SANOFI GENZYME

AMENDED CLINICAL TRIAL PROTOCOL 13

COMPOUND: olipudase alfa/GZ402665

A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency

STUDY NUMBER: DFI12712

STUDY NAME: ASCEND

VERSION DATE/STATUS: 02-Feb-2021 / Approved

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NAMES AND ADDRESSES OF

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 13	All	02-Feb-2021, version 1 (electronic 16.0)
Amended Clinical Trial Protocol 12	All	15 April 2020, version 2 (electronic 15.0)
Amended Clinical Trial Protocol 11	All	12 Aug 2019, version 2 (electronic 13.0)
Amended Clinical Trial Protocol 10	All	05 December 2018, version 1 (electronic 11.0)
Amended Clinical Trial Protocol 09	All	18 September 2018, version 2 (electronic 10.0)
Amended Clinical Trial Protocol 08	All	26 January 2018, version 1 (electronic 8.0)
Protocol Amendment 10	All	26 January 2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 07	All	24 August 2017, version 1 (electronic 7.0)
Protocol Amendment 9	All	24 August 2017, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 06	All	08 February 2017, version 1 (electronic 6.0)
Protocol Amendment 08	All	08 February 2017, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 05	All	01 February 2016, version 1 (electronic 4.0)
Protocol Amendment 07	All	01 February 2016, version 2 (electronic 2.0)
Amended Clinical Trial Protocol 05-DE	Germany Only	28 September 2015, version 1 (electronic 1.0)
Protocol Amendment 06 - DE	Germany Only	28 September 2015, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 05-GB	United Kingdom Only	22 July 2015, version 1 (electronic 2.0)
Protocol Amendment 05- GB	United Kingdom Only	22 July 2015, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 04	All	08 May 2015, version 2 (electronic 5.0)
Protocol Amendment 04	All	31 March 2015, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 03	All	28 January 2015, version 1 (electronic 3.0)
Protocol Amendment 03	All	28 January 2015, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02	All	05 December 2014, version 1 (electronic 2.0)
Protocol Amendment 02	All	05 December 2014, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	05 September 2014, version 1 (electronic 1.0)
Protocol Amendment 01	All	05 September 2014, version 1 (electronic 1.0)
Original Protocol		02 April 2013, version 1 (electronic 2.0)

AMENDED PROTOCOL 13 (02-Feb-2021)

This amended protocol 13 is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment are as follows:

1. During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic, to allow more flexibility with regard to additional options for monitoring techniques in compliance with applicable country-specific regulations.
2. During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic that can lead to site closure or extenuating circumstances that prevent an in-person site visit, [redacted] adding the possibility to perform the first infusion at home for eligible patients in agreement between the Sponsor and the Investigator and in compliance with applicable country-specific regulations.
3. Liver function test (LFT) monitoring post infusion is already included in this protocol. However, review of the interim data from the clinical development program has identified "Transient elevation in transaminases associated with ceramide release during the dose escalation phase with olipudase alfa" as an important identified risk. Therefore, additional recommendations for the management of transaminase elevation during dose escalation have been added to the protocol.

Other important changes include:

1. The conduct of treatment experience interviews to understand patient's experience living with acid sphingomyelinase deficiency (ASMD) and participating in this study has been added.
2. The assessments have been streamlined to reduce patient burden in the extension phase of this trial. Assessments to ensure patient safety have been preserved. This change will be implemented after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 (the first cutoff on 17 October 2019 was at the end of the PAP [primary analysis period]).
3. Other changes, omissions and corrections have also been addressed.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary - endpoint(s)	Exploratory efficacy endpoints: addition of treatment experience interviews	Semi-structured patient interviews have been added to understand the patient experience of living with ASMD and participating in this study
Clinical trial summary - Statistical considerations	**Pharmacodynamics** Only lyso-sphingomyelin and ceramide will be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.	Analysis of sphingomyelin, ceramide and other metabolites (sphingosine-1- phosphate) in plasma or DBS through 52 weeks of treatment has been completed (PAP) for all patients. Lyso-sphingomyelin and ceramide which represent the most informative readouts for pharmacodynamic response to treatment will be maintained throughout the study to continue to monitor levels of substrate and its metabolic product. The other assessments have been streamlined to reduce patient burden in the extension phase of this trial. Assessments to ensure patient safety have been preserved.
Section 1.2 - Schedule of assessments	Schedule of assessments: previous flow charts will be only applicable before the implementation of changes that will occur after the cutoff date of the second database lock.	Clarification to avoid confusion with the complementary flow chart
	[redacted]	Clarification on olipudase alfa manufacturing process changes
Section 1.2 - Schedule of assessments	A complementary flow chart (Section 1.2.2.4) has been added to be effective after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. Assessment added: • Treatment experience interview Assessments removed: • Sphingomyelin in plasma • ACE • Metabolites in dried blood spot (DBS) • 48 hours after infusion: vital sign measurements, LFTs, hematology, and safety during dose re-escalation • NMR of HDL • Multiplex assay of vascular biomarkers Timing changed from quarterly to every 6 months, pre-infusion only: • Ceramide • Lyso-sphingomyelin • Serum chitotriosidase • CCL18 • Bone biomarkers (serum bone specific ALP, C-telopeptide) Timing Changed from every 6 months to yearly: • Chest X-ray • Treadmill ergometry	The assessments have been streamlined to reduce patient burden in the extension phase of this trial. Assessments to ensure patient safety have been preserved.

Section # and Name	Description of Change	Brief Rationale
	48 hours post-infusion sampling removed for: • hsCRP, iron, ferritin, cardiac-specific troponin I, calcitonin • LFTs and coagulation • Multiplex assay of pro-inflammatory biomarkers	
Section 6.1 Description of the protocol	Text about home infusion during a regional or national emergency such as COVID-19 clarified.	
Section 8.1.1 Treatments administered	Following two paragraphs are added: During clinical development of olipudase alfa, incremental changes were made to the olipudase alfa manufacturing process. [redacted] the patient should receive the first infusion at the site. However, If the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic), the first infusion [redacted] is allowed during home infusion for eligible patients in agreement between the Sponsor and the Investigator in compliance with applicable country-specific regulations	Clarification on the olipudase alfa manufacturing process. Adding the possibility to perform the first infusion at home in the context of site closure or extenuating circumstances that prevent an in-person site visit in compliance with applicable country-specific regulations. No safety risks are anticipated based on the following: 1. [redacted] 2. 3. There is appropriate selection of patients in home infusion setting with appropriate medical support
Section 8.1.3.2 – Dosing delays or missed doses	After the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021, removal of: For the fifth paragraph related to the "outside the dose escalation" the following change has been done: • 48 hours post-infusion: vital sign measurements, LFTs and hematology tests and safety biomarkers and if available during home infusion from the same blood sample, clinical chemistry, multiplex assay and pharmacodynamic biomarkers Addition of: Assessment of the transaminases obtained after infusion during the dose escalation period; if any AST or ALT value is > 2x baseline and >ULN, the test should be repeated prior to the next scheduled infusion. Depending on the test results, the dose can be adjusted (repeated or reduced) or treatment can be withheld to allow additional transaminase monitoring, based on the physician's clinical judgment. Baseline is defined as the following: • For initial dose escalation: last values prior to first dose of olipudase alfa • For dose re-escalation: last values prior to the first re-escalation dose	The 48 hours post-infusion assessments will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021; however, 24 hours post-infusion assessments remain. Therefore, patient safety is not being compromised. Transient elevation in transaminases associated with ceramide release during the dose escalation phase with olipudase alfa has been added as an important identified risk. Therefore, additional recommendations for the management of transaminase elevation during dose escalation have been added to the protocol

Section # and Name	Description of Change	Brief Rationale
Section 9.1.3 Tertiary and exploratory efficacy endpoints	ACE, NMR of HDL, Multiplex assay of vascular biomarkers will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. Addition of patient treatment experience interview	The assessments have been streamlined to reduce patient burden in the extension phase of this trial. Given current knowledge about the study drug, assays can be replaced by targeted testing. Analysis of ACE through 52 weeks (PAP) of treatment has been completed for all patients. Initial objective to monitor for changes with treatment were achieved; no further longitudinal analysis is required. Since the lipid profiles are informative efficacy biomarkers, the exploratory NMR of HDL will be removed from the protocol. This change is harmonized with the ongoing LTS13632 protocol also part of the olipudase clinical development program. Semi-structured patient interview has been added to understand the patient experience of living with ASMD and participating in this clinical trial.
Section 9.1.4 Assessment of efficacy endpoints	Assessments reduced from every 6 months to yearly after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. • Chest X-ray • Treadmill ergometry	The assessments have been streamlined to reduce patient burden in the extension phase of this trial.
Section 9.1.4.7 Biomarkers	ACE will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.	See rationale for Section 9.1.3 above for further details.
Section 9.1.4.12 Multiplex assay of inflammatory and vascular biomarkers	Only the multiplex assay of proinflammatory panel will be maintained after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 and the vascular multiplex panels will no longer be assessed.	Given current knowledge about the study drug, assays can be replaced by targeted testing. The assessments have been streamlined to reduce patient burden in the extension phase of this trial: IL-6, IL-8, TNF alpha and IFN gamma. will be assessed.
Section 9.1.4.14 Treatment experience interviews	To allow the conduct of treatment experience interviews	Semi-structured patient interviews were added to understand the patient experience of living with ASMD and participating in this study.
Section 9.2 Safety endpoints	Multiplex assay for vascular biomarkers will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.	The assessments have been streamlined to reduce patient burden in the extension phase of this trial.
Section 9.2.8 Multiplex assays	IL-6, IL-8, TNF alpha, and IFN gamma were identified as key safety biomarkers during the PAP; as the multiplex assay of proinflammatory panel captures all these biomarkers, this panel only will be maintained for exploratory safety endpoint after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.	The assessments have been streamlined to reduce patient burden in the extension phase of this trial.
Section 9.2.9 Immunogenicity assessments	During the study period, [redacted] collection will be monthly for the first 6 months after starting the new update, and quarterly after that	Clarification on the updated manufacturing process

Section # and Name	Description of Change	Brief Rationale
Section 9.3.1 Pharmacodynamic endpoints	No further analysis of sphingomyelin or other metabolites will be conducted after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.	Analysis of sphingomyelin, ceramide and other metabolites (sphingosine-1- phosphate) in plasma or DBS through 52 weeks (PAP) of treatment has been completed for all patients. Lyso-sphingomyelin and ceramide which represent the most informative readouts for pharmacodynamic response to treatment will be maintained throughout the study to continue to monitor levels of substrate and its metabolic product. The other assessments have been streamlined to reduce patient burden in the extension phase of this trial.
Section 9.3.1.2 Sphingomyelin and metabolites in plasma and dried blood spot	No further analysis of sphingomyelin or other metabolites will be conducted after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. Lyso-sphingomyelin and ceramide will be maintained to continue to monitor levels of substrate and its metabolic product.	See rationale for section 9.3.1 above for further details.
Section 9.3.2.1 Pharmacokinetic sampling time	During the study period, [redacted] samples for PK will be collected at the second dose that is administered [redacted].	Clarification on the updated manufacturing process
Section 9.7 Appropriateness of measurements	NMR of HDL and ACE will be removed from the protocol after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. CCL18 and chitotriosidase will continue to be monitored to assess overall disease burden.	The assessments have been streamlined to reduce patient burden in the extension phase of this trial. See rationale for Section 9.1.3 above for further details.
Section 10.1 Visits schedule	After the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021, the 48 hours post-infusion blood samplings will no longer be collected. Text about home infusion during a regional or national emergency such as COVID-19 clarified.	The assessments have been streamlined to reduce patient burden in the extension phase of this trial.
Section 10.1.1 Home infusion	Addition of: If the site visit is not possible during regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, and home infusion already approved for the eligible patient, the investigator can decide whether reintroduction should occur at the hospital/study site or home visit. [redacted] if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, the first infusion of [redacted] is allowed during home infusion for eligible patients in agreement between the Sponsor and the Investigator in compliance with applicable country-specific regulations.	To facilitate treatment continuation via home infusion when site visit is not available for eligible patients during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
Section 13.1 Responsibilities of the Investigator (s)	Language added for clarification: The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.	During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic, to allow more flexibility with regards to additional options for monitoring techniques in compliance with applicable country-specific regulations. To further clarify the responsibilities of the Investigator(s).
Section 13.2 Responsibilities of the Sponsor.	The following language has been added: Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.	To include the possibility to perform remote monitoring during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic.
Section 17 Protocol amendment history – Appendix C	The protocol amendment history section has been updated.	To conform with the usual process for amendment history.

CLINICAL TRIAL SUMMARY

COMPOUND: olipudase alfa (formerly recombinant human acid sphingomyelinase) GZ402665	**STUDY No: DFI12712** **STUDY NAME: ASCEND**
TITLE	A Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled, repeat dose study to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of olipudase alfa in patients with acid sphingomyelinase deficiency
INVESTIGATOR/TRIAL LOCATION	Multinational – Multicenter
PHASE OF DEVELOPMENT	2/3
STUDY OBJECTIVE(S)	**Primary objective** The primary objective of this Phase 2/3 study is to evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with acid sphingomyelinase deficiency (ASMD) by assessing changes in: 1) spleen volume as measured by abdominal magnetic resonance imaging (MRI) (and, for the United States [US] only, in association with patient perception related to spleen volume as measured by splenomegaly-related score [SRS]); and 2) infiltrative lung disease as measured by the pulmonary function test, diffusing capacity of the lung for carbon monoxide (DL_{CO}). **Secondary objectives** • To confirm the safety of olipudase alfa administered intravenously once every 2 weeks for 52 weeks • To characterize the effect of olipudase alfa on the patient perception related to spleen volume as measured by SRS after 52 weeks of study drug administration (For the US, the effect of olipudase alfa on SRS is part of the primary objective) • To characterize the effect of olipudase alfa on the following endpoints assessed sequentially: 1. The effect of olipudase alfa on liver volume after 52 weeks of study drug administration 2. The effect of olipudase alfa on platelet count after 52 weeks of study drug administration 3. The effect of olipudase alfa after 52 weeks of study drug administration on fatigue 4. The effect of olipudase alfa after 52 weeks of study drug administration on pain 5. The effect of olipudase alfa after 52 weeks of study drug administration on dyspnea **Additional objectives** • To characterize the effect of olipudase alfa on liver function tests • To characterize the effect of olipudase alfa on infiltrative lung disease via pulmonary imaging • To characterize the effect of olipudase alfa on pulmonary functioning • To characterize the effect of olipudase alfa on the fasting lipid profile • To characterize the effect of olipudase alfa on bone disease • To characterize the effect of olipudase alfa on cardiopulmonary

	functioning • To characterize the effect of olipudase alfa on biomarkers • To characterize the effect of olipudase alfa on hematology parameters • To characterize the effect of olipudase alfa on selected health-related quality of life questionnaires and questions therein • To characterize the pharmacodynamic effect of olipudase alfa on clearing sphingomyelin accumulation in liver and/or blood • To characterize the multiple-dose plasma pharmacokinetic profile of olipudase alfa • To explore the effect of olipudase alfa on Physician's global assessment of change • To explore the effect of olipudase alfa on the nuclear magnetic resonance (NMR) profile of high-density lipoprotein (HDL) • To explore the effect of olipudase alfa on liver function via echo-Doppler ultrasound • To explore the effect of olipudase alfa on inflammatory and vascular biomarkers
STUDY DESIGN	This Phase 2/3, multicenter, repeat-dose, clinical trial will be divided into 2 consecutive major periods: 1) a randomized placebo-controlled, double-blind primary analysis period (PAP) from Day -60 to Week 52 to be followed by 2) an extension treatment period (ETP). Initially, the ETP will be double-blind as patients in the placebo arm cross over to active treatment. The PAP will include a screening/baseline period and a treatment period. During the screening/baseline period, from Day -60 to Day 1 preinfusion, approximately 36 patients will provide informed consent and undergo screening assessments to determine trial eligibility and undergo baseline measurements. If all eligibility criteria are met, then patients will be randomized and enter the treatment period on Day 1. Day 1 is the day the first infusion is administered. The visit schedule is calculated using Day 1 of the dose escalation period as the reference. Treatment assignment and randomization will be performed using an Interactive Voice Response System/Interactive Web Response System. Patients will be randomly and centrally assigned across sites and using blocks of fixed size to placebo (saline, 0.9% sodium chloride solution) or 3.0 mg/kg olipudase alfa in a 1:1 ratio. After completing the PAP, patients will enter the ETP and those who had been randomized to active arm will continue receiving the dose to which they were randomized during the PAP (or the highest tolerated dose [HTD], if the randomized dose was intolerable). Patients randomized to the placebo arm in the PAP will cross over to active treatment in the ETP and will undergo dose escalation to a target dose of 3.0 mg/kg of olipudase alfa. To maintain the double-blind, all patients will dose-escalate using the schedule provided (ie, true dose escalation for patients who were in the placebo arm during the PAP and mock dose escalation for patients who were in the active arm during the PAP). Study drug will be defined during the PAP as olipudase alfa or placebo and during the ETP as olipudase alfa and will be administered intravenously once every 2 weeks. Dose escalation during the PAP and ETP will occur according to the following schedule: (True dose-escalation for patients in the active arm during the PAP or the placebo arm during the ETP; mock dose-escalation for patients in the active arm during the ETP or placebo arm during the PAP).

Study week	Scheduled dose of study drug in mg/kg	
Week 0	0.1	
Week 2	0.3	
Week 4	0.3	
Week 6	0.6	
Week 8	0.6	
Week 10	1.0	
Week 12	2.0	
Week 14	3.0	
Week 16	3.0	End of the mock dose escalation for patients assigned to placebo; end of true dose escalation for patients assigned to target dose 3.0 mg/kg.

Note: a Schedule does not account for rechallenge.
Study drug includes olipudase alfa and placebo

During the PAP, one rechallenge each will be allowed for doses administered at Week 0 (0.1 mg/kg or placebo) and at Week 4 (0.3 mg/kg or placebo). Patients who are unable to tolerate the rechallenge at those doses will be discontinued from the study. If a patient is discontinued due to inability to tolerate rechallenge (ie, a second dose of 0.3 mg/kg olipudase alfa), then an additional patient may be randomized. Any patient who successfully dose-escalates through Week 4, but cannot tolerate study drug infusions at later weeks, will continue in the trial at the Week 4 dose (ie, 0.3 mg/kg olipudase alfa or placebo) until the end of treatment; likewise, any patient unable to tolerate a dose administered during later weeks will receive the HTD even if that dose is less than the target randomized dose and will continue in the ETP at this dose. The minimum active dose administered will be 0.3 mg/kg olipudase alfa.

The same dose-escalation schedule and conditions will apply for patients who cross over from the placebo arm during the PAP to the active arm in the ETP, except that patients unable to tolerate the one rechallenge each allowed for doses administered at Week 54 (0.1 mg/kg olipudase alfa) and Week 58 (0.3 mg/kg olipudase alfa) will discontinue from the study and will not be replaced.

During the PAP and ETP, in-patient hospitalization will be required before and for at least 24 hours after the end of infusion during dose escalation (ie, through Week 16 and Week 70, respectively) and may be required during the quarterly and yearly visits up through the end of Year 2; in-patient hospitalization may be necessary during quarterly and yearly study visits in Years 3 through 5. For all other study infusions, patients will be monitored for at least 1 hour after the end of infusion for safety.

