total bilirubin ≥2 ULN during the study with at least one of them being post first infusion will be also provided.

Descriptive statistics

For laboratory parameters, observed raw data, change from baseline and percent change from baseline will be summarized in descriptive statistics.

Listings

All individual data, including rechecked values, for planned hematology and biochemistry evaluations, will be listed. If any, data from unscheduled laboratory tests will be also listed. In these listings, individual data will be flagged when lower or higher than the lower or upper laboratory limits and/or when reaching the absolute limit of PCSA criteria, when defined. A data listing of individual post-baseline abnormalities by patient and time point will be provided.

11.4.2.3 Vital signs

Heart rate and blood pressure

Heart rate and blood pressure, systolic and diastolic, will be analyzed as observed parameter value and change from baseline.

The values to be used as the baselines will be the Day 1/Week 0 pre-infusion value. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be considered as baselines, provided they were done pre-infusion.

Abnormality analysis

For all parameters, an “on-treatment” analysis will be performed using all post-baseline assessments done during the on-treatment period, including rechecked values. Counts of patients with post-baseline PCSAs will be provided in summary tables regardless of the normal or abnormal status of the baseline by age group.

Descriptive statistics

For heart rate (in beats/minute) and blood pressure (in mmHg) observed raw data and change from baseline will be summarized in descriptive statistics, for each type of measurement, parameter and time point.

Listings

All individual data, including rechecked values, will be listed by type of measurement. In the listings, values will be flagged when reaching the limits of the PCSA criteria, when defined. A data listing of individual post-baseline abnormalities by patient will be provided.

Comments related to vital sign evaluations will also be listed, if any.

11.4.2.4 Electrocardiogram

Heart rate (in bpm), PR (in ms), QRS (in ms), QT-intervals (in ms) and corrected QT-intervals (QTc) will be analyzed as raw parameter values and change from baseline (for HR, PR, QT, QTc). Outlier summaries for the ECG parameters (eg, QTc) will also be created.

The values to be used as the baselines will be the mean of the triplicate measurements on Day 1/Week 0 pre-IMP values. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be considered as baselines, provided they were done prior to the first olipudase alfa infusion.

Abnormality analysis

For all parameters, an “on-treatment” analysis will be performed using all post-baseline assessments done during the on-treatment period, including rechecked values. Counts of patients with post-baseline PCSAs will be provided in summary tables regardless of the normal or abnormal status of the baseline by age group.

Descriptive statistics

For all parameters, raw data and changes from baseline will be summarized in descriptive statistics for each time point.

Listings

All individual data, including rechecked values, will be listed by type of measurement. In the listings, values will be flagged when reaching the limits of the PCSA criteria, when defined. A data listing of individual post-baseline abnormalities by patient will be provided.

Comments related to vital sign evaluations will also be listed, if any.

11.4.2.5 Physical examinations and neurological examinations

The frequencies and percent of patients with normal/abnormal findings at baseline and successive visits will be summarized.

11.4.2.6 Echocardiogram and liver ultrasound Doppler

Echocardiogram and liver ultrasound Doppler data will be presented for appropriate visits using raw data in listings and/or by descriptive statistics. Likewise, categorical data will be summarized using frequencies and percents at appropriate visits.

11.4.2.7 Safety biomarkers

For safety biomarkers of ceramide, cardiac troponin I, hsCRP, calcitonin, iron, ferritin, IL-6 and IL-8 raw values and change from baseline will be summarized using descriptive statistics by age group cohort, time point, highest tolerated dose and overall time point.

11.4.2.8 Anti-olipudase alfa IgG antibodies, neutralizing antibodies, and other immune response assessments

Percentage of patients who seroconverted to olipudase alfa, time to seroconversion and peak IgG antibody titer will be summarized using descriptive statistics. IgG antibody titer values will be summarized using descriptive statistics at each study visit. All data will be presented in listings for each patient.

By patient listings will also display results of neutralizing antibody, circulating immune complex, anti-olipudase alfa IgE antibody, serum tryptase activity, complement activation, and skin testing performed. Descriptive summaries may also be provided as appropriate.

11.4.3 Pharmacokinetic analyses

Plasma concentration-time data will be analyzed by non-compartmental methods, nonlinear mixed effects modeling or by population-based analysis, based upon patient age and data suitability. Values will be reported for individual subjects and summarized using descriptive statistics by dose level and study week as appropriate. These will use the pharmacokinetic population.

11.4.4 Pharmacodynamic analyses

Pharmacodynamic endpoints are defined in Section 9.2.3.

Concentration-time data for sphingomyelin and metabolite levels (eg, ceramide, lyso-sphingomyelin) will be summarized using descriptive statistics. If appropriate, the following parameters will also be assessed: C_{max}, T_{max}, and area under the effect-time curve. Individual and descriptive statistics will be presented.