Home infusion may be initiated during the COVID-19 pandemic in the ETP by trained home nurses if agreed between the investigator and the sponsor, in compliance with applicable country-specific regulations. Patients must meet the eligibility requirements outlined in Section 10.1.1.

For treatment periods during the PAP and the ETP, dose-limiting toxicity criteria will apply. A rescue strategy will be implemented for patients who experience significant clinical decline.

STUDY POPULATION **Main selection criteria**	**Inclusion criteria** • The patient is willing and able to provide signed written informed consent. • The patient is male or female aged 18 years or older. • The patient has documented deficiency of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes; and a clinical diagnosis consistent with Niemann-Pick disease type B. • The patient has diffusing capacity of the lung for carbon monoxide (DLCO) ≤70% of the predicted normal value. • The patient has a spleen volume ≥6 multiples of normal (MN) measured by MRI; patients who have had partial splenectomy will be allowed if the procedure was performed ≥1 year before screening/baseline and the residual spleen volume is ≥6 MN. • The patient has an SRS ≥5. • Female patients of childbearing potential must have a negative serum pregnancy test for beta-human chorionic gonadotropin (β-HCG). • 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 for up to 15 days following their last dose of study drug. **Exclusion criteria** • The patient has received an investigational drug within 30 days before study enrollment. • The patient has a medical condition, including significant intercurrent illness; significant cardiac disease (eg, clinically significant arrhythmia, moderate or severe pulmonary hypertension or clinically significant valve dysfunction, or <40% left ventricular ejection fraction by echocardiogram [ECHO]); active hepatitis B or hepatitis C, or infection with human immunodeficiency virus (HIV); malignancy diagnosed within the past 5 years (other than non-melanoma skin cancer), or any other serious medical condition that may preclude participation in the study. • The patient has a platelet count <60 x 10^3/μL based on the average of 2 samples. • The patient has an international normalized ratio (INR) >1.5. • The patient has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >250 IU/L or total bilirubin >1.5 mg/dL (except for patients with Gilbert's syndrome). • The patient has had a major organ transplant (eg, bone marrow or liver). • The patient is scheduled during the study for in-patient hospitalization including elective surgery and excluding the liver biopsies required per protocol. • The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study. • The patient is unwilling or unable to abstain from the use of alcohol for 1 day before and 3 days after each study drug infusion. Testing for blood alcohol levels will not be required. • The patient is unwilling or unable to avoid 10 days before and 3 days after the protocol scheduled liver biopsies, that are required at

	screening/baseline, at Week 52 and at Week 104, the use of medications or herbal supplements that are potentially hepatotoxic (eg, 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, erythromycin, valproic acid, anti-depressants, kava, echinacea) and/or may cause or prolong bleeding (eg, anti-coagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng). • The patient requires medications that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine, tricyclic antidepressants [eg, imipramine, or desipramine]). • The patient requires use of invasive ventilatory support. • The patient requires use of noninvasive ventilator support while awake for longer than 12 hours daily. • The patient is breast-feeding.
Total expected number of patients	Approximately 36 patients
STUDY TREATMENT(s)	
Investigational medicinal product **Formulation** **Placebo**	Olipudase alfa (GZ402665) Olipudase alfa will be provided as a sterile lyophilized powder and will be reconstituted with sterile water for injection. The prepared solution will be further diluted with 0.9% sodium chloride in a covered infusion bag and/or syringe to a specific volume based on dose to be administered. Placebo will be used as the reference treatment in this study and will be provided by the hospital pharmacy as 0.9% sodium chloride solution in an identical covered infusion bag and/or syringe. Saline (0.9% sodium chloride solution)
Route of administration	Intravenous infusion
Dose regimen	Once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1) for each patient Home infusion may be initiated during the COVID-19 pandemic in the ETP by trained home nurses if agreed between the investigator and the sponsor, in compliance with applicable country-specific regulations. Patients must meet specific eligibility requirements in (Section 10.1.1).
ENDPOINT(S)	**Efficacy** **Primary efficacy endpoints** • Percentage change in spleen volume (in MN) from baseline to Week 52 (combined with change in SRS from baseline to Week 52 in the US only, and referred to as the "combination spleen endpoint") • Percentage change in DLCO (in % predicted of normal) from baseline to Week 52 **Secondary efficacy endpoints** Secondary efficacy endpoints will include the following: • Percentage change in liver volume (in MN) from baseline to Week 52 • Percentage change in platelet counts from baseline to Week 52 • Week 52 change from baseline in fatigue severity as measured by Item 3 of the BFI scale • Week 52 change from baseline in pain severity as measured by Item 3 of the BPI-SF scale • Week 52 change from baseline in dyspnea severity as measured by the

	FACIT dyspnea tool • Change in SRS from baseline to Week 52 (except US, where it is part of the primary "combination spleen endpoint") **Tertiary efficacy endpoints** • Percentage change from baseline to Week 52 in liver function tests (ALT, AST, total and direct bilirubin) • Pulmonary imaging by high-resolution computed tomography (HRCT) and chest X-ray (in selected sites) to quantify infiltrative lung disease. • Other components of the pulmonary function test (ie, forced vital capacity [FVC], volume of air expired during the first second of FVC [FEV1], total lung capacity) • Fasting lipid profile (eg, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, total cholesterol, triglycerides, apolipoprotein B, apolipoprotein A1, lipoprotein [a]) • Bone disease assessments: MRI and dual energy X-ray absorptiometry of lumbar spine and entire bilateral femur for bone marrow burden score and bone mineral density measurements including total density as well as T- and Z-score measurements. • Cardiopulmonary performance by treadmill ergometry • Biomarkers: angiotensin-converting enzyme (ACE), chitotriosidase, chemokine (C-C motif) ligand 18 (CCL18), bone-specific alkaline phosphatase, C-telopeptide. • Hematology parameters • Other quality of life questionnaires: - Brief Pain Inventory - Short form - Brief Fatigue Inventory - Functional Assessment of Chronic Illness Therapy (FACIT) - Dyspnea Short form - NPB - Health Assessment Questionnaire - Short Form-36v2 Health Survey - EuroQol - quality of life questionnaire in 5 dimensions - Health-related productivity questionnaire **Exploratory efficacy endpoints will include the following:** • Physician's global assessment of change • NMR of HDL • Echo-Doppler imaging to assess liver functioning • Multiplex assay of inflammatory and vascular biomarkers. • Patient Global Impression of Symptom Severity (PGIS) of ASMD questionnaire • Patient Global Impression of Change (PGIC) scale • Treatment experience interviews **Safety endpoints** • Assessment of adverse events (AEs), including SAEs, infusion-associated reactions (eg, cytokine release syndrome [CRS], acute phase reactions) and adverse events of special interest (AESIs) • Clinical laboratory tests • Vital signs

	• Electrocardiogram • Physical examinations • Doppler echocardiography • Biomarkers • Immune response assessments - Multiplex assay of inflammatory and vascular biomarkers (Meso Scale) **Pharmacokinetics** Plasma parameters include C_{max}, t_{max}, $AUC_{0\text{-last}}$, AUC, $t_{1/2}$, CL, and V_{ss} **Pharmacodynamics** • Clearance of sphingomyelin accumulation from baseline to Week 52 in liver tissue • Change from baseline to Week 52 in levels of sphingomyelin, ceramide and other metabolites in plasma or dried blood spot
ASSESSMENT SCHEDULE	Screening assessments will be completed within a 60-day window before Day 1 and results will be available before the first study drug infusion. Assessments for baseline measurements will be made before randomization. Schedules for efficacy, safety, pharmacodynamic, and pharmacokinetic assessments as well as eDiary assessments are presented in Section 1.2. The patient schedule for completing eDiary assessments at home is presented in Section 1.3.
STATISTICAL CONSIDERATIONS	**Sample size determination** The sample size calculations are based on the 2 primary efficacy endpoints of percentage change from baseline in spleen volume (expressed in MN) at Week 52 and the percentage change from baseline in DL_{CO} (expressed as % predicted of normal) at Week 52. The assumptions for the spleen volume endpoint are the following: • An 11.8% common standard deviation based on data from previous ASMD and Gaucher disease type 1 studies • A 30% mean difference from baseline to Week 52 between 3.0 mg/kg olipudase alfa and placebo in percentage change in spleen volume MN • An expected exclusion rate from the modified intent-to-treat (mITT) population of 11% Based on the above assumptions, a comparison between 3.0 mg/kg olipudase alfa and placebo would have over 95% power using a t-test at a 2-sided 5.0% significance level with 36 patients randomized 1:1 to placebo or 3.0 mg/kg olipudase alfa. At a 2.5% significance level, the power would still be over 95%. The following assumptions for the DL_{CO} endpoint are based on results obtained from the olipudase alfa Phase 1b study DFI13412: • A 20% common standard deviation • A 25% mean difference from baseline to Week 52 between 3.0 mg/kg olipudase alfa and placebo in percentage change in DLCO (in % predicted) • An expected exclusion rate from the mITT population of 11% Based on these assumptions, a comparison between the 3.0 mg/kg treatment arm and the placebo arm will have 93% power using a t-test at

	a 2-sided 5.0% significance level and with 36 patients randomized 1:1 to placebo or 3.0 mg/kg. The assumptions for the splenomegaly-related score endpoint came from the Sanofi-sponsored clinical trial in myelofibrosis (JAKARTA, NCT# 01437787). The assumptions for the power calculations are: • A common standard deviation of 9.4 • A mean difference of 8.0 from baseline to Week 52 between 3.0 mg/kg of olipudase alfa and placebo in the SRS • An expected exclusion rate from the mITT population of 11% Based on the above assumptions, a comparison between 3.0 mg/kg of olipudase alfa and placebo will have 82% power using a t-test to detect a statistical trend, defined as 2-sided p-value ≤0.15, with 36 patients randomized 1:1 to placebo and 3.0 mg/kg of olipudase alfa. For the US protocol, in which a combination spleen endpoint is used, using the simplifying assumption that the 2 components of the combination spleen endpoint (spleen volume and SRS) are independent, the likelihood that statistical significance (spleen volume significance based on Hochberg procedure and SRS p-value ≤0.15) will be declared for the combination spleen endpoint is greater than 80%. **Analysis populations** The **randomized population** will include any patient who had been allocated to a randomized treatment arm regardless if study drug was administered. The **safety population** is a subset of the randomized population and will include randomized patients who received at least 1 infusion (partial or total). This is the primary population for the safety analysis. The **mITT population** is the same as the safety population, and is used as the primary population for the efficacy analysis. The **per protocol population** will be a subset of the mITT population who have no major protocol deviations that are expected to interfere with assessments of the 2 primary efficacy endpoints. The **extension treatment population** will consist of patients who completed the PAP and who continue into the extension treatment period. The **pharmacokinetic** (**PK) population** will consist of mITT patients who have evaluable drug concentration data. The **pharmacodynamic** (**PD) population** will consist of mITT patients who have at least 1 evaluable PD marker data available post-baseline. Patients who are included in the safety population and have rescue therapy initiated are included in the **rescue therapy population**. Since in the ETP all subjects get olipudase alfa, the rescue therapy is relevant only for the PAP.
	Analysis of efficacy The 2 primary efficacy endpoints (percentage change in spleen volume in MN from baseline to 52 weeks and percentage change in DL_{CO} in % predicted from baseline to 52 weeks) will be analyzed in the mITT population using the mixed model for repeated measures. The secondary efficacy endpoints will also be analyzed using this method. In the United States, spleen volume is combined with change in SRS from baseline to Week 52 and is referred to as the “combination spleen endpoint”. The primary and secondary endpoints will be tested using a 2-stage

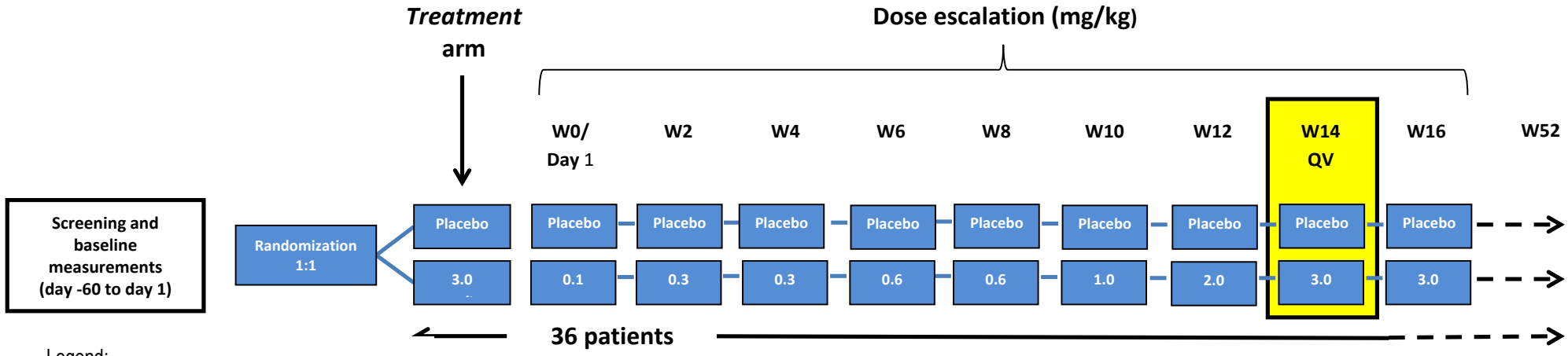
	gatekeeping strategy to maintain the 5% familywise error rate. A Hochberg method will be used to test the 2 primary endpoints. For the US only, if spleen volume is significant, change in SRS from baseline to Week 52 will be tested at the 0.15% level. The secondary endpoints will be tested in a closed, hierarchical fashion. **Analysis of safety** Safety analyses may be performed using the safety population. Additional summaries will be conducted using the most recent dose the patient received before the event of interest. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event (AE) incidence tables will present by system organ class (SOC) (sorted by internationally agreed order) and preferred term (PT) and the number 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 within each treatment arm. All treatment-emergent AEs (TEAEs), all TEAEs potentially related to study drug, all TEAEs leading to treatment discontinuation and/or study discontinuation, all TEAEs that are IARs, all treatment-emergent SAEs (including treatment-related SAEs), and all AEs with fatal outcome will be summarized. The TEAE observation period will be defined as the time from the first infusion of study drug through the end of study visit or 30 to 37 days after the last infusion of study drug whichever one occurs later. Detailed listings of TEAEs, SAEs, AESIs, related TEAEs, and discontinuations due to TEAEs will be provided and include the randomized treatment arm and olipudase alfa dose of the infusion or placebo before or during the occurrence of the TEAE, when applicable. The number of TEAEs and annualized rate, and the number and proportion of patients reporting specific TEAEs will be tabulated for the overall analyses of TEAEs. The ECG data will be analyzed using the Bazett's and Fridericia's QT correction methods. All ECG variables will be summarized for each randomization dose group/dose and time point. Change from baseline will also be calculated and summarized using descriptive statistics.
	Pharmacokinetics Plasma concentration-time data will be analyzed using actual dosing and sampling times by non-compartmental methods. Pharmacokinetic parameters will be summarized by dose level, study week as appropriate, and in relation to immunogenicity. If data do not lend to non-compartmental analysis, or for additional analyses, model based approaches such as nonlinear mixed effects modeling may be used. **Pharmacodynamics** Concentration-time data for sphingomyelin and metabolites will be summarized using descriptive statistics. Individual and summary statistics will be presented. All other pharmacodynamic parameters will be summarized using descriptive statistics. Change from baseline will be calculated and summarized. Exploratory correlation analyses will be attempted to evaluate relationships between different pharmacodynamic markers and between sphingomyelin and/or lyso-sphingomyelin levels from different sources. Lyso-sphingomyelin and ceramide represent most informative readouts for

	pharmacodynamic response to treatment. Only these 2 parameters will be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. **Pharmacokinetics-pharmacodynamics** Exploratory PK-PD analyses may be performed to elucidate dose-response and concentration response relationships with biomarkers of safety and/or efficacy. The PK-PD relationships may be explored graphically and if a relationship is apparent, PK-PD modeling may be attempted and results reported, as appropriate.
Interim analysis	No interim analysis is planned during PAP. However during ETP, a formal summary of data or interim CSRs may be produced to support regulatory approval(s) and/or other submission/application requirement(s).
DURATION OF STUDY PERIOD (per patient)	The longest study duration per patient will be for at least 3 years and up to 5 years and 3 months dependent upon continued regulatory approval of this protocol: • Screening/baseline: up to 60 days • Primary analysis period: approximately 52 weeks • Extension treatment period: until study completion (up to 4 years) • End of study visit within 2 weeks after the last treatment • Follow up phone call 30-37 days after the last treatment visit
STUDY COMMITTEES	Independent Data Monitoring Committee

1 FLOW CHARTS AND SCHEDULES OF ASSESSMENTS

1.1 STUDY FLOW CHARTS

1.1.1 Flow chart for primary analysis period through Week 52

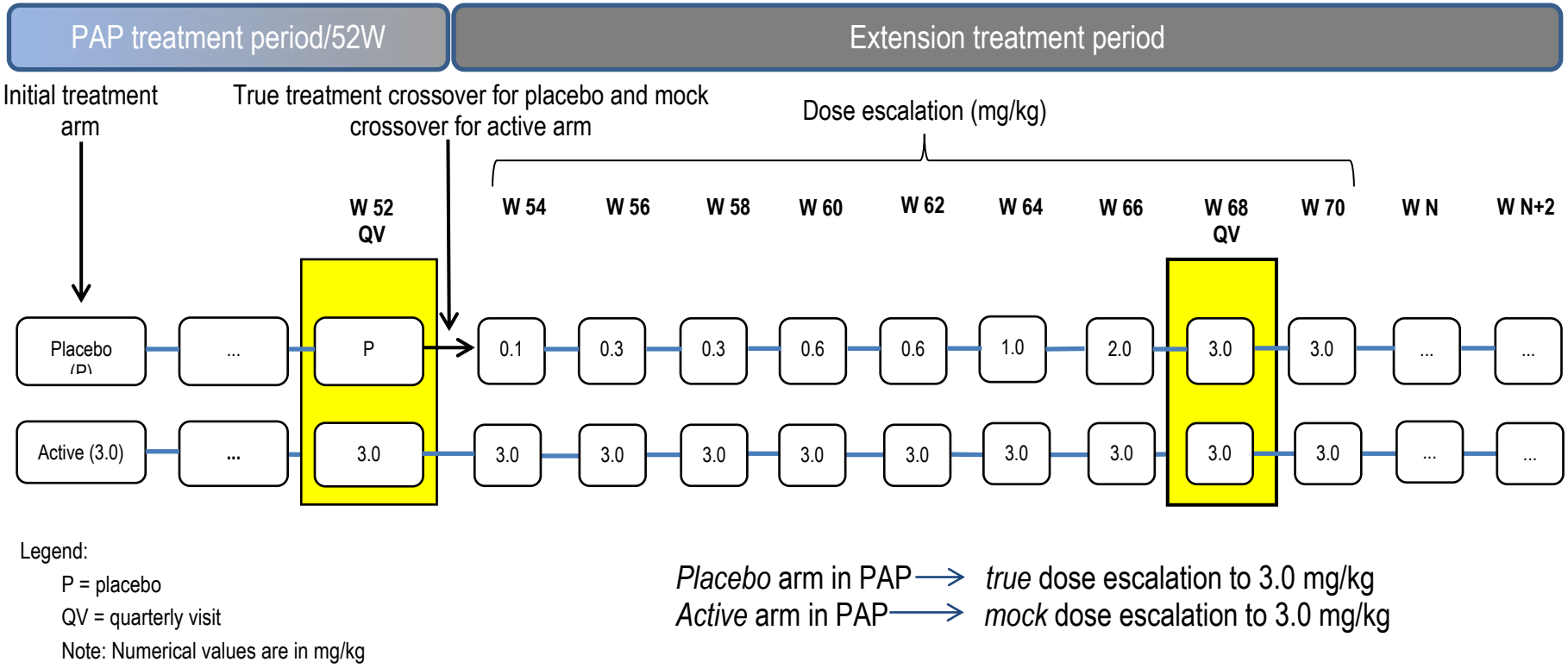


Legend:

QV = quarterly visit

Note: Numerical values are in mg/kg

1.1.2 Flow chart for extension treatment period



Legend:

P = placebo

QV = quarterly visit

Note: Numerical values are in mg/kg

Placebo arm in PAP → *true* dose escalation to 3.0 mg/kg

Active arm in PAP → *mock* dose escalation to 3.0 mg/kg

1.2 SCHEDULES OF ASSESSMENTS

1.2.1 Primary analysis period

1.2.1.1 Schedule of assessments: Year 1 - PAP screening to Week 16

Year 1: PAP **Screening to Week 16**	**Screening**	**Dose escalation period[a]**								
Study procedures	**Day** **-60 to -1[b]**	**W0** **Day 1[c]**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14** **QV**	**W16**
SCREENING[d]/ENROLLMENT/BASELINE										
Informed consent	X									
Assign patient number	X									
Inclusion/exclusion criteria review	X									
Medical/surgical history including medications administered within 30 days	X									
Alcohol and tobacco usage	X									
Demographics and baseline characteristics	X									
Screening eDiary[e]	X									
ASM activity in peripheral leukocytes and dried blood spot	X									
Genotyping:[f] *SMPD1*, *CHIT1*, *UGT1A1*	X									
Lab testing for enrollment										
• HIV antibody testing	X									
• Hepatitis B surface antigen test	X									
• Hepatitis C antibody test	X									
• β-HCG pregnancy test[g]	X									

Year 1: PAP **Screening to Week 16**	**Screening**	**Dose escalation period**[a]								
Study procedures	**Day -60 to -1**[b]	**W0 Day 1**[c]	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14 QV**	**W16**
Optional blood sample for pharmacogenetic assessment Pharmacogenetic informed consent form		Any time after the pharmacogenetic ICF has been obtained								
Randomization to placebo or olipudase alfa[h]		X								
SAFETY										
AE/SAE assessment[i]	Continuous monitoring									
Concomitant medications and therapies	Continuous monitoring									
Complete physical examination[j]	X	X							X	
Abbreviated physical examination[k]		X	X	X	X	X	X	X	X	X
Weight, BMI	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	
Height	X									
Vital sign measurements	X	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Electrocardiogram[n]	X	X							X	
Echocardiogram with Doppler	X								X	
Clinical laboratory sampling										
Liver function testing and coagulation	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]
Hematology[p]	X	X	X	X	X	X	X	X	X	X
Clinical chemistry and urinalysis (dipstick only)	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]
β-HCG pregnancy test[g]	X	X		X		X		X		X
Sampling[q] for hsCRP, iron, ferritin, ceramide, cardiac-specific troponin I, calcitonin		X	X	X	X	X	X	X	X	X
Immune response monitoring										
Multiplex assay[q]		X	X	X	X	X	X	X	X	X
Anti-olipudase alfa IgG		X		X		X		X		X

Year 1: PAP **Screening to Week 16**	**Screening**	**Dose escalation period**[a]								
Study procedures	**Day -60 to -1**[b]	**W0 Day 1**[c]	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14 QV**	**W16**
Neutralizing antibodies		Only in patients positive for IgG olipudase alfa								
If a patient develops IAR - hypersensitivity reaction(s):										
• Anti-olipudase alfa IgG • Anti-olipudase alfa IgE		For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample ≥3 days after the event or before the next infusion.								
• Tryptase activity • Complement activation		For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample 1 to 3 hours after the event.								
Skin testing		As needed for hypersensitivity reactions - See study manual								
In case of cytokine release syndrome:										
Multiplex assay (Meso Scale)		For suspicion of CRS, collect immediately, unless already collected within the past 30 minutes								
Calcitonin										
EFFICACY/PHARMACODYNAMICS										
Abdominal MRI[r]	X									
Echo-Doppler of liver	X									
Chest X-ray[s]	X									
Pulmonary HRCT scan	X									
Pulmonary function tests	X									
Treadmill ergometry	X									
Fasting lipid profile	X								X	
NMR of HDL	X									
MRI scans of lumbar spine and bilateral femur	X									
DXA scans of lumbar spine and bilateral femur	X									
Sphingomyelin, ceramide, and other metabolites in plasma[q]		X	X	X	X	X	X	X	X	X
Metabolites in dried blood spot		X	X	X	X	X	X	X	X	X
Chitotriosidase, ACE, CCL18	X								X	
Serum bone-specific ALP and C-telopeptide	X								X	

Year 1: PAP **Screening to Week 16**	**Screening**	**Dose escalation period**[a]								
Study procedures	**Day -60 to -1**[b]	**W0 Day 1**[c]	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14 QV**	**W16**
Health-related quality of life instruments										
• BFI, BPI-SF, EQ-5D, SF-36	X									
• Health-Related Productivity Questionnaire, PGIS and PGIC, and NPB-HAQ	X[t]								X	
• eDiary[u]										
- Distribute eDiary device to patients	X							X		
- Collect eDiary device from patients		X							X	
Physician global assessment	X									
Liver biopsy[v]	X									
STUDY DRUG INFUSION AND PHARMACOKINETICS										
Study drug infusion[w]		X	X	X	X	X	X	X	X	X
PK sampling[x]			X				X		X	

Abbreviations: ACE = angiotensin-converting enzyme; AE=adverse event; ALP = alkaline phosphatase; ASM = acid sphingomyelinase; β-HCG = beta-human chorionic gonadotropin; BFI = Brief Fatigue Inventory; BMI=body mass index; BPI-SF = Brief Pain Inventory - Short Form; CCL18 = chemokine (C-C motif) ligand 18; DXA = dual-energy X-ray absorptiometry; EQ-5D = EuroQOL-5 dimensions questionnaire; HIV = human immunodeficiency virus; HDL = high-density lipoprotein; HRCT = high-resolution computed tomography; hsCRP = heat-sensitive C-reactive protein; IAR = infusion-associated reaction; IgE=immunoglobulin E; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NMR = nuclear magnetic resonance; NPB-HAQ = NPB - Health Assessment Questionnaire; PAP = primary analysis period; PGIC=Patient Global Impression of Change scale; PGIS=Patient Global Impression of Symptom Severity questionnaire; PK=pharmacokinetic; SAE=serious adverse event; SF-36 = Short Form-36; QV = quarterly visit; W = study week.

a Study drug infusions will occur once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1). Assessments will be performed at the indicated visits ±7 days, unless otherwise specified. Unless specified otherwise, study procedures should preferably occur before infusion and during approximately the same time of day for each visit (in reference to the screening/baseline visit). When multiple assessments are required, the order will be vital signs before ECG before blood draw.

b In exceptional circumstances, screening may be extended beyond the 60 day window after consultation with the sponsor. In this case, some assessments done at the beginning of screening may have to be repeated.

c Day 1 is the day the first infusion is administered. The visit schedule is calculated using Day 1 of the PAP as the reference.

d Rescreening may be possible for patients who screen failed, but is subject to sponsor approval. Imaging, function tests (eg, PFTs, ergometry), and questionnaires performed within 12 weeks of the expected date of randomization can be used for rescreening. All labs will be repeated, except genotyping and ASM activity measurements. The eDiary will not be repeated.

e The e-Diary will be administered once at the beginning of the screening period to check the related inclusion criterion, and a second time as baseline just before the first infusion (see footnote u).

f *SMPD1*, *CHIT1*, and *UGT1A1* will be genotyped only if historical results are not available, or if historical results are available, but mutations were not annotated using the guidelines of the Human Genome Variation Society (http://www.hgvs.org/).

g Serum β-HCG test for pregnancy at screening only; urine β-HCG up to 24 hours before the first infusion of the study; then before infusion once every 4 weeks; if positive, repeat test with serum.

h Randomization can occur a few days before the first infusion. All baseline assessments will be done before the first infusion.

i Adverse events will be captured from the time the patient provides signed informed consent through the safety follow-up period (30 to 37 days after the patient's last study infusion).

j The complete physical examination will include a neurological examination (mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, and coordination); examinations of lymph nodes, heart, lungs, abdomen, and extremities/joints; and an assessment of the general appearance, skin, and HEENT (head, eyes, ears, nose, and throat).

k The abbreviated examination of general appearance only will be carried out before and after each study drug infusion.

l The patient's weight at the previous visit, instead of the weight at the current visit, can be used to calculate the dose of drug to be infused at the current visit if the weight at the current visit is missing.

m Vital sign measurements will include blood pressure, heart rate, respiratory rate, and temperature. At all visits during the dose escalation period and at all quarterly visits, collection times will be prior to the infusion (within 30 ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion (±10 minutes); 2 hours ±10 minutes, 4 hours ±10 minutes, and 6 hours ±10 minutes after the end of the infusion; and every 8 hours ±1 hour until the patient has been discharged. At these visits, vital signs should also be measured at discharge ±10 minutes, which may or may not represent an additional measurement to the schedule described above. For these visits, patients should remain hospitalized at the site for at least 24 hours after the end of the infusion. The investigator may decide that longer monitoring is required.

n Electrocardiograms will be performed before any blood is collected. At screening, 1 ECG will be performed. On Day 1 of Week 0, ECG will be performed in triplicate (3 ECGs in a row) within 24 hours before infusion and as a singlet 4 hours ±10 minutes, 12 hours ±1 hour, and 24 hours ±3 hours after the end of infusion. At all other study visits, 1 ECG will be administered each before infusion and 4 hours ±10 minutes, 12 hours ±1 hour, and 24 hours ±3 hours after the end of infusion.

o Samples will be taken for liver function testing and coagulation within 24 hours before infusion and at 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion. Samples will be taken for urinalysis and clinical chemistry within 24 hours before infusion.

p At screening, 2 samples will be taken at least 24 hours and up to 2 weeks apart, 1 sample for complete blood count and 1 sample for hemoglobin, white blood cell count, and platelet count. From Day 1 to W16, 1 sample for complete blood count with differential will be taken within 24 hours before infusion and one 24 hours ±3 hours after the end of infusion.

q Sample will be taken within 24 hours before infusion and 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion for metabolites in plasma and biomarkers including but not limited to: hsCRP, iron, ceramide, ferritin, cardiac troponin-I, calcitonin, and multiplex assay (Meso Scale) for other biomarkers indicative of inflammation and vascular damage.

r Spleen and liver volumes will be measured from the abdominal MRI. Patients will be required to fast from solid foods (liquids such as water or juice will be permitted) for ≥6 hours before an abdominal MRI to reduce the effect of a meal on MRI data.

s Chest X-ray will be performed in selected sites.

t Questionnaires will be completed at all indicated visits, except PGIC will not be completed at screening.

u Patients will fill out the eDiary as part of the baseline assessments during the evening of the 7 consecutive days before the first infusion and each quarterly visit (see Section 1.3). If the patient does not fill out the eDiary on the day before infusion, (ie, missing the Day 7 entry), then the patient will be allowed to make the day 7 eDiary entry in the clinic before study drug infusion.

v Liver biopsy samples will be collected at screening to determine baseline histopathology. See the study manual for guidelines on prohibited medications and therapies that are not to be taken within 10 days before and 3 days after the procedure.

w Patients must be hospitalized before the start of the infusion and remain hospitalized for at least 24 hours after the end of infusion during dose escalation period. Blood will be collected and safety assessments (including vital signs [footnote m]) will be performed. Study drug infusions will occur once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1) for each patient.

x See or the PK sampling schedule.

1.2.1.2 Schedule of assessments: Year 1 - PAP Week 18 through Week 52

Year 1: PAP Week 18 through Week 52	**Study week[a]**																	
Study procedures	**W18**	**W20**	**W22**	**W24**	**W26 QV**	**W28**	**W30**	**W32**	**W34**	**W36**	**W38 QV**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52 QV**
SAFETY																		
AE/SAE assessment[b]	Continuous monitoring																	
Concomitant medications and therapies	Continuous monitoring																	
Alcohol and tobacco use																		X
Complete physical examination[c]					X						X							X
Abbreviated physical examination[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight					X						X							X
Height																		X
Vital sign measurements[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[f]					X						X							X
Echocardiogram with doppler																		X
Clinical laboratory sampling																		
• Liver function testing and coagulation[g]					X						X							X
• Hematology[h]					X						X							X
• Clinical chemistry and urinalysis (dipstick only)[g]					X						X							X
• β-HCG pregnancy test[i]		X		X		X		X		X		X		X		X		X
Sampling for hsCRP, iron, ferritin, cardiac-specific					X						X							X

Year 1: PAP Week 18 through Week 52	**Study week[a]**																	
Study procedures	**W18**	**W20**	**W22**	**W24**	**W26 QV**	**W28**	**W30**	**W32**	**W34**	**W36**	**W38 QV**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52 QV**
troponin I, calcitonin, ceramide[j]																		
Immune response monitoring																		
Multiplex assay[j]					X						X							X
Anti-olipudase alfa IgG [k]					X						X							X
• Neutralizing antibodies	Only in patients positive for IgG olipudase alfa																	
If a patient develops IAR - hypersensitivity reaction(s):																		
• Anti-olipudase alfa IgG • Anti-olipudase alfa IgE	For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample ≥3 days after the event or before the next infusion.																	
• Tryptase activity • Complement activation	For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample 1 to 3 hours after the event.																	
Skin testing	As needed for hypersensitivity reactions – See study manual																	
If cytokine release syndrome:																		
Multiplex assay (Meso Scale)	For suspicion of CRS, collect immediately unless already collected within the past 30 minutes																	
Calcitonin																		
EFFICACY/PHARMACODYNAMICS																		
Abdominal MRI[l]					X													X
Liver biopsy[m]																		X
Echodoppler of liver																		X
Chest X-ray[n]					X													X
Pulmonary HRCT scan					X													X
Pulmonary function tests					X													X
Treadmill ergometry					X													X
Fasting lipid profile					X						X							X
NMR of HDL					X													X

Year 1: PAP Week 18 through Week 52	Study week[a]																	
Study procedures	**W18**	**W20**	**W22**	**W24**	**W26 QV**	**W28**	**W30**	**W32**	**W34**	**W36**	**W38 QV**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52 QV**
MRI scans of lumbar spine and bilateral femur																		X
DXA scans of lumbar spine and bilateral femur																		X
Sphingomyelin, ceramide, and other metabolites in plasma[j]					X						X							X
Metabolites in dried blood spot					X						X							X
Chitotriosidase, ACE, CCL18					X						X							X
Serum bone-specific ALP and C-telopeptide					X						X							X
Health-related quality of life instruments																		
• BFI, BPI-SF, EQ-5D, SF-36					X													X
• Health-Related Productivity Questionnaire, PGIS and PGIC, and NPB-HAQ					X						X							X
• eDiary[o]																		
- Distribute eDiary device to patients				X						X							X	
- Collect eDiary device from patients					X						X							X
Physician global assessment					X													X
STUDY DRUG INFUSION AND PHARMACOKINETICS																		
Study drug infusion[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling[q]					X						X							X

Abbreviations: ACE = angiotensin-converting enzyme; AE=adverse event; ALP = alkaline phosphatase; β-HCG = beta-human chorionic gonadotropin; BFI = Brief Fatigue Inventory; BPI-SF = Brief Pain Inventory - Short Form; CCL18 = chemokine (C-C motif) ligand 18; DXA = dual-energy X-ray absorptiometry; EQ-5D = EuroQOL-5 dimensions questionnaire; HDL = high-density lipoprotein; HRCT = high-resolution computed tomography; hsCRP = heat-sensitive C-reactive protein; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NMR = nuclear magnetic resonance;

NPB-HAQ = NPB - Health Assessment Questionnaire; PAP = primary analysis period; PGIC = Patient Global Impression of Change scale; PGIS = Patient Global Impression of Symptom Severity questionnaire; PK = pharmacokinetic; SAE = serious adverse event; SF-36 = Short form-36; QV = quarterly visit; W = study week.

a Study drug infusions will occur once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1). Assessments will be performed at the indicated visits ±7 days, unless otherwise specified. Unless specified otherwise, study procedures should preferably occur before infusion and during approximately the same time of day for each visit (in reference to the screening/baseline visit). When multiple assessments are required, the order will be vital signs before ECG before blood draw.

b Adverse events will be captured from the time the patient provides signed informed consent through the safety follow-up period (30 to 37 days after the patient's last study infusion).

c The complete physical examination will include a neurological examination (mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, and coordination); examinations of lymph nodes, heart, lungs, abdomen, and extremities/joints; and an assessment of the general appearance, skin, and HEENT (head, eyes, ears, nose, and throat).

d The abbreviated examination of general appearance only will be carried out before and after each study drug infusion.

e Vital sign measurements will include blood pressure, heart rate, respiratory rate, and temperature. At quarterly visits, collection times will be prior to the infusion (within 30 ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion (±10 minutes); 2 hours ±10 minutes, 4 hours ±10 minutes, and 6 hours ±10 minutes after the end of the infusion; and every 8 hours ±1 hour until the patient has been discharged. Vitals signs should also be measured at discharge ±10 minutes, which may or may not represent an additional measurement to the schedule described above. For these quarterly visits, patients should remain at the site for at least 24 hours after the end of infusion. The investigator may decide that longer monitoring is required. At all visits except quarterly visits and dose escalation visits, vital sign collection times will be prior to the infusion (within 30 minutes ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion ±10 minutes; and at discharge ±10 minutes (1 hour post-infusion). At any visit the investigator may decide that longer monitoring is required.

f A single ECG will be administered each before infusion and 4 hours ±10 minutes, 12 hours ±1 hour, and 24 hours ±3 hours after the end of infusion. Electrocardiograms will be performed before the blood draw scheduled at the same time point.

g Samples will be taken for liver function testing and coagulation within 24 hours before and 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion. Samples will be taken for urinalysis and clinical chemistry within 24 hours before infusion.

h For hematology at quarterly visits, except yearly visits, 1 sample for complete blood count with differential will be taken within 24 hours before infusion and one 24 ±3 hours after the end of infusion. At yearly visits, 2 samples will be taken at least 24 hours and up to 2 weeks apart before infusion, the first for complete blood count with differential and the second for hemoglobin and white blood cell and platelet counts only. In addition, at yearly visits, 1 sample for complete blood count with differential will be taken 24 ±3 hours after the end of infusion.

i Urine β-HCG up to 24 hours before infusion, once every 4 weeks; if positive, repeat test with serum.

j Sample will be taken within 24 hours before infusion and 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion for metabolites in plasma and biomarkers including but not limited to: hsCRP, iron, ceramide, ferritin, cardiac troponin-I, calcitonin, and multiplex assay (Meso Scale) for other biomarkers indicative of inflammation and vascular damage.

k [redacted] collection will be monthly for the first 6 months after starting the new update, and quarterly after that.

l Spleen and liver volumes will be measured from the abdominal MRI. Patients will be required to fast from solid foods (liquids such as water or juice will be permitted) for ≥6 hours before an abdominal MRI to reduce the effect of a meal on MRI data.

m See the study manual for guidelines on prohibited medications and therapies that are not to be taken within 10 days before and 3 days after the liver biopsy.

n Chest X-ray will be performed in selected sites.

o Patients will fill out the eDiary during the evening of the 7 consecutive days before each quarterly visit (see Section 1.3). If the patient does not fill out the eDiary on the day before infusion, (ie, missing the Day 7 entry), then the patient will be allowed to make the day 7 eDiary entry in the clinic before study drug infusion.

p Patients must be hospitalized before the start of the infusion and remain hospitalized for at least 24 hours after the end of infusion during quarterly visits during PAP. Blood will be collected and safety assessments (including vital signs [footnote e]) will be performed. For all other visits, patients will be observed after the end of infusion for at least 3 hours. Study drug infusions will occur once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1) for each patient.

q See for the PK sampling schedule.