Pharmacodynamic parameters will be summarized using descriptive statistics using the pharmacodynamics population. Change from baseline will be calculated and summarized.

Exploratory correlation analyses will be attempted to evaluate relationships between different pharmacodynamic markers and between sphingomyelin levels from different sources.

These analyses will be conducted by age cohort – in overall population as well as by manufacturing scale, as appropriate.

11.4.5 Exploratory efficacy analyses

Efficacy assessments are described in Section 9.2.2.

Efficacy analyses will be performed on the modified intent-to-treat analysis set. For each exploratory efficacy assessment, observed measures, change from baseline and/or percent change from baseline to week 52 or 64, as appropriate, will be listed and summarized using descriptive statistics overall and separately by timepoint and age cohort, including 95% confidence intervals.

Categorical variables (eg, pulmonary imaging, chest X-ray) will be summarized using frequencies and percentages according to time points collected from screening or baseline to Week 52 (or last study assessment).

The same efficacy analyses will also be performed by manufacturing scale.

11.4.6 Pharmacokinetic-pharmacodynamic analyses

Exploratory PK-PD analyses may be performed to elucidate exposure-response relationships with biomarkers of safety and/or efficacy. The PK-PD relationships may be explored graphically. If a relationship is apparent, PK-PD modeling may be attempted and results reported, as appropriate.

11.5 INTERIM ANALYSIS

Analysis of data, including summary tables, figures and listings, may be conducted intermittently during the study and upon completion of a cohort's key milestones, eg, week 26 or 52 efficacy assessments.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the sponsor, the investigator, delegated investigator staff and subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in free, publicly accessible, internet-based registries, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The investigator (according to applicable regulatory requirements), or a person designated by the investigator, and under the investigator's responsibility, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient's parents or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. If only 1 one parent or guardian signs the consent form, the investigator must document the reason why only 1 parent or guardian's signature. A copy of the signed and dated written informed consent form will be provided to the patient.

Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in the presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form used by the investigator for obtaining the patient's informed consent must be reviewed and approved by the sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the investigator or the sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the investigator will not start the study before the written and dated approval/favorable opinion is received by the investigator and the sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the sponsor (including security rules). The investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The investigator may appoint such other individuals as he/she may deem appropriate as subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All subinvestigators shall be appointed and listed in a timely manner. The subinvestigators will be supervised by and work under the responsibility of the investigator. The investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the monitoring team is to help the investigator and the sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF. The informed consent form will include a statement by which the patient allows the sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the sponsor to record (according to sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the sponsor may generate additional requests (DRF) to which the investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the sponsor and investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each investigator and subinvestigator will be signed, dated and provided to the sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The investigator must notify the sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the e-CRFs, the investigator’s Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The subinvestigators shall be bound by the same obligation as the investigator. The investigator shall inform the subinvestigators of the confidential nature of the clinical trial.

The investigator and the subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party’s account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the sponsor or its designee are and remain the sole property of the sponsor.

The investigator shall not and shall cause the delegated investigator staff/subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the sponsor.

The sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the investigator and/or the subinvestigators shall provide all assistance required by the sponsor, at the sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient’s personal data, which are included in the sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the investigator and/or to the patients, the sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The sponsor also collects specific data regarding investigator as well as personal data from any person involved in the study which may be included in the sponsor’s databases, shall be treated by both the sponsor and the investigator in compliance with all applicable laws and regulations.
- Subject race or ethnicity (ethnicity: not Hispanic or Latino; race: American Indian or Alaska native, Asian, Black, Native Hawaiian or other Pacific Islander, White and “not reported”) will be collected in this study because these data are required by several health authorities.

14.6 INSURANCE COMPENSATION

The sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not relieve the investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the investigator should permit auditing by or on the behalf of the sponsor and inspection by regulatory authorities.

The investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the investigator is notified of a planned inspection by the authorities, he will inform the sponsor and authorize the sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the investigator to the sponsor.

The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the sponsor

The sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The investigator has received from the sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the investigator or sub-investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the sponsor will notify the investigator of its decision by written notice.

14.8.2 By the Investigator

The investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the investigator. The coordinating investigator who will sign off on the study report will be the investigator who first enrolled the largest number of patients in the trial.

14.10 PUBLICATIONS AND COMMUNICATIONS

The investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the sponsor's written consent, being understood that the sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the investigator shall have the right to publish or present independently the results of this study in agreement with other investigators and stakeholders. The investigator shall provide the sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the sponsor deems appropriate to establish and preserve its proprietary rights.

The investigator shall not use the name(s) of the sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the sponsor. The sponsor shall not use the name(s) of the investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
[redacted]	Clinical Approval	[redacted]
[redacted]	Regulatory Approval	[redacted]