1.2.2 Schedule of assessments: extension treatment period

1.2.2.1 Schedule of assessments: ETP - Year 2 Week 54 to Week 70

Year 2: ETP Week 54 to Week 70	**Dose escalation period[a]**								
Study procedures	**W54**	**W56**	**W58**	**W60**	**W62**	**W64**	**W66**	**W68 QV**	**W70**
Treatment crossover[b]	X								
SAFETY									
AE/SAE assessment[c]	Continuous monitoring								
Concomitant medications and therapies	Continuous monitoring								
Complete physical examination[d]	X							X	
Abbreviated physical examination[e]	X	X	X	X	X	X	X	X	X
Weight[f]	X	X	X	X	X	X	X	X	
Vital sign measurements[g]	X	X	X	X	X	X	X	X	X
Electrocardiogram[h]	X							X	
Echocardiogram with Doppler								X	
Clinical laboratory sampling									
Liver function testing and coagulation[i]	X	X	X	X	X	X	X	X	X
Hematology[j]	X	X	X	X	X	X	X	X	X
Clinical chemistry and urinalysis (dipstick only)[i]	X	X	X	X	X	X	X	X	X
β-HCG pregnancy test[k]		X		X		X		X	
Sampling for hsCRP, iron, ferritin, cardiac-specific troponin I, calcitonin, ceramide[l]	X	X	X	X	X	X	X	X	X
Immune response monitoring									
Multiplex assay[l]	X	X	X	X	X	X	X	X	X

Year 2: ETP Week 54 to Week 70	**Dose escalation period**[a]								
Study procedures	**W54**	**W56**	**W58**	**W60**	**W62**	**W64**	**W66**	**W68 QV**	**W70**
Anti-olipudase alfa IgG	X		X		X		X		X
Neutralizing antibodies	Only in patients positive for IgG olipudase alfa								
If a patient develops IAR - hypersensitivity reaction(s):									
• Anti-olipudase alfa IgG • Anti-olipudase alfa IgE	For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample ≥3 days after the event or before the next infusion.								
• Tryptase activity • Complement activation	For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample 1 to 3 hours after the event.								
Skin testing	As needed for hypersensitivity reactions - See study manual								
In case of cytokine release syndrome:									
Multiplex assay (Meso Scale) Calcitonin	For suspicion of CRS, collect immediately unless already collected within the past 30 minutes								
EFFICACY/PHARMACODYNAMICS									
Fasting lipid profile								X	
Sphingomyelin, ceramide, and other metabolites in plasma[l]	X	X	X	X	X	X	X	X	X
Metabolites in dried blood spot	X	X	X	X	X	X	X	X	X
Chitotriosidase, ACE, CCL18								X	
Serum bone-specific ALP and C-telopeptide								X	
Health-related quality of life instruments									
• Health-Related Productivity Questionnaire, PGIS and PGIC, and NPB-HAQ								X	
• eDiary[m]									
- Distribute eDiary device to patients							X		
- Collect eDiary device from patients								X	

Year 2: ETP Week 54 to Week 70	Dose escalation period[a]								
Study procedures	**W54**	**W56**	**W58**	**W60**	**W62**	**W64**	**W66**	**W68 QV**	**W70**
STUDY DRUG INFUSION AND PHARMACOKINETICS									
Study drug infusion[n]	X	X	X	X	X	X	X	X	X
PK sampling[o]	X							X	

Abbreviations: ACE=angiotensin-converting enzyme; AE = adverse event; ALP = alkaline phosphatase; β-HCG = beta-human chorionic gonadotropin; BFI = Brief Fatigue Inventory; BPI-SF = Brief Pain Inventory - Short Form; CCL18 = chemokine (C-C motif) ligand 18; EQ-5D = EuroQOL-5 dimensions questionnaire; ETP = extension treatment period; hsCRP = heat-sensitive C-reactive protein; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; NPB-HAQ = NPB - Health Assessment Questionnaire; PAP = primary analysis period; PGIC = Patient Global Impression of Change scale; PGIS = Patient Global Impression of Symptom Severity questionnaire; PK = pharmacokinetic; SAE = serious adverse event; SF-36 = Short Form-36; QV = quarterly visit; W = study week.

a Study drug infusions will occur once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1). Assessments will be performed at the indicated visits ±7 days, unless otherwise specified. Unless specified otherwise, study procedures should preferably occur before infusion and during approximately the same time of day for each visit (in reference to the screening/baseline visit). When multiple assessments are required, the order will be vital signs before ECG before blood draw.

b True crossover for patients on placebo during the PAP and mock crossover for patients already on active treatment.

c Adverse events will be captured from the time the patient provides signed informed consent through the safety follow-up period (30 to 37 days after the patient's last study infusion).

d The complete physical examination will include a neurological examination (mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, and coordination); examinations of lymph nodes, heart, lungs, abdomen, and extremities/joints; and an assessment of the general appearance, skin, and HEENT (head, eyes, ears, nose, and throat)

e The abbreviated examination of general appearance only will be carried out before and after each study drug infusion.

f The patient's weight at the previous visit, instead of the weight at the current visit, can be used to calculate the dose of drug to be infused at the current visit if the weight at the current visit is missing.

g Vital sign measurements will include blood pressure, heart rate, respiratory rate, and temperature. At all visits during the dose escalation period and at quarterly visits, collection times will be prior to the infusion (within 30 ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion (±10 minutes); 2 hours ±10 minutes, 4 hours ±10 minutes, and 6 hours ±10 minutes after the end of the infusion; and every 8 hours ±1 hour until the patient has been discharged. Vital signs should also be measured at discharge ±10 minutes, which may or may not represent an additional measurement to the schedule described above. For these visits, patients should remain at the site for at least 24 hours. The investigator may decide that longer monitoring is required.

h Electrocardiograms will be performed before any blood is collected. One ECG will be performed each before infusion and 4 hours ±10 minutes, 12 hours ±1 hour, and 24 hours ±3 hours after the infusion.

i Samples will be taken for liver function testing and coagulation within 24 hours before infusion and at 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion. Samples will be taken for urinalysis and clinical chemistry within 24 hours before infusion.

j One sample for complete blood count with differential will be taken within 24 hours before infusion and one 24 hours ±3 hours after the end of infusion.

k Urine β-HCG test for pregnancy before infusion, once every 4 weeks; if positive, retest using serum.

l Sample will be taken within 24 hours before infusion and 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion for metabolites in plasma and biomarkers including but not limited to: hsCRP, iron, ceramide, ferritin, cardiac troponin-I, calcitonin, and multiplex assay (Meso Scale) for other biomarkers indicative of inflammation and vascular damage.

m Patients will fill out the eDiary during the evening of the 7 consecutive days before each quarterly visit (see Section 1.3). If the patient does not fill out the eDiary on the day before infusion, (ie, missing the Day 7 entry), then the patient will be allowed to make the day 7 eDiary entry in the clinic before study drug infusion.

n Patients must be hospitalized before the start of the infusion and remain hospitalized for at least 24 hours after the end of infusion during the dose escalation period and during quarterly visits. Blood will be collected and safety assessments (including vital signs [footnote g]) will be performed. Study drug infusions will occur once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1) for each patient.

o See for the PK sampling schedule.

1.2.2.2 Schedule of assessments: ETP - Year 2 Week 72 to Week 104 only applicable before the implementation of changes that will occur after the cutoff date of the second database lock

Year 2: ETP Year 2 Week 72 to Week 104	**Study week[a]**																
Study procedures	**W72**	**W74**	**W76**	**W78**	**W80 QV**	**W82**	**W84**	**W86**	**W88**	**W90**	**W92 QV**	**W94**	**W96**	**W98**	**W100**	**W102**	**W104 QV**
SAFETY																	
AE/SAE assessment[b]	Continuous monitoring																
Concomitant medications and therapies	Continuous monitoring																
Alcohol and tobacco usage																	X
Complete physical examination[c]					X						X						X
Abbreviated physical examination[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[e], BMI					X						X						X
Height																	X
Vital sign measurements[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[g]					X						X						X
Echocardiogram with Doppler																	X
Clinical laboratory sampling																	
• Liver function testing and coagulation[h]					X						X						X
• Hematology[i]					X						X						X
• Clinical chemistry and urinalysis (dipstick only)[h]					X						X						X
• β-HCG pregnancy test[j]	X		X		X		X		X		X		X		X		X
Sampling for hsCRP, iron, ferritin, cardiac-specific troponin I, calcitonin, ceramide[l]					X						X						X

Year 2: ETP Year 2 Week 72 to Week 104	**Study week[a]**																
Study procedures	**W72**	**W74**	**W76**	**W78**	**W80 QV**	**W82**	**W84**	**W86**	**W88**	**W90**	**W92 QV**	**W94**	**W96**	**W98**	**W100**	**W102**	**W104 QV**
Immune response monitoring																	
Multiplex assay[l]					X						X						X
Anti-olipudase alfa IgG[k]					X						X						X
• Neutralizing antibodies	Only in patients positive for IgG olipudase alfa																
If a patient develops IAR/hypersensitivity reaction(s):																	
• Anti-olipudase alfa IgG • Anti-olipudase alfa IgE	For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample ≥3 days after the event or before the next infusion.																
• Tryptase activity • Complement activation	For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample 1 to 3 hours after the event.																
Skin testing	As needed for hypersensitivity reactions - See study manual																
In case of cytokine release syndrome:																	
Multiplex assay (Meso Scale)	For suspicion of CRS, collect immediately unless already collected within the past 30 minutes																
Calcitonin																	
EFFICACY/PHARMACODYNAMICS																	
Abdominal MRI[m]					X												X
Liver biopsy[n]																	X
Echodoppler of liver																	X
Chest X-ray[o]					X												X
Pulmonary HRCT scan					X												X
Pulmonary function tests					X												X
Treadmill ergometry					X												X
Fasting lipid profile					X						X						X
NMR of HDL					X												X
MRI scans of lumbar spine and bilateral femur																	X

Year 2: ETP Year 2 Week 72 to Week 104	**Study week[a]**																
Study procedures	**W72**	**W74**	**W76**	**W78**	**W80 QV**	**W82**	**W84**	**W86**	**W88**	**W90**	**W92 QV**	**W94**	**W96**	**W98**	**W100**	**W102**	**W104 QV**
DXA scans of lumbar spine and bilateral femur																	X
Sphingomyelin, ceramide, and other metabolites in plasma[l]					X						X						X
Metabolites in dried blood spot					X						X						X
Chitotriosidase, ACE, CCL18					X						X						X
Serum bone-specific ALP and C-telopeptide					X						X						X
Health-related quality of life instruments																	
• BFI, BPI-SF, EQ-5D, SF-36					X												X
• Health-Related Productivity Questionnaire, PGIC and PGIS, and NPB-HAQ					X						X						X
• eDiary[p]																	
- Distribute eDiary device to patients				X						X						X	
- Collect eDiary device from patients					X						X						X
Physician global assessment					X												X

Year 2: ETP Year 2 Week 72 to Week 104	Study week[a]																
Study procedures	**W72**	**W74**	**W76**	**W78**	**W80 QV**	**W82**	**W84**	**W86**	**W88**	**W90**	**W92 QV**	**W94**	**W96**	**W98**	**W100**	**W102**	**W104 QV**
STUDY DRUG INFUSION AND PHARMACOKINETICS																	
Study drug infusion[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling[r]					X												

Abbreviations: ACE = angiotensin-converting enzyme; AE=adverse event; ALP = alkaline phosphatase; β-HCG = beta-human chorionic gonadotropin; BFI = Brief Fatigue Inventory; BMI = body mass index; BPI-SF = Brief Pain Inventory - Short Form; CCL18 = chemokine (C-C motif) ligand 18; DXA = dual-energy X-ray absorptiometry; EQ-5D = EuroQOL-5 dimensions questionnaire; ETP = extension treatment period; HDL = high-density lipoprotein; HRCT = high resolution computed tomography; hsCRP = heat-sensitive C-reactive protein; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NMR = nuclear magnetic resonance; NPB-HAQ = NPB – Health Assessment Questionnaire; PGIC = Patient Global Impression of Change scale; PGIS = Patient Global Impression of Symptom Severity questionnaire; PK = pharmacokinetic; SAE=serious adverse event; SF-36 = Short Form-36; QV = quarterly visit; W = study week.

a Study drug infusions will occur once every 2 weeks (±3 days) at the study site or at home (during the Covid-19 pandemic) if agreed between the investigator and the sponsor, for eligible patients), in reference to the date of the first infusion (Day 1). Assessments will be performed at the indicated visits ±7 days, unless otherwise specified. Unless specified otherwise, study procedures should preferably occur before infusion and during approximately the same time of day for each visit (in reference to the screening/baseline visit). Quarterly visits will occur at the site. During the COVID-19 pandemic, if site visits are not possible and home infusion is already approved for the eligible patient, quarterly visits will be done at home, quarterly visit assessments will not be done, and home infusion visits will continue with biweekly assessments. In such a case, some of the quarterly visit assessments can be done by the site through the phone (eg, Health-related quality of life instruments) and the rest of missed quarterly visit assessments will be done as unscheduled, as soon as site visits become available. When multiple assessments are required, the order will be vital signs before ECG before blood draw. Telehealth visits are an acceptable alternative to site visits during the COVID-19 pandemic, in accordance with institutional policy and with applicable country-specific regulations.

b Adverse events will be captured from the time the patient provides signed informed consent through the safety follow-up period (30 to 37 days after the patient's last study infusion).

c The complete physical examination will include a neurological examination (mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, and coordination); examinations of lymph nodes, heart, lungs, abdomen, and extremities/joints; and an assessment of the general appearance, skin, and HEENT (head, eyes, ears, nose, and throat).

d The abbreviated examination of general appearance only will be carried out before and after each study drug infusion.

e Weight at previous on-site quarterly visit or home visit (during COVID-19 pandemic, if ≥3 months passed since last on-site quarterly visit) may be used to calculate drug dosage at current visit.

f Vital sign measurements will include blood pressure, heart rate, respiratory rate, and temperature. At quarterly visits, collection times will be prior to the infusion (within 30 ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion (±10 minutes); 2 hours ±10 minutes, 4 hours ±10 minutes, and 6 hours ±10 minutes after the end of infusion; and every 8 hours ±1 hour until the patient has been discharged. Vital signs should also be measured at discharge ±10 minutes, which may or may not represent an additional measurement to the schedule described above. For these quarterly visits, patients should remain at the site for at least 24 hours. The investigator may decide that longer monitoring is required. At all visits except quarterly visits and dose escalation visits, vital sign collection times will be prior to the infusion (within 30 minutes ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion ±10 minutes; and at discharge ±10 minutes (1 hour post-infusion). At any visit the investigator may decide that longer monitoring is required.

g Electrocardiograms will be performed before any blood draws. Single ECGs will be performed before infusion and 4 hours ±10 minutes, 12 hours ±1 hour, and 24 hours ±3 hours after the end of infusion.

h Samples will be taken for liver function testing and coagulation within 24 hours before infusion and at 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion. Samples will be taken for urinalysis and clinical chemistry within 24 hours before infusion.

i For hematology at quarterly visits, except yearly visits, 1 sample for complete blood count with differential will be taken within 24 hours before infusion and one 24 hours after the end of infusion. At yearly visits, 2 samples will be taken at least 24 hours and up to 2 weeks apart before infusion, the first for complete blood count with differential and the second for hemoglobin and white blood cell and platelet counts only. [redacted]

j Urine β-HCG up to 24 hours before infusion, once every 4 weeks; if positive, then retest with serum.

k [redacted], collection will be monthly for the first 6 months after starting the new update, and quarterly after that.

l Sample will be taken within 24 hours before infusion and 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion for metabolites in plasma and biomarkers including but not limited to: hsCRP, iron, ceramide, ferritin, cardiac troponin-I, calcitonin, and multiplex assay (Meso Scale) for other biomarkers indicative of inflammation and vascular damage.

m Spleen and liver volumes will be measured from the abdominal MRI. Patients will be required to fast from solid foods (liquids such as water or juice will be permitted) for ≥6 hours before an abdominal MRI to reduce the effect of a meal on MRI data.

n See the study manual for guidelines on prohibited medications and therapies that are not to be taken within 10 days before and 3 days after the liver biopsy procedure.

o Chest X-ray will be performed in selected sites.

p Patients will fill out the eDiary during the evening of the 7 consecutive days before each quarterly visit (see Section 1.3). If the patient does not fill out the eDiary on the day before infusion, (ie, missing the Day 7 entry), then the patient will be allowed to make the day 7 eDiary entry in the clinic before study drug infusion.

q Patients may be hospitalized before the start of the infusion and remain hospitalized for at least 24 hours after the end of infusion during quarterly visits (ie, W80, W92, and W104). Blood will be collected and safety assessments (including vital signs [footnote f]) will be performed. Study drug infusions will occur once every 2 weeks (±3 days) at the site or at home (during the Covid-19 pandemic) if agreed between the investigator and the sponsor, for eligible patients, once every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1) for each patient. Quarterly visits will occur at the site. During the COVID-19 pandemic, if home infusion approved for the eligible patient, quarterly visits will be done at home.

r See or the PK sampling schedule.

1.2.2.3 Schedule of assessments: ETP - Year 3 until end of study only applicable before the implementation of changes that will occur after the cutoff date of the second database lock

Year 3 Year 4 Year 5		Study weeks[a]								End of study[b] (early d/c)	Safety follow-up phone call
			QV		QV		QV		QV		
Study procedures	Year 3	W106-W116	W118	W120-W130	W132	W134-W142	W144	W146-W154	W156		
	Year 4	W158-W168	W170	W172-W182	W184	W186-W194	W196	W198-W206	W208		
	Year 5	W210-W220	W222	W224-W234	W236	W238-W246	W248	W250-W258	W260		
SAFETY											
AE/SAE assessment[c]		Continuous monitoring									
Concomitant medications and therapies		Continuous monitoring									
Alcohol and tobacco usage									X		
Complete physical examination[d]			X		X		X		X	X	
Abbreviated physical examination[e]		X	X	X	X	X	X	X	X		
Weight[f], BMI			X		X		X		X		
Height									X		
Vital sign measurements		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X	
Electrocardiogram			X[h]		X[h]		X[h]		X[h]	X	
Echocardiogram with Doppler										X	
Clinical laboratory sampling											
• Liver function testing and coagulation			X[i]		X[i]		X[i]		X[i]	X	
• Hematology			X[j]		X[j]		X[j]		X[j]	X[k]	
• Clinical chemistry and urinalysis (dipstick only)			X[i]		X[i]		X[i]		X[i]	X	
• β-HCG pregnancy test[l]		Every 4 weeks								X	
Sampling for hsCRP, iron, ferritin, cardiac-specific troponin I, calcitonin, ceramide			X[n]		X[n]		X[n]		X[n]	X	

Year 3 Year 4 Year 5		Study weeks[a]								End of study[b] (early d/c)	Safety follow-up phone call
			QV		QV		QV		QV		
Study procedures	Year 3	W106-W116	W118	W120-W130	W132	W134-W142	W144	W146-W154	W156		
	Year 4	W158-W168	W170	W172-W182	W184	W186-W194	W196	W198-W206	W208		
	Year 5	W210-W220	W222	W224-W234	W236	W238-W246	W248	W250-W258	W260		
Immune response monitoring											
Multiplex assay			X[n]		X[n]		X[n]		X[n]	X	
Anti-olipudase alfa IgG[m]			X		X		X		X	X	
• Neutralizing antibodies		Only in patients positive for IgG olipudase alfa									
If a patient develops IAR - hypersensitivity reaction(s):											
• Anti-olipudase alfa IgG • Anti-olipudase alfa IgE		For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample ≥3 days after the event or before the next infusion.									
• Tryptase activity • Complement activation		For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample 1 to 3 hours after the event.									
Skin testing		As needed for hypersensitivity reactions - See study manual									
In case of cytokine release syndrome:											
Multiplex assay (Meso Scale)		For suspicion of CRS, collect immediately unless already collected within the past 30 minutes									
Calcitonin											
EFFICACY/PHARMACODYNAMICS											
Abdominal MRI[o]					X				X	X	
Echodoppler of liver									X	X	
Chest X-ray[p]					X				X	X	
Pulmonary HRCT scan					X				X	X	
Pulmonary function tests					X				X	X	
Treadmill ergometry					X				X	X	
Fasting lipid profile			X		X		X		X	X	
NMR of HDL									X		

Year 3 Year 4 Year 5		Study weeks[a]								End of study[b] (early d/c)	Safety follow-up phone call
			QV		QV		QV		QV		
Study procedures	Year 3	W106-W116	W118	W120-W130	W132	W134-W142	W144	W146-W154	W156		
	Year 4	W158-W168	W170	W172-W182	W184	W186-W194	W196	W198-W206	W208		
	Year 5	W210-W220	W222	W224-W234	W236	W238-W246	W248	W250-W258	W260		
MRI scans of lumbar spine and bilateral femur									X	X	
DXA scans of lumbar spine and bilateral femur									X	X	
Sphingomyelin, ceramide, and other metabolites in plasma[n]			X		X		X		X	X	
Metabolites in dried blood spot			X		X		X		X	X	
Chitotriosidase, ACE, CCL18			X		X		X		X	X	
Serum bone-specific ALP and C-telopeptide			X		X		X		X		
Health-related quality of life instruments											
• BFI, BPI-SF, EQ-5D, SF-36					X				X	X	
• Health-Related Productivity Questionnaire, PGIC and PGIS, and NPB-HAQ			X		X		X		X	X	
• eDiary[q]											
- Collect eDiary device from patients			X		X		X		X		
Treatment experience interview[r]					X						
Physician global assessment					X				X	X	
STUDY DRUG INFUSION AND PHARMACOKINETICS											
Study drug infusion[s]		X	X	X	X	X	X	X	X		
PK sampling[t]					X						

Abbreviations: ACE = angiotensin-converting enzyme; AE=adverse event; ALP = alkaline phosphatase; β-HCG = beta-human chorionic gonadotropin; BFI = Brief Fatigue Inventory; BMI = body mass index; BPI-SF = Brief Pain Inventory - Short Form; CCL18 = chemokine (C-C motif) ligand 18; DXA = dual-energy X-ray absorptiometry; EQ-5D = EuroQOL-5 dimensions questionnaire; ETP = extension treatment period; HD = high-density lipoprotein; HRCT = high resolution computed tomography; hsCRP = heat-sensitive C-reactive protein; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G;

MRI = magnetic resonance imaging; NMR = nuclear magnetic resonance; NPB-HAQ = NPB - Health Assessment Questionnaire; q4w = once every 4 weeks; PGIC = Patient Global Impression of Change scale; PGIS = Patient Global Impression of Symptom Severity questionnaire; PK = pharmacokinetic; SAE = serious adverse event; SF-36 = Short Form-36; QV = quarterly visit; W = study week.

a Study drug infusions will occur once every 2 weeks (±3 days) at the site or at home (during the COVID-19 pandemic) if agreed between the investigator and the sponsor, for eligible patients, in reference to the date of the first infusion (Day 1). Assessments will be performed at the indicated visits ±7 days, unless otherwise specified. Unless specified otherwise, study procedures should preferably occur before infusion and during approximately the same time of day for each visit (in reference to the screening/baseline visit). Quarterly visits will occur at the site. During the COVID-19 pandemic, if site visits are not possible and home infusion is already approved for the eligible patient, quarterly visits will be done at home, quarterly visit assessments will not be done, and home infusion visit will continue with biweekly assessments. In such a case, some of the quarterly visit assessments can be done by the site through the phone (eg, Health-related quality of life instruments). the rest of the missed quarterly visit assessments will be done as unscheduled, as soon as site visits become available. When multiple assessments are required, the order will be vital signs before ECG before blood draw. Telehealth visits are an acceptable alternative to site visits during the COVID-19 pandemic, in accordance with institutional policy and with applicable country-specific regulations.

b The EOS visit will be completed within 2 weeks after the final treatment. At the EOS visit and for patients who discontinue after the dose escalation period of the PAP or the ETP, NPB Health Assessment, NPB-HAQ, PGIS questionnaires, abdominal MRI, liver echo Doppler, HRCT, chest X-ray, pulmonary function tests, treadmill ergometry, and echocardiogram with Doppler will not be repeated if they had been done within 3 months prior; DXA and bone MRI will not be repeated if they had been done within 6 months prior. Patients who discontinue during the dose escalation period of the PAP or the ETP will have more limited assessments (see detail in Section 10.1).

c Adverse events will be captured from the time the patient provides signed informed consent through the safety follow-up period (30 to 37 days after the patient's last study infusion).

d The complete physical examination will include a neurological examination (mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, and coordination); examinations of lymph nodes, heart, lungs, abdomen, and extremities/joints; and an assessment of the general appearance, skin, and HEENT (head, eyes, ears, nose, and throat).

e The abbreviated examination of general appearance only will be carried out before and after each study drug infusion.

f Weight at previous on-site or home visit (during COVID-19 pandemic, if ≥3 months passed since last on-site quarterly visit) may be used to calculate drug dosage at current visit.

g Vital sign measurements will include blood pressure, heart rate, respiratory rate, and temperature. At quarterly visits, collection times will be prior to the infusion (within 30 ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion (±10 minutes); 2 hours ±10 minutes, 4 hours ±10 minutes, and 6 hours ±10 minutes after the end of the infusion; and every 8 hours ±1 hour until the patient has been discharged. Vital signs should also be measured at discharge ±10 minutes, which may or may not represent an additional measurement to the schedule described above. For these visits, patients should remain at the site for at least 24 hours. The investigator may decide that longer monitoring is required. At all visits except quarterly visits and dose escalation visits, vital sign collection times will be prior to the infusion (within 30 minutes ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion ±10 minutes; and at discharge ±10 minutes (1 hour post-infusion). At any visit the investigator may decide that longer monitoring is required.

h Electrocardiograms will be performed before any blood draws. Single ECGs will be performed before infusion and 4 hours ±10 minutes, 12 hours ±1 hour, and 24 hours ±3 hours after the end of infusion.

i Samples will be taken for liver function testing and coagulation within 24 hours before infusion and at 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion. Samples will be taken for urinalysis and clinical chemistry within 24 hours before infusion.

j For hematology at quarterly visits except yearly visits, 1 sample for complete blood count with differential will be taken within 24 hours before infusion and one 24 hours ±3 hours after the end of infusion. At yearly visits, 2 samples will be taken at least 24 hours and up to 2 weeks apart before infusion, the first for complete blood count with differential and the second for hemoglobin and white blood cell and platelet counts only. In addition, at yearly visits, 1 sample for complete blood count with differential will be taken 24 hours ±3 hours after the end of infusion. [redacted] 2 samples will be taken during an infusion 3 months after the introduction of the drug from the updated manufactured process, at least 24 hours and up to 2 weeks apart.

k At the end of study visit, 1 sample will be taken for complete blood count with differential.

l Urine β-HCG up to 24 hours before infusion, once every 4 weeks; if positive, then retest with serum.

m [redacted], collection will be monthly for the first 6 months after starting the new update, and quarterly after that.

n Sample will be taken within 24 hours before infusion and 24 hours ±3 hours and 48 hours ±3 hours after the end of infusion for metabolites in plasma and biomarkers including but not limited to: hsCRP, iron, ceramide, ferritin, cardiac troponin-I, calcitonin, and multiplex assay (Meso Scale) for other biomarkers indicative of inflammation and vascular damage.

o Spleen and liver volumes will be measured from the abdominal MRI. Patients will be required to fast from solid foods (liquids such as water or juice will be permitted) for ≥6 hours before an abdominal MRI to reduce the effect of a meal on MRI data.

p Chest X-ray will be performed in selected sites.

q Patients will fill out the eDiary during the evening of the 7 consecutive days before each quarterly visit (see Section 1.3). If the patient does not fill out the eDiary on the day before infusion, (ie, missing the Day 7 entry), then the patient will be allowed to make the Day 7 eDiary entry in the clinic before study drug infusion.

r Only for patients consenting to the qualitative structured interviews

s In-patient hospitalization may be needed throughout the infusion and for at least 24 hours after the end of infusion during quarterly visits and yearly visits in years 3 to 5. Blood will be collected and safety assessments (including vital signs [footnote g]) will be performed. For all other visits, patients will be observed after the end of infusion for at least 1 hour Study drug infusions will occur once every 2 weeks (±3 days) at the site or at home (during the COVID-19 pandemic) if agreed between the investigator and the sponsor, for eligible patients, in reference to the date of the first infusion (Day 1) for each patient. Quarterly visits will occur at the site. During the COVID-19 pandemic if home infusion already approved for the eligible patient, quarterly visits will be done at home.

t See for the PK sampling schedule.

1.2.2.4 Schedule of assessments ETP Year 3 until the end of study only applicable after the cutoff date for a planned second database lock of the study:

Year 3 Year 4 Year 5		Study weeks[a]								End of study[b] (early d/c)	Safety follow-up phone call
			QV		QV		QV		QV		
Study procedures	Year 3	W106-W116	W118	W120-W130	W132	W134-W142	W144	W146-W154	W156		
	Year 4	W158-W168	W170	W172-W182	W184	W186-W194	W196	W198-W206	W208		
	Year 5	W210-W220	W222	W224-W234	W236	W238-W246	W248	W250-W258	W260		
SAFETY											
AE/SAE assessment[c]		Continuous monitoring									
Concomitant medications and therapies		Continuous monitoring									
Alcohol and tobacco usage									X		
Complete physical examination[d]			X		X		X		X	X	
Abbreviated physical examination[e]		X	X	X	X	X	X	X	X		
Weight[f], BMI			X		X		X		X		
Height									X		
Vital sign measurements		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X	
Electrocardiogram			X[h]		X[h]		X[h]		X[h]	X	
Echocardiogram with Doppler										X	
Clinical laboratory sampling											
• Liver function testing and coagulation			X[i]		X[i]		X[i]		X[i]	X	
• Hematology			X[j]		X[j]		X[j]		X[j]	X[k]	
• Clinical chemistry and urinalysis (dipstick only)			X[i]		X[i]		X[i]		X[i]	X	
• β-HCG pregnancy test[l]		Every 4 weeks								X	
Sampling for hsCRP, iron, ferritin, cardiac-specific troponin I, calcitonin[n]			X[n]		X[n]		X[n]		X[n]	X	

Year 3 Year 4 Year 5		Study weeks[a]								End of study[b] (early d/c)	Safety follow-up phone call
			QV		QV		QV		QV		
Study procedures	Year 3	W106-W116	W118	W120-W130	W132	W134-W142	W144	W146-W154	W156		
	Year 4	W158-W168	W170	W172-W182	W184	W186-W194	W196	W198-W206	W208		
	Year 5	W210-W220	W222	W224-W234	W236	W238-W246	W248	W250-W258	W260		
Immune response monitoring											
Multiplex pro-inflammatory panel			X[n]		X[n]		X[n]		X[n]	X	
Anti-olipudase alfa IgG[m]			X		X		X		X	X	
• Neutralizing antibodies		Only in patients positive for IgG olipudase alfa									
If a patient develops IAR - hypersensitivity reaction(s):											
• Anti-olipudase alfa IgG • Anti-olipudase alfa IgE		For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample ≥3 days after the event or before the next infusion.									
• Tryptase activity • Complement activation		For a moderate/severe or recurrent IAR that is suggestive of hypersensitivity, collect sample 1 to 3 hours after the event.									
Skin testing		As needed for hypersensitivity reactions - See study manual									
In case of cytokine release syndrome:											
Multiplex pro-inflammatory panel (Meso Scale)		For suspicion of CRS, collect immediately unless already collected within the past 30 minutes									
Calcitonin											
EFFICACY/PHARMACODYNAMICS											
Abdominal MRI[o]					X				X	X	
Echodoppler of liver									X	X	
Chest X-ray[p]									X	X	
Pulmonary HRCT scan					X				X	X	
Pulmonary function tests					X				X	X	
Treadmill ergometry									X	X	
Fasting lipid profile			X		X		X		X	X	

Year 3 Year 4 Year 5		Study weeks[a]								End of study[b] (early d/c)	Safety follow-up phone call
			QV		QV		QV		QV		
Study procedures	Year 3	W106-W116	W118	W120-W130	W132	W134-W142	W144	W146-W154	W156		
	Year 4	W158-W168	W170	W172-W182	W184	W186-W194	W196	W198-W206	W208		
	Year 5	W210-W220	W222	W224-W234	W236	W238-W246	W248	W250-W258	W260		
MRI scans of lumbar spine and bilateral femur									X	X	
DXA scans of lumbar spine and bilateral femur									X	X	
Ceramide, lyso-sphingomyelin in plasma[q]					X				X	X	
Chitotriosidase, CCL18[q]					X				X	X	
Serum bone-specific ALP and C-telopeptide[q]					X				X		
Health-related quality of life instruments											
• BFI, BPI-SF, EQ-5D, SF-36					X				X	X	
• Health-Related Productivity Questionnaire, PGIC and PGIS, and NPB-HAQ			X		X		X		X	X	
• eDiary[s]											
- Collect eDiary device from patients			X		X		X		X		
Treatment experience interviews[r]					X						
Physician global assessment					X				X	X	
STUDY DRUG INFUSION AND PHARMACOKINETICS											
Study drug infusion[t]		X	X	X	X	X	X	X	X		
PK sampling[u]					X						

Abbreviations: ACE = angiotensin-converting enzyme; AE=adverse event; ALP = alkaline phosphatase; β-HCG = beta-human chorionic gonadotropin; BFI = Brief Fatigue Inventory; BMI = body mass index; BPI-SF = Brief Pain Inventory - Short Form; CCL18 = chemokine (C-C motif) ligand 18; DXA = dual-energy X-ray absorptiometry; EQ-5D = EuroQOL-5 dimensions questionnaire; ETP = extension treatment period; HD = high-density lipoprotein; HRCT = high resolution computed tomography; hsCRP = heat-sensitive C-reactive protein; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NMR = nuclear magnetic resonance; NPB-HAQ = NPB - Health Assessment Questionnaire; q4w = once every 4 weeks; PGIC = Patient Global Impression of Change scale; PGIS = Patient Global Impression of Symptom Severity questionnaire; PK = pharmacokinetic; SAE = serious adverse event; SF-36 = Short Form-36; QV = quarterly visit; W = study week.

a Study drug infusions will occur once every 2 weeks (±3 days) at the site or at home (during the COVID-19 pandemic) if agreed between the investigator and the sponsor, for eligible patients, in reference to the date of the first infusion (Day 1). [redacted] if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, to permit the first infusion [redacted] to be at home for eligible patients in agreement between the Sponsor and the Investigator in compliance with applicable country-specific regulations.
Assessments will be performed at the indicated visits ±7 days, unless otherwise specified. Unless specified otherwise, study procedures should preferably occur before infusion and during approximately the same time of day for each visit (in reference to the screening/baseline visit). Quarterly visits will occur at the site. During the COVID-19 pandemic, if site visits are not possible and home infusion is already approved for the eligible patient, quarterly visits will be done at home, quarterly visit assessments will not be done, and home infusion visit will continue with biweekly assessments. In such a case, some of the quarterly visit assessments can be done by the site through the phone (eg, Health-related quality of life instruments). the rest of the missed quarterly visit assessments will be done as unscheduled, as soon as site visits become available. When multiple assessments are required, the order will be vital signs before ECG before blood draw. Telehealth visits are an acceptable alternative to site visits during the COVID-19 pandemic, in accordance with institutional policy and with applicable country-specific regulations.

b The EOS visit will be completed within 2 weeks after the final treatment. At the EOS visit and for patients who discontinue after the dose escalation period of the PAP or the ETP, NPB Health Assessment, NPB-HAQ, PGIS questionnaires, abdominal MRI, liver echo Doppler, HRCT, chest X-ray, pulmonary function tests, treadmill ergometry, and echocardiogram with Doppler will not be repeated if they had been done within 3 months prior; DXA and bone MRI will not be repeated if they had been done within 6 months prior. Patients who discontinue during the dose escalation period of the PAP or the ETP will have more limited assessments (see detail in Section 10.1).

c Adverse events will be captured from the time the patient provides signed informed consent through the safety follow-up period (30 to 37 days after the patient's last study infusion).

d The complete physical examination will include a neurological examination (mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, and coordination); examinations of lymph nodes, heart, lungs, abdomen, and extremities/joints; and an assessment of the general appearance, skin, and HEENT (head, eyes, ears, nose, and throat).

e The abbreviated examination of general appearance only will be carried out before and after each study drug infusion.

f Weight at previous on-site or home visit (during COVID-19 pandemic, if ≥3 months passed since last on-site quarterly visit) may be used to calculate drug dosage at current visit.

g Vital sign measurements will include blood pressure, heart rate, respiratory rate, and temperature. At quarterly visits, collection times will be prior to the infusion (within 30 ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion (±10 minutes); 2 hours ±10 minutes, 4 hours ±10 minutes, and 6 hours ±10 minutes after the end of the infusion; and every 8 hours ±1 hour until the patient has been discharged. Vital signs should also be measured at discharge ±10 minutes, which may or may not represent an additional measurement to the schedule described above. For these visits, patients should remain at the site for at least 24 hours. The investigator may decide that longer monitoring is required. At all visits except quarterly visits and dose escalation visits, vital sign collection times will be prior to the infusion (within 30 minutes ±10 minutes of infusion start); halfway through (ie, when half the expected time for infusion duration has elapsed); at the end of infusion ±10 minutes; and at discharge ±10 minutes (1 hour post-infusion). At any visit the investigator may decide that longer monitoring is required.

h Electrocardiograms will be performed before any blood draws. Single ECGs will be performed before infusion and 4 hours ±10 minutes, 12 hours ±1 hour, and 24 hours ±3 hours after the end of infusion.

i Samples will be taken for liver function testing and coagulation within 24 hours before infusion and 24 hours ±3 hours after the end of infusion. Samples will be taken for urinalysis and clinical chemistry within 24 hours before infusion.

j For hematology at quarterly visits except yearly visits, 1 sample for complete blood count with differential will be taken within 24 hours before infusion and one 24 hours ±3 hours after the end of infusion. At yearly visits, 2 samples will be taken at least 24 hours and up to 2 weeks apart before infusion, the first for complete blood count with differential and the second for hemoglobin and white blood cell and platelet counts only. In addition, at yearly visits, 1 sample for complete blood count with differential will be taken 24 hours ±3 hours after the end of infusion. [redacted] 2 samples will be taken during an infusion 3 months after the introduction of the drug from the updated manufactured process, at least 24 hours and up to 2 weeks apart.

k At the end of study visit, 1 sample will be taken for complete blood count with differential.

l Urine β-HCG up to 24 hours before infusion, once every 4 weeks; if positive, then retest with serum.

m [redacted] collection will be monthly for the first 6 months after starting the new update, and quarterly after that.

n Sample will be taken within 24 hours before infusion and 24 hours ±3 hours after the end of infusion for biomarkers including but not limited to hsCRP, iron, ferritin, cardiac troponin-I, calcitonin, and multiplex pro-inflammatory panel (Meso Scale) for other biomarkers indicative of inflammation.

o Spleen and liver volumes will be measured from the abdominal MRI. Patients will be required to fast from solid foods (liquids such as water or juice will be permitted) for ≥6 hours before an abdominal MRI to reduce the effect of a meal on MRI data.

p Chest X-ray will be performed in selected sites.

q Samples will be taken within 24 hours before infusion.

r Only for patients consenting to the qualitative structured interviews

s Patients will fill out the eDiary during the evening of the 7 consecutive days before each quarterly visit (see Section 1.3). If the patient does not fill out the eDiary on the day before infusion, (ie, missing the Day 7 entry), then the patient will be allowed to make the Day 7 eDiary entry in the clinic before study drug infusion.

t In-patient hospitalization may be needed throughout the infusion and for at least 24 hours after the end of infusion during quarterly visits and yearly visits in years 3 to 5. Blood will be collected and safety assessments (including vital signs [footnote g]) will be performed. For all other visits, patients will be observed after the end of infusion for at least 1 hour. Study drug infusions will occur once every 2 weeks (±3 days) at the site or at home (during the COVID-19 pandemic) if agreed between the investigator and the sponsor, for eligible patients, in reference to the date of the first infusion (Day 1) for each patient. Quarterly visits will occur at the site. During the COVID-19 pandemic if home infusion already approved for the eligible patient, quarterly visits will be done at home.

u See for the PK sampling schedule.

1.2.3 Pharmacokinetic sampling during the primary analysis and extension treatment periods

	Before infusion[a]	Midway through	End of infusion	Hours after the infusion[b]						
				1 hour	4 hours	8 hours	24 hours	48 hours	96 hours	168 hours
Study week 2	X	X	X	X	X	X	X	X	X	X
Study week 10	X	X	X	X	X	X	X	X	X	X
Study week 14	X	X	X	X	X	X	X	X	X	X
Study week 26	X	X	X	X	X	X	X	X	X	X
Study week 38	X	X	X	X	X	X	X	X	X	X
Study week 52	X	X	X	X	X	X	X	X	X	X
Study week 54	X	X	X	X	X	X	X	X	X	X
Study week 68	X	X	X	X	X	X	X	X	X	X
Study week 80	X	X	X	X	X	X	X	X	X	X
Study week 132	X	X	X	X	X	X	X	X	X	X
Study week 184	X	X	X	X	X	X	X	X	X	X
Study week 236	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X

a Preinfusion sample to be collected within 24 hours before infusion start.

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

c [redacted] samples for PK will be collected at the second dose that is administered [redacted] following the same PK sampling schedule

1.3 PATIENT HOME-BASED ACTIVITIES

Prepare to complete eDiary during these study weeks	Complete eDiary at home during the evening: 7 consecutive days before Day 1 and quarterly visit infusions								Bring eDiary device to clinic for these study week infusion visits
	Early during screening period for 7 consecutive days	7 days before next infusion	6 days before next infusion	5 days before next infusion	4 days before next infusion	3 days before next infusion	2 days before next infusion	Evening before next infusion	
Complete eDiary early during screening for inclusion criterion verification[a]	X								
Receive eDiary device before first infusion		X	X	X	X	X	X	X	Day 1
W13-W14		X	X	X	X	X	X	X	W14 QV
W25-W26		X	X	X	X	X	X	X	W26 QV
W37-W38		X	X	X	X	X	X	X	W38 QV
W51-W52		X	X	X	X	X	X	X	W52 QV
W67-W68		X	X	X	X	X	X	X	W68 QV
W79-W80		X	X	X	X	X	X	X	W80 QV
W91-W92		X	X	X	X	X	X	X	W92 QV
W103-W104		X	X	X	X	X	X	X	W104 QV
W117-W118		X	X	X	X	X	X	X	W118 QV
W131-W132		X	X	X	X	X	X	X	W132 QV
W143-W144		X	X	X	X	X	X	X	W144 QV
W155-W156		X	X	X	X	X	X	X	W156 QV
W169-W170		X	X	X	X	X	X	X	W170 QV
W183-W184		X	X	X	X	X	X	X	W184 QV

Prepare to complete eDiary during these study weeks	Complete eDiary at home during the evening: 7 consecutive days before Day 1 and quarterly visit infusions								Bring eDiary device to clinic for these study week infusion visits
	Early during screening period for 7 consecutive days	7 days before next infusion	6 days before next infusion	5 days before next infusion	4 days before next infusion	3 days before next infusion	2 days before next infusion	Evening before next infusion	
W195-W196		X	X	X	X	X	X	X	W196 QV
W207-W208		X	X	X	X	X	X	X	W208 QV
W221-W222		X	X	X	X	X	X	X	W222 QV
W235-W236		X	X	X	X	X	X	X	W236 QV
W247-W248		X	X	X	X	X	X	X	W248 QV
W259-W260		X	X	X	X	X	X	X	W260 QV

Abbreviations: QV = quarterly visit; W = study week

a The e-Diary will be administered once at the beginning of the screening period to check the related inclusion criterion, and a second time as baseline just before the first infusion.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

3 LIST OF ABBREVIATIONS

ACE:	angiotensin-converting enzyme
AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
APR:	acute phase reaction
ASM:	acid sphingomyelinase
ASMD:	acid sphingomyelinase deficiency
ASMKO:	ASM 'knock-out'
AST:	aspartate aminotransferase
BMB:	bone marrow burden
BMI:	body mass index
CCL18:	chemokine (C-C motif) ligand 18
CRS:	cytokine release syndrome
DBS:	dried blood spot
DL_{CO}:	diffusing capacity of the lung for carbon monoxide
DLT:	dose-limiting toxicity
DMC:	Data Monitoring Committee
DXA:	dual energy X-ray absorptiometry
ECHO:	echocardiogram
eCRF:	electronic case report form
EOS:	end of study
EQ-5D:	EuroQol-5 dimensions quality of life questionnaire
EQ-5D-5L:	EuroQol 5 dimension, 5 level health status measure
ETP:	extension treatment period
FEV_1:	volume of air expired during the first second of FVC
FVC:	forced vital capacity
hsCRP:	high sensitivity C-reactive protein
HTD:	highest tolerated dose
IARs:	infusion-associated reactions
ILD:	infiltrative lung disease
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB/IEC:	Institutional Review Board/Independent Ethics Committee
IV:	intravenous(ly)
IXRS:	Interactive (Voice or Web) Response System
LFT:	liver function test
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intent-to-treat
MN:	multiples of normal
MRI:	magnetic resonance imaging
NMR:	nuclear magnetic resonance

NPB-HAQ:	NPB Health Assessment Questionnaire
NPD:	Niemann-Pick disease
NPD B:	NPD type B
PAP:	primary analysis period
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PFT:	pulmonary function test
PGIC:	Patient Global Impression of Change
PGIS:	Patient Global Impression of Symptom Severity
PK:	pharmacokinetic
PT:	preferred term
QV:	quarterly visit
SAEs:	serious adverse events
SF-36:	Short Form-36 Health Survey
SMPD1:	sphingomyelin phosphodiesterase 1, acid lysosomal
SOC:	system organ class
SRS:	splenomegaly-related score
TEAEs:	treatment-emergent adverse events
TLC:	total lung capacity
ULN:	upper limit of normal
β-HCG:	β-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

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 the gene sphingomyelin phosphodiesterase 1, acid lysosomal (SMPD1), whose transcription and translation results in a defective enzyme acid sphingomyelinase (ASM). Inactivity of ASM leads to the lysosomal accumulation of sphingomyelin and, secondarily, increases in cholesterol and other related lipids, mostly in the spleen, liver, lung, and bone marrow.

Historically, ASMD has been diagnosed as Niemann-Pick disease (NPD) and of either Types A or B disease. Niemann-Pick disease type A is characterized as the early-onset and acute neuronopathic form of NPD 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. Of the more common disease manifestations are hepatosplenomegaly and dyslipidemia; other, more variable features include liver dysfunction, pulmonary disease, skeletal involvement, retinal stigmata, and growth retardation. Niemann-Pick disease type 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. As an autosomal recessive single gene disease, ASMD generates a spectrum of phenotypes and cases have been classified that are intermediate to the A and B extremes. Patients with this intermediate form, Niemann-Pick disease type A/B, may develop neurologic symptoms during childhood and have a chronic neurodegenerative disease course.

Genzyme has been developing a potential enzyme therapy, olipudase alfa, for the treatment of the non-neurological manifestations of ASMD. This recombinantly-derived enzyme is expressed in Chinese hamster ovary cells (CHO) 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 (IV) 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 mouse model is limited because 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 (PD), pharmacokinetic (PK), 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, ASMKO mice given single high bolus doses of olipudase alfa (≥10 mg/kg) showed evidence of toxicity. 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 of olipudase alfa 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) did not cause toxicity.

In a Phase 1 study (SPHINGO-00605), 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 after dosing 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 adverse events (SAEs) related to olipudase alfa treatment were not reported. The study was terminated by the sponsor after the single patient dosed at 1.0 mg/kg olipudase alfa presented with hyperbilirubinemia and an acute phase reaction (APR) with clinical symptoms. Subsequently, the patient was confirmed to have Gilbert's syndrome. Because no other signs of liver toxicity or hemolysis were evident, the observed hyperbilirubinemia may have been secondary to specific inhibition of bilirubin uptake into hepatocytes and/or glucuronide conjugation of bilirubin within hepatocytes.

In the completed Phase 1b, open-label, multicenter, 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). After receiving an initial intravenous dose of 0.1 mg/kg olipudase alfa, patients dose-escalated in a step-wise manner to a target intravenous dose of 3.0 mg/kg. All patients remained at the 3.0 mg/kg olipudase alfa dose for the remainder of the treatment period. Upon study completion, patients enrolled into an open-label, long term treatment study (LTS13632) (7).

The progressive, within-patient olipudase alfa dose escalation regimen was well tolerated in adult patients with ASMD. 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 26 week treatment period, improvements were observed in several individual efficacy parameters and included mean decreases in spleen and liver volumes by 25.3% and 17.1%, respectively; decreased interstitial lung disease scores; increased percent predicted diffusing capacity of the lung for carbon monoxide (DL_{CO}); reduction in serum chitotriosidase, chemokine (C-C motif) ligand 18 (CCL18), and angiotensin-converting enzyme (ACE), biomarkers indicative of disease burden; a positive trend towards a less pro-atherogenic lipid profile; and trends for improvement in quality of life assessments for fatigue and pain.

This Phase 2/3 study has been designed as double-blinded and placebo-controlled to demonstrate the efficacy of olipudase alfa in decreasing spleen volume and improving pulmonary function after 52 weeks of study drug administration. Secondarily, the clinical benefit of olipudase alfa for patients with ASMD will be assessed based on symptom-based disease scores from patient reported outcome instruments. The effect of study drug on the common ASMD symptom complaints of pain, fatigue, dyspnea, and SRS will be examined from responses to an eDiary. The effect of study drug on the disease-relevant clinical manifestations of liver volume and platelet counts will be analyzed.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this Phase 2/3 study is to evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD by assessing changes in: 1) spleen volume as measured by abdominal magnetic resonance imaging (MRI) (and for the United States [US] only, in association with patient perception related to spleen volume as measured by splenomegaly-related score [SRS]); and, 2) infiltrative lung disease as measured by the pulmonary function test DL_{CO}.

5.2 SECONDARY

Secondary and additional objectives include the following:

Secondary objectives

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

Additional objectives

- To characterize the effect of olipudase alfa on liver function tests (LFTs)
- To characterize the effect of olipudase alfa on infiltrative lung disease via pulmonary imaging
- To characterize the effect of olipudase alfa on pulmonary functioning
- To characterize the effect of olipudase alfa on the fasting lipid profile
- To characterize the effect of olipudase alfa on bone disease

- To characterize the effect of olipudase alfa on cardiopulmonary functioning
- To characterize the effect of olipudase alfa on biomarkers
- To characterize the effect of olipudase alfa on hematology parameters
- To characterize the effect of olipudase alfa on selected health-related quality of life questionnaires and questions therein
- To characterize the pharmacodynamic effect of olipudase alfa on clearing sphingomyelin accumulation in liver and/or blood
- To characterize the multiple-dose plasma pharmacokinetic profile of olipudase alfa
- To explore the effect of olipudase alfa on Physician's global assessment of change
- To explore the effect of olipudase alfa on the nuclear magnetic resonance (NMR) profile of high-density lipoprotein (HDL)
- To explore the effect of olipudase alfa on liver function via echo-Doppler ultrasound
- To explore the effect of olipudase alfa on inflammatory and vascular biomarkers

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This Phase 2/3, multicenter, repeat-dose, clinical trial will be divided into 2 consecutive major periods: 1) a randomized placebo-controlled, double-blind primary analysis period (PAP) from Day -60 to Week 52 to be followed by 2) an extension treatment period (ETP). Initially, the ETP will be double-blind as patients in the placebo arm cross over to active treatment.

The PAP will include a screening/baseline period and a treatment period. During the screening/baseline period, from Day -60 to Day 1 preinfusion, approximately 36 patients will provide informed consent and undergo screening assessments to determine trial eligibility and undergo baseline measurements. If all eligibility criteria are met, then patients will be randomized and enter the treatment period on Day 1. Day 1 is the day the first infusion is administered. The visit schedule is calculated using Day 1 of the dose escalation period as the reference. Treatment assignment and randomization will be performed using an Interactive Voice Response System/Interactive Web Response System (IXRS). Patients will be randomly and centrally assigned in a 1:1 ratio across sites using blocks of fixed size into 1 of 2 arms, placebo, saline 0.9% sodium chloride solution, or 3.0 mg/kg olipudase alfa target dose. Dose-escalation during the PAP to the randomized target doses will occur according to the schedule provided in Section 8.1.3 and Table 1. To maintain the double-blind, all patients will dose-escalate using the schedule provided (true dose escalation for patients who were in the placebo arm during the PAP and mock dose escalation for patients in the active arm during the PAP).

After completing the PAP, patients will enter the ETP. Those who were randomized to the active arm will continue receiving the dose to which they were randomized during the PAP (or the highest tolerated dose [HTD], if the randomized dose was intolerable). Patients randomized to the placebo arm in the PAP will cross over to active treatment in the ETP and will undergo dose escalation to a target dose of 3.0 mg/kg olipudase alfa.

Study drug will be defined during the PAP as olipudase alfa or placebo and during the ETP as olipudase alfa and will be administered intravenously once every 2 weeks.

During the PAP, one rechallenge each will be allowed for doses administered at Week 0 (0.1 mg/kg olipudase alfa or placebo) and at Week 4 (0.3 mg/kg olipudase alfa or placebo). Patients who are unable to tolerate the rechallenge at those doses will be discontinued from the study. If a patient is discontinued due to inability to tolerate rechallenge (ie, a second dose of 0.3 mg/kg olipudase alfa), then an additional patient may be randomized. Any patient who successfully dose-escalates through Week 4, but cannot tolerate study drug infusions at later weeks, will continue in the trial at the Week 4 dose (ie, 0.3 mg/kg olipudase alfa or placebo) until end of study; likewise, any patient unable to tolerate a dose administered during later weeks will receive the HTD even if that dose is less than the target randomized dose and will continue in the ETP at this dose. The minimum active dose administered will be 0.3 mg/kg olipudase alfa.

During the ETP, the same dose-escalation conditions will apply for patients who cross over from the placebo arm during the PAP to the active treatment arm, except that patients unable to tolerate the rechallenge allowed each at Week 54 (0.1 mg/kg olipudase alfa) and at Week 58 (0.3 mg/kg olipudase alfa) will discontinue from the study and will not be replaced.

During the PAP and ETP, in-patient hospitalization will be required preinfusion and for at least 24 hours after the infusion during dose escalation (ie, through Week 16 and Week 70, respectively) and may be required at the quarterly and yearly visits up through the end of Year 2; in-patient hospitalization may be necessary during quarterly and yearly study visits in Years 3 through 5. For all other infusions, patients will be monitored for safety in the clinic for at least 1 hour. All patients will have an end of study/early discontinuation visit within 2 weeks after the last infusion of study treatment. In addition, all patients will receive a follow-up phone call for safety approximately 30 to 37 days after the last infusion of study drug.

Home infusion may be initiated during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic in the ETP by trained home nurses if agreed between the investigator and the sponsor, in compliance with applicable country-specific regulations. Patients must meet specific eligibility requirements (Section 10.1.1).

For treatment periods during the PAP and the ETP, dose-limiting toxicity (DLT) criteria will apply. A rescue strategy will be implemented for patients who experience significant clinical decline. See Section 8.1.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The length of a patient's participation will be defined from Day 1 until the last planned assessment/visit, for at least 3 years and up to 5 years and 3 months dependent upon continued regulatory approval of this protocol. The approximate longest study duration per patient will be as follows:

- Screening period will be up to 60 days
- PAP treatment period will be approximately 52 weeks. A patient will be considered “PAP completed” when the patient has been administered study drug at the target randomized or HTD and has completed the Week 52 assessments.
- After 52 weeks in the PAP, patients will enter and remain in the ETP for at least 2 years and up to 4 years dependent upon continued regulatory approval of this protocol. A patient will be considered ‘ETP completed’ when the patient completes the end of study visit (within 2 weeks after the last treatment) or has responded to the final safety follow-up phone call from the study site made 30 to 37 days after the patient’s final administration of study drug (as applicable).

6.2.2 Determination of end of clinical trial (all patients)

The study will be considered completed when the last patient has their follow-up phone call.

6.3 INTERIM ANALYSIS

No interim analysis is planned during PAP. However during ETP, a formal summary of data or interim CSR(s) may be produced to support regulatory approval(s) and/or other submission/application requirement(s).

6.4 STUDY COMMITTEES

An independent Data Monitoring Committee (DMC), composed of members independent from the sponsor and the study investigators, is implemented to monitor patient safety by conducting formal reviews of accumulated safety data. The DMC will provide the sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the patients enrolled in the study (ie, exposure to study drug). All activities and responsibilities of the DMC are described in the DMC charter, in compliance with applicable guidance (8).

Data Monitoring Committee meetings will occur at regular intervals as outlined in the DMC charter. The report of a potential DLT to the sponsor or the occurrence of any safety related issues identified by the 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. Additional responsibilities of the DMC will be contained in the DMC charter.

The first formal meeting of the DMC will occur approximately 3 months after the first patient has been treated in the study.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. The patient is willing and able to provide signed written informed consent.

I 02. The patient is male or female, aged 18 years or older.

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

I 04. The patient has DL_{CO} ≤70% of the predicted normal value.

I 05. The patient has spleen volume ≥6 multiples of normal (MN) measured by MRI; patients who have had partial splenectomy will be allowed if the procedure was performed ≥1 year before screening/baseline and the residual spleen volume is ≥6 MN.

I 06. The patient has an SRS ≥5.

I 07. Female patients of childbearing potential must have a negative serum pregnancy test for beta-human chorionic gonadotropin (β-HCG).

I 08. 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 for up to 15 days following their last dose of study drug.

7.2 EXCLUSION CRITERIA

Patients who have met all the above 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 30 days before study enrollment.

E 02. The patient has a medical condition, including significant intercurrent illness; significant cardiac disease (eg, clinically significant arrhythmia, moderate or severe pulmonary hypertension or clinically significant valve dysfunction, or <40% left ventricular ejection fraction by echocardiogram ECHO); active hepatitis B or hepatitis C, or infection with human immunodeficiency virus (HIV); malignancy diagnosed within the past 5 years (other than non-melanoma skin cancer), or any other serious medical condition that may preclude participation in the study.

E 03. The patient has a platelet count <60 x 10^3/μL based on the average of 2 samples.

E 04. The patient has an international normalized ratio (INR) >1.5.

E 05. The patient has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >250 IU/L or total bilirubin >1.5 mg/dL (except for patients with Gilbert's syndrome).

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

E 07. The patient is scheduled during the study for in-patient hospitalization including elective surgery and excluding the liver biopsies required per protocol.

E 08. The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study.

E 09. The patient is unwilling or unable to abstain from the use of alcohol for 1 day before and 3 days after each study drug infusion. Testing for blood alcohol levels will not be required.

E 10. The patient is unwilling or unable to avoid 10 days before and 3 days after the protocol scheduled liver biopsies, that are required at screening/baseline, at Week 52 and at Week 104, the use of medications or herbal supplements that are potentially hepatotoxic (eg, 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, erythromycin, valproic acid, anti-depressants, kava, echinacea) and/or may cause or prolong bleeding (eg, anti-coagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng).

E 11. The patient requires medications that may decrease olipudase alfa activity (eg, fluoxetine, chlorpromazine, tricyclic antidepressants [eg, imipramine, or desipramine]).

E 12. The patient requires use of invasive ventilatory support.

E 13. The patient requires the use of noninvasive ventilator support while awake for longer than 12 hours daily.

E 14. The patient is breast-feeding.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

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.

The lyophilized powder will be reconstituted with 5.1 mL of sterile water for injection to yield a concentration of 4.0 mg/mL olipudase alfa, which will be further diluted in 0.9% sodium chloride solution to a specific volume based on the dose to be administered.

Detailed instructions on the preparation, storage, and administration for study drug will be provided in the pharmacy manual.

See Section 8.7 for product handling and complaints reporting.

8.1.1 Treatments administered

The term “study drug” will refer to olipudase alfa and placebo (saline [0.9% sodium chloride solution]), but only olipudase alfa is an IMP.

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

Dosing with study drug will be by intravenous infusion every 2 weeks (±3 days) in reference to the date of the first infusion (Day 1) for each patient. The 52-week treatment period of the PAP will begin on Day 1 with the first infusion of study drug.

To maintain the double-blind, all patients regardless of treatment assignment will undergo dose escalation under the same conditions and according to the schedule provided in Table 1.

All infusions will take place in a monitored setting with ready access to emergency resuscitation equipment and medications (see Section 10.1 for information on timing for in-patient hospitalization). One rechallenge each will be allowed for doses administered at Week 0 (0.1 mg/kg olipudase alfa or placebo) and at Week 4 (0.3 mg/kg olipudase alfa or placebo). Patients who are unable to tolerate the rechallenge at those doses will be discontinued from the study. If a patient is discontinued due to inability to tolerate rechallenge, (ie, a second dose of 0.3 mg/kg olipudase alfa), then an additional patient may be randomized but only during the PAP. During the PAP and ETP, in-patient hospitalization will be required preinfusion and for at least 24 hours after the infusion during dose escalation (ie, through Week 16 and Week 70, respectively) and may be required at the quarterly and yearly visits up through the end of Year 2; in-patient hospitalization may be necessary during quarterly and yearly study visits in Years 3 through 5.

Home infusion may be initiated during COVID-19 (ETP) by trained home nurses every 2 weeks (±3 days), if agreed between the investigator and the sponsor, in compliance with applicable country-specific regulations. Patients must meet specific eligibility requirements (Section 10.1.1).

[redacted] the patient should receive the first infusion at the site. However, If the site visit is not possible due to site closure or extenuating circumstances that prevent an in-person site visit (eg, during COVID-19 pandemic), the first infusion [redacted] is allowed during home infusion for eligible patients in agreement between the Sponsor and the Investigator, in compliance with applicable country-specific regulations.

For treatment periods during both the PAP and ETP, DLT criteria will apply. A rescue strategy will be implemented for patients who experience significant clinical decline (see Section 8.1.6).

Dose escalation will follow criteria described in Section 8.1.3.3. Patients unable to tolerate the target randomized dose will receive the highest dose tolerable once every 2 weeks for the remainder of the study. The minimum active dose administered will be 0.3 mg/kg olipudase alfa.

8.1.2 Route and method of administration

Duration of study drug infusions will be the same regardless of treatment assignment and each infusion will last for approximately 220 minutes, except at W0 when it will last approximately 35 minutes and at W54 where it will last approximately 255 minutes.

For each patient, intravenous infusion with study drug should occur at approximately the same time of day. There are no restrictions on the infusion timing with respect to meals.

See Section 8.1.3.2 for information on dose adjustments following dosing delays or missed infusions.

8.1.3 Dosing considerations

Dosing will be based on an individual patient's mass (ie, weight) as outlined in Section 8.1.1. For patients with a body mass index (BMI) >30, the dose will be based on the mass (in kilograms) corresponding to a BMI of 30 given the specific patient's height.

8.1.3.1 Dose adjustments

Dose adjustments may also be considered at any time in consultation with the sponsor and may be recommended based on current safety or efficacy analysis results obtained from completed or ongoing clinical studies with olipudase alfa.

8.1.3.2 Dosing delays or missed doses

Patients will be infused with study drug once every 2 weeks (±3 days) with all infusions scheduled relative to the first study infusion on Day 1 of Week 0. If a study drug infusion is

delayed by more than 3 days, then that infusion will be considered a missed infusion and will not be administered. The patient will receive the last previously tolerated dose of study drug upon return to the clinic for the next scheduled visit. During any dose escalation period, if more than 1 consecutive infusion is missed, then the next infusion will be reduced by 1 dose level.

Outside a dose escalation period, or if the patient has already reached his/her maximum tolerated dose, for a patient who has missed 2 consecutive doses:

- If the last dose was 0.3 mg/kg or 0.6 mg/kg, the patient should receive the same dose at the next scheduled infusion and for the rest of the study period.
- If the last dose was 1, 2, or 3 mg/kg, the first reintroduction dose should be 1 level below the last dose.
    - During this dose re-escalation, the schedule of assessments (except PK) will be similar to dose escalation period starting from the corresponding dose.
    - If this dose re-escalation happened during the PAP, re-escalation of 0.6 mg/kg will correspond to Week 6, repetition of 0.6 mg/kg will correspond to Week 8, 1 mg/kg to Week 10, 2 mg/kg to Week 12 and 3 mg/kg to Week 14 assessments.

Outside a dose escalation period, or if the patient has already reached his/her maximum tolerated dose, a patient who has missed 3 or more consecutive doses:

- If the last dose was 0.3 mg/kg, the patient will receive a dose of 0.3 mg/kg at the next scheduled infusion and for the rest of the study period.
- If the last dose was 0.6, 1, 2, or 3 mg/kg, the first reintroduction dose will be 0.3 mg/kg (0.3 mg/kg should be repeated at the subsequent infusion, similar to dose escalation schedule).
    - During this dose re-escalation, the schedule of assessments (except PK) will be similar to dose escalation period starting from the corresponding dose.
    - If this dose re-escalation happened during the PAP, re-escalation of 0.6 mg/kg will correspond to Week 6, repetition of 0.6 mg/kg will correspond to Week 8, 1 mg/kg to Week 10, 2 mg/kg to Week12 and 3 mg/kg to Week 14 assessments.

Following this first reintroduction dose, the dose will be escalated at subsequent infusions up to the dose the patient had previously reached prior to the interruption (target dose or maximum tolerated dose) following the standard escalation process described in Table 1.

Outside the dose escalation period during ETP, patients who require dose reintroduction will have the following assessments at each infusion until reaching their target or maximum tolerated dose of olipudase alfa:

- Continuous monitoring of AE/SAE and concomitant medications and therapies (see study manual).
- Abbreviated examination of general appearance before and after infusion

- Before infusion: vital sign measurements, liver function tests (LFTs), hematology tests and safety biomarkers and if available during home infusion from the same blood sample, clinical chemistry, multiplex assay and pharmacodynamic biomarkers.
- Immediately after infusion: vital sign measurements.
- 24 hours after infusion: vital sign measurements, LFTs, hematology and safety biomarkers and if available during home infusion from the same blood sample, clinical chemistry, multiplex assay and pharmacodynamic biomarkers.
- 48 hours after infusion: vital sign measurements, LFTs, hematology and safety biomarkers and if available during home infusion from the same blood sample, clinical chemistry, multiplex assay and pharmacodynamic biomarkers.
  The 48 hours assessments after infusion will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.
- Urine β-HCG for pregnancy every 4 weeks as described in "footnote k" in Section 1.2.2.1.

During the dose escalation period, for transaminases assessed after infusion, if any AST or ALT value is > 2x baseline and >ULN, the test should be repeated prior to the next scheduled infusion. Depending on the test results, the dose can be adjusted (repeated or reduced) or treatment can be withheld to allow additional transaminase monitoring, based on the physician's clinical judgment.

Baseline is defined as the following:

- For initial dose escalation: last values prior to first dose of olipudase alfa
- For dose re-escalation: last values prior to the first re-escalation dose

Dose reintroduction will be done at the site. During a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic or extenuating circumstances that prevent an in-person site visit, dose reintroduction can take place via home visits in compliance with applicable country-specific regulations, applying criteria in Section 10.1.1 and performing the same dose reintroduction list of assessments (see study manual for details).

8.1.3.3 Escalation schema

See Table 1 and Figure 1 for the dose escalation schedule and algorithm, respectively. During dose escalation (PAP and ETP), patients will be admitted to the hospital as described in Section 10.1.

Table 1 - Dose escalation scheme during the PAP

Study week PAP[a]	Scheduled study drug[b] dose	
Week 0[c]	0.1 mg/kg	
Week 2	0.3 mg/kg	
Week 4[c]	0.3 mg/kg	
Week 6	0.6 mg/kg	
Week 8	0.6 mg/kg	
Week 10	1.0 mg/kg	
Week 12	2.0 mg/kg	
Week 14	3.0 mg/kg	
Week 16	3.0 mg/kg	End of the mock dose escalation for patients assigned to placebo; end of true dose escalation for patients assigned to target dose 3.0 mg/kg.

a Study weeks do not account for rechallenges.
b Study drug means olipudase alfa and placebo.
c A rechallenge will be permitted only once at Week 0 and at Week 4.

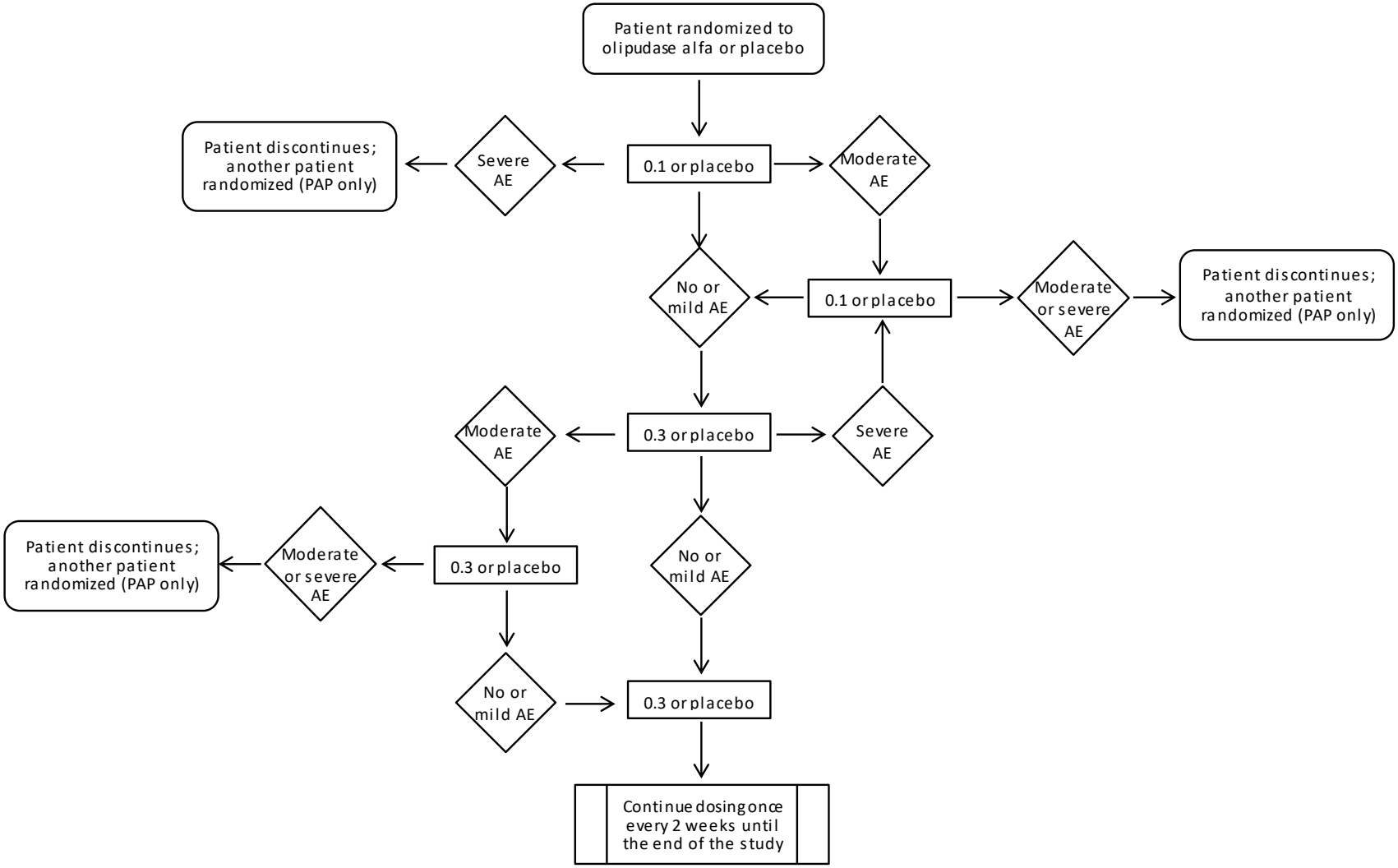
The same dose-escalation schedule and conditions will apply for patients who cross over from the placebo arm during the PAP to the active treatment arm in the ETP, except that patients unable to tolerate the 1 rechallenge each allowed for doses administered at Week 54 (0.1 mg/kg olipudase alfa) and Week 58 (0.3 mg/kg olipudase alfa) will discontinue from the study and will not be replaced.

The following criteria will determine the next dose of study drug to be administered, provided the patient does not experience an AE that meets the DLT (Section 8.1.4). 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
3. If the patient experiences a severe AE, decrease to the prior dose

If a patient presents on the day of infusion either with an unresolved AE or an acute illness, neither of which meets the patient DLT criteria (Section 8.1.4), then study drug 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 8.1.3.2.

Figure 1 - Dose escalation algorithm



8.1.4 Dose-limiting toxicities

For the purpose of this study, the events listed below are considered indicative of a potential DLT for study drug 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 6.4). Screening for eligible patients may continue during DMC review of patient or study stopping events.

If any of the following AEs occur, dosing will be temporarily stopped for the specific patient who experienced the AE, pending DMC review and recommendation (taking into consideration the relatedness of the AE to study treatment):

- Any SAE, not related to the patient's underlying condition and considered related to the study treatment.
- Any increase in AST, 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, right upper quadrant pain or tenderness, 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.

When study drug dosing is interrupted for a particular patient, safety monitoring of the patient will continue. If the AE(s) is/are reversible and the clinical laboratory tests (including LFTs) have normalized, the patient will resume dosing and receive the previously-tolerated lower dose (ie, dose administered on a previous week without incident). Depending on the patient's response, dose escalation will either continue (as described in Section 8.1.1) or the patient will remain at the previously tolerated dose (ie, the patient's HTD).

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

8.1.5 Study interruption criteria

If either of these criteria are met:

- 2 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.

See the study manual and the IXRS manual for unblinding procedures.

8.1.6 Rescue treatment

If during the course of the study, a patient satisfies one or more of the following criteria indicative of clinical decline due to ASMD progression and after excluding other possible causes, study drug will be unblinded and the patient will be switched to the 3.0 mg/kg olipudase alfa group; dose escalating procedures and caveats provided in Table 1 and Section 8.1.3 will apply. See the study manual and the IXRS manual for unblinding procedures.

- Hemoglobin level falls below 7 g/dL and remains below 7 g/dL when hematology laboratory testing is repeated after approximately 2 weeks.
- Platelet count falls below 30 000/mm^3 and remains below 30 000/mm^3 when hematology laboratory testing is repeated after approximately 2 weeks.
- A clinically significant bleeding episode assessed by the investigator as related to a low platelet count.

These patients will continue to be followed in the study. Upon confirmation of the need for rescue treatment, patients will have organ volume MRI and PFTs performed if prior tests were performed more than 12 weeks before.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

No noninvestigational medicinal product will be required for this study.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

This study has a double-blind, placebo-controlled design. During both the PAP and the first part of the ETP, patients, investigators, and the sponsor will be blinded to the identity of study treatment. Also, patients and investigators will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2, until after the database lock for PAP and dose escalation in ETP has completed (sponsor will be blinded until database lock for

PAP). To maintain the double-blind, all patients regardless of treatment assignment will undergo dose escalation (true or mock) in the same manner in both the PAP and ETP.

The investigators and the sponsor will also be blinded to the PK data. Genzyme Clinical Supplies will remain unblinded throughout the study to provide the appropriate study drug to patients.

At the facilities where the PK measurements, ADA, and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team and a process will be set up to prevent any potential unblinding.

8.3.2 Randomization code breaking during the study

In case of an AE, the code should only be broken in circumstances when knowledge of the identity of study drug is required for treating the patient and in consultation with the sponsor.

Code breaking can be performed at any time by using the proper module of the IXRS and/or by calling any other phone number provided by the sponsor for that purpose. If the blind is broken, including for rescue treatment (Section 8.1.6), the investigator should document the date, the hour, and the reason for breaking the code. See the IXRS manual for the code breaking process.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Upon confirmation by the medical monitor that the patient meets all eligibility criteria and completion of the screening and baseline assessments, eligible patients will be randomized as described below.

Treatment assignment and randomization will be performed using an IXRS. Approximately 36 patients will be randomly assigned across sites, using blocks of fixed size into 1 of 2 treatment arms, placebo or 3.0 mg/kg olipudase alfa target dose, in a 1:1 ratio.

Olipudase alfa will be packaged with kit codes and sent to an unblinded pharmacist at the investigational site for preparation. The appropriate quantity of vials will be assigned via IXRS based on patient weight, current dose level, and randomization group. The randomization will be performed centrally by the IXRS, which will generate the patient randomization list. The patient number allocated by the IXRS is a specific 9-digit number consisting of the following: 3-digit country code (ISO), 3-digit site number, and 3-digit sequential number at the site with leading zeroes, beginning with 001. Once randomized in the PAP, the patient's identification number will not change during the entire study.

8.5 PACKAGING AND LABELING

Olipudase alfa will be provided as a sterile lyophilized powder to be reconstituted with sterile water for injection, and further diluted with a 0.9% sodium chloride solution for administration in a covered infusion bag and/or syringe. Placebo will be the reference treatment in this study and will be provided by the hospital pharmacy as 0.9% sodium chloride solution in an identical

covered infusion bag and/or syringe. The sponsor will supply olipudase alfa vials and coordinate the packaging and distribution services in accordance with the administration schedule. The diluent bags and placebo will be provided by the investigational sites.

The olipudase alfa label text will meet the national legislations requirements of the participating countries and will comply with Good Manufacturing Practice. The label text will minimally include the protocol number, description of vial contents, packaging number, storage conditions, the sponsor's name and address, and any required caution statement as mandated by the countries involved. The study drug is to be prescribed only by the investigator. Under no circumstance will the study drug be used other than as directed by the protocol.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Olipudase alfa must be kept in a secure area with restricted access, and stored under adequate refrigerated temperature conditions, 2°C to 8°C (36°F 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.

8.7 RESPONSIBILITIES

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

Study drug will be dispensed in accordance with the investigator's prescription. It is the responsibility of the unblinded designee 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) will 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 or designee 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 or designee 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.

The investigator is responsible for notifying the IRB/IEC in writing when a potential DLT is being evaluated at his/her investigative site.

8.7.1 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 periods. Every effort should be made to ensure that no infusion is missed.

Noncompliance is defined as missing 4 total infusions (not for cause, such as when the missed doses are required by the protocol due to a DLT) per each 12-month period. As they are identified, the investigator should discuss noncompliant patients on a case by case basis with the sponsor's medical monitor (or designee).

8.7.2 Return and/or destruction of treatments

Reconciliation of study drug must be performed at the site by an unblinded designee of the investigator and an unblinded monitor using treatment log forms and documented on center study drug inventory.

If appropriate, a written authorization for destruction will be provided by the sponsor clinical trial team once the reconciliation is achieved. Destruction of study drug may be performed at the site depending on the site and local requirements; alternatively, study drug may be returned to the sponsor for destruction.

8.8 CONCOMITANT MEDICATION

Medications and therapeutic procedures received by the patient in the 30 days before the first scheduled infusion with study drug until the final follow-up phone call will be recorded on the Prior and Concomitant Medication field of the electronic case report form (eCRF) 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 in the 30 days before the first infusion of study drug.
- Concomitant medications will be defined as medications that are taken after the first infusion of study drug.

During the entire 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 information on 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.

Only during the 10 days before and 3 days after the scheduled liver biopsies will patients be prohibited from using medications or herbal supplements that are potentially hepatotoxic (eg, 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, erythromycin, valproic acid, anti-depressants, kava, echinacea) and/or may cause or prolong bleeding (eg, anticoagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng). See the study manual for guidance on concomitant medications that can affect bleeding time and/or are potentially hepatotoxic, including over-the-counter and prescription products containing nonsteroidal anti-inflammatory drugs or aspirin.

Pretreatment for prophylactic management of IARs should not be used systematically. In patients who experience moderate to severe or recurrent IARs with evidence of hypersensitivity (as defined in Section 10.4.4), pretreatment 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.

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 pretreatment medications (eg, antihistamines, antipyretics, and/or glucocorticoids) if the symptoms are suggestive of hypersensitivity reaction, in addition to infusion rate reductions, interruptions, or discontinuations. 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 study drug infusion will be managed according to the general standards of care consistent with the treatment of such reactions. If anaphylaxis or other severe allergic reactions occur, the infusion will be discontinued immediately, and appropriate medical treatment will 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 EFFICACY ENDPOINTS

9.1.1 Primary efficacy endpoints

The primary efficacy endpoints are the percentage change in spleen volume (in MN) from baseline to Week 52 (combined with change in SRS from baseline to Week 52 in the US only, and referred to as the "combination spleen endpoint") and percentage change in DLco (in % predicted of normal) from baseline to Week 52 (assessments described in Section 1.2 and Section 9.1.4).

Spleen volume will be assessed by abdominal MRI to quantitate the degree of splenomegaly at the time points specified in Section 1.2. Magnetic resonance imaging data will be collected and read centrally by a medical imaging core laboratory, blinded to patient, treatment arm, and time point, where it will be processed and coded.

The procedure for administering the DLco PFT to measure gas exchange across the alveolocapillary membrane is standardized in accordance with American Thoracic Society/European Respiratory Society guidelines.

9.1.2 Secondary efficacy endpoints

Secondary efficacy endpoints include the following:

- Percentage change in liver volume (in MN) from baseline to Week 52
- Percentage change in platelet counts from baseline to Week 52
- Week 52 change from baseline in fatigue severity as measured by item 3 of the BFI scale
- Week 52 change from baseline in pain severity as measured by item 3 of the BPI-SF scale
- Week 52 change from baseline in dyspnea severity as measured by the FACIT dyspnea tool
- Change in SRS from baseline to Week 52 (except US, where it is part of the primary "combination spleen endpoint") (Section 9.1.4.4, Section 9.1.4.13)

9.1.3 Tertiary and exploratory efficacy endpoints

Tertiary efficacy endpoints are the following:

- Percentage change from baseline to Week 52 in liver function tests (ALT, AST, and direct and total bilirubin)
- Pulmonary imaging by HRCT and chest X-ray (in selected sites) to quantify infiltrative lung disease (ILD).

- Other components of the pulmonary function test (ie, forced vital capacity [FVC], volume of air expired during the first second of FVC [FEV_1], total lung capacity [TLC])
- Fasting lipid profile (eg, high-density lipoprotein [HDL], low-density lipoprotein, very low-density lipoprotein, total cholesterol, triglycerides, apolipoprotein B, apolipoprotein A1, lipoprotein [a])
- Bone disease assessments: MRI and dual energy X-ray absorptiometry (DXA) of lumbar spine and entire bilateral femur will provide bone marrow burden (BMB) score and bone mineral density measurements including total density as well as T- and Z-score measurements
- Cardiopulmonary performance by treadmill ergometry
- Biomarkers: ACE, chitotriosidase, CCL18, bone-specific AP, C-telopeptide
  ACE will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.
- Hematology parameters
- Other quality of life questionnaires:
  - Brief Pain Inventory - Short form
  - Brief Fatigue Inventory
  - Functional Assessment of Chronic Illness Therapy (FACIT) - Dyspnea Short form
  - NPB - Health Assessment Questionnaire (NPB-HAQ)
  - Short Form - 36v2 Health Survey (SF-36)
  - EuroQol - quality of life questionnaire in 5 dimensions (EQ-5D)
  - Health-related productivity questionnaire

Exploratory efficacy endpoints will include the following:

- Physician's global assessment of change
- NMR of HDL (will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021)
- Echo-Doppler imaging to assess liver functioning and portal hypertension
- Multiplex assay of inflammatory and vascular biomarkers (Multiplex assay of vascular biomarkers will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021)
- Patient Global Impression of Symptom Severity (PGIS) of ASMD questionnaire
- Patient treatment experience interview
- Patient Global Impression of Change (PGIC) scale
- An additional questionnaire about home infusion experience may be added for patients who received home infusion treatment.

9.1.4 Assessment of efficacy endpoints

The schedule for all assessments related to efficacy endpoints is provided in Section 1.2. Study procedures will occur before infusion and during approximately the same time for each visit (in reference to the screening/baseline visit), unless stated otherwise.

9.1.4.1 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 the study flow charts. Patients will be required to fast from solid foods (liquids such as water or juice will be allowed) for at least 6 hours before an abdominal MRI to reduce the effect of a meal on the MRI data.

Abdominal MRI will be performed as described in the vendor manual. Magnetic resonance imaging data will be collected and read centrally by a medical imaging core laboratory, blinded to patient, treatment arm, and time point where it will be processed and coded.

9.1.4.2 Pulmonary imaging

High resolution computed tomography scans of the chest will be obtained to quantitate the degree of infiltrative lung disease, if present. Lung imaging data will be collected, processed, and coded centrally by a medical imaging core laboratory and evaluated by readers blinded to patient, treatment arm, and time point.

The bilateral lung boundaries are determined from the following 4 predefined levels on the HRCT images

- 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 of the ILD, ground glass appearance, reticular, nodular density, and pleura thickening, of the right and left lungs for each pre-defined levels above according to the following criteria (9):

- 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

Chest X-rays will be collected in selected sites and sent to a medical imaging core laboratory where they will be digitized (if not already done at the site) and coded. Frequency of chest X-ray

will be reduced from every 6 months to yearly after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. The lung fields will be assessed by central reviewers blinded to patient, treatment arm, and time point and scored subjectively for the degree of infiltrative lung (9):

- 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)
- NE = Not evaluable

9.1.4.3 Pulmonary function tests

Pulmonary function tests (PFTs) will be performed to assess evidence of infiltrative lung disease by measuring lung volume, air flow, and gas exchange (10). Pulmonary function testing equipment calibration and test administration protocols will be standardized according to the guidelines put forth by the American Thoracic Society (11). Pulmonary function tests will be administered approximately at the same daily time for each assessment (ie, in reference to the screening assessment) and will be collected and analyzed by a central reader.

- *Diffusing capacity of carbon monoxide* (DL_{CO}): diffusing capacity measures the rate of diffusion of a diffusion limited gas (carbon monoxide [CO]) per minute across the alveolocapillary membrane. Diffusing capacity of CO will be calculated by comparing the amount of CO exhaled following a known amount of inhaled CO. Helium, which does not diffuse across the alveolocapillary membrane, will be included as a tracer with the inspired CO to control for air trapping
- *Forced vital capacity* (FVC): The FVC is the total volume of air expired during a forced maneuver and will be measured using standard spirometric techniques
- *Forced expiratory volume in 1 second* (FEV_1): The FEV_1 is the volume of air expired during the first second of FVC and will be measured using standard spirometric techniques
- *Total lung capacity* (TLC): The TLC is the total volume of air within the lungs following a maximal inspiratory effort and will be measured using standard techniques

Please refer to the vendor manual for details about PFTs.

Patients who routinely take bronchodilators must withhold bronchodilators before PFTs as follows:

- Short-acting inhaled or oral bronchodilators (eg, albuterol) - 8 hours
- Medium-acting inhaled bronchodilators (eg, atrovent) - 12 hours
- Long-acting inhaled or oral bronchodilators (eg, salmeterol) - 24 hours

9.1.4.4 eDiary assessments

An eDiary will be distributed to patients according the schedule provided in Section 1.2. The eDiary will be completed by patients according to the schedule provided in Section 1.3 and will be composed of the following:

- Item 3 from the BPI-SF
- Item 3 from the BFI
- The FACIT-dyspnea Short form (Section 9.1.4.13), except for the screening eDiary
- The SRS (Section 9.1.4.13)

If the patient does not fill out the eDiary on the day before infusion, (ie, missing the Day 7 entry), then the patient will be allowed to make the Day 7 eDiary entry in the clinic before study drug infusion.

9.1.4.5 Cardiopulmonary assessments (treadmill ergometry)

Cardiopulmonary status will be assessed using a treadmill ergometer to measure patient work output under controlled conditions. Frequency of treadmill ergometry will be reduced from every 6 months to yearly after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. As the patient walks on treadmill, the workload will be incrementally increased until the patient can no longer proceed. Patients will breathe through a tube connected to a one-way valve to continuously measure oxygen (O2) uptake, carbon dioxide (CO2) output, and tidal volume throughout the test. Heart rate, respiratory rate, and digital O2 saturation will also be monitored continuously. For each workload, steady state levels will be calculated for O2 uptake, CO2 output, tidal volume, ventilation, and respiratory exchange ratio. The following parameters will be used for analysis:

- Maximum O_2 uptake (absolute and % predicted)
- Maximum CO_2 output
- Maximum tidal volume
- Maximum respiratory rate (breaths/min)
- Maximum respiratory exchange ratio
- Maximum ventilation (L/min)
- Maximum O_2 saturation
- Maximum heart rate (absolute and % predicted)
- Maximum workload (absolute and % predicted)
- Working time

Treadmill ergometry assessments must occur approximately at the same daily time as the screening assessment (in reference to the screening assessment) to ensure consistency of results.

Procedures for treadmill ergometry are detailed in the treadmill procedure manual.

9.1.4.6 Fasting lipid profile

The fasting lipid profile will include but not be limited to:

- High density lipoprotein
- Low density lipoprotein
- Very low density lipoprotein
- Total cholesterol
- Triglycerides
- Apolipoprotein B, apolipoprotein A1, and lipoprotein [a]

Additionally, the NMR profile of HDL will be characterized (12, 13). NMR profile of HDL will no longer be assessed after the cutoff date for a planned second database lock of the study for regulatory submissions in 2021.

9.1.4.7 Biomarkers

Samples for serum chitotriosidase, CCL18, and ACE will be collected as specified in Section 1.2 and analyzed for efficacy. ACE will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.

9.1.4.8 Liver function tests

Although blood samples will be taken for liver function testing as part of the standard laboratory assessment (Section 9.2.2), AST, ALT, and total and direct bilirubin will be assayed at baseline and at Week 52 as part of the analysis of tertiary efficacy endpoints.

9.1.4.9 Hematology

Although hemoglobin level, platelet count, and white blood cell count are part of the standard safety laboratory assessments (Section 9.2.2), they will also be analyzed at screening, Week 52, and at yearly visits (at the time points in Section 1.2.1.1 and Section 1.2.1.2, respectively) as part of the analysis of secondary (platelet counts) and tertiary (hematology) efficacy endpoints.

As specified in Section 1.2, at screening, Week 52, and at yearly visits, the mean of 2 preinfusion samples taken at least 24 hours and up to 2 weeks apart will be used for white blood cell count, platelet count, and hemoglobin.

9.1.4.10 Liver ultrasound with Doppler

Liver ultrasound with echo-Doppler imaging 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 which 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 with echo-Doppler imaging will be performed using methods that are compatible with the standard institutional procedures of the investigational site.

Some of the above mentioned parameters will be used to detect the likelihood of portal hypertension, and if detected whether it was severe, as described in the vendor's manual.

Liver ultrasound will be performed as described in the vendor's manual.

9.1.4.11 Skeletal involvement

Bone imaging

Bone scan images of the femurs and lumbar spine will be obtained at the time points provided in Section 1.2 using DXA and MRI to evaluate bone mineral density and BMB. All bone images will be sent to a central reviewer, blinded to patient, treatment assignment, and time point, for analysis of bone disease.

Bone mineral densities will be calculated for each patient and from which T- and Z-scores will be derived. The T-score ranks a patient's bone density to that of a healthy person of the same gender. Z-scores rank a patient's bone density to that of a healthy person of the same age, sex, weight, and ethnicity.

From serial MRI scans, BMB will be evaluated using the BMB scoring system. The bone marrow signal intensity scoring system is described in previous publications (14, 15, 16) as a categorical score out of a possible 8 points for the lumbar spine and a categorical score out of a possible 8 points for the femurs (score averaged from the left and right femurs) to give a total BMB score out of 16 points.

Serum bone-specific alkaline phosphatase and C-telopeptide

Samples will be collected to quantify bone-specific ALP, a marker for active bone formation, and C-telopeptide, an indicator of bone resorption, according to the time points specified in Section 1.2.

9.1.4.12 Multiplex assay of inflammatory and vascular biomarkers

Analysis of multiple cytokines and chemokines using inflammatory and vascular multiplex panels (Meso Scale) will be analyzed as both exploratory efficacy and safety endpoints for all patients with available data during PAP and ETP. Only the inflammatory panel (multiplex assay of proinflammatory panel) will be maintained after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021 and the vascular multiplex panels will no longer be assessed. See also Section 9.2.8.

9.1.4.13 Health-related quality of life questionnaires

The following health-related quality of life instruments will be completed by patients according to the time points specified in Section 1.2.

- The BFI is a validated, self-administered questionnaire that was originally developed to assess fatigue severity in cancer patients (17). The BFI has 9 items, using numeric rating scales from 0 to 10. Patients are asked in 3 items to rate the severity of their fatigue at its worst, usual, and now during normal waking hours. The amount that fatigue has interfered with different aspects of the patient's life during the preceding 24 hours (including general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life) is assessed in 6 items. Item 3 of the BFI is also separately administered via eDiary (Section 9.1.4.4).
- The BPI-SF is a validated, self-administered questionnaire designed to measure a patient's perceived level of pain. The BPI-SF measures the patient's intensity of pain (sensory dimension), the interference of pain in the patient's life (reactive dimension), and asks the patient about pain relief, pain quality, and the patient's perception of the cause of pain (18, 19). The BPI-SF consists of 15 items that use a numeric rating scale to assess pain severity and pain interference in the past 24 hours and the past week. Item 3 of the BPI-SF is also separately administered via eDiary (Section 9.1.4.4).
- The SRS rates 5 items: abdominal pain, abdominal discomfort, early satiety, abdominal body image, and ability to bend down. The 5 items were selected from the Myelofibrosis Symptom Assessment Form (MF-SAF) (JAKARTA, NCT# 01437787). Using a numerical rating scale of 0 (absent) to 10 (worst imaginable), these questions assess within the last 24 hours the impact of splenomegaly-related items that are common in patients with ASMD. The scores are collected via an eDiary over 7 days (Section 9.1.4.4). Then, the 7-day mean of the daily sum of the scores is calculated.
- The FACIT-dyspnea Short form is a 2-part questionnaire: 10 questions in each part. In Part 1, patients are asked to rate how short of breath they felt during the past 7 days doing activities, such as dressing, walking, and common household chores; in Part 2, patients rate how functionally limiting the dyspnea experienced was while doing the activities presented in Part 1. This instrument is administered via eDiary (Section 9.1.4.4).
- The NPB-HAQ is a disease-specific questionnaire that covers various aspects of fatigue, pain, respiratory, abdominal complaints, and quality of life as well as questions specific to ASMD symptoms and physical activity. The questionnaire administered at baseline will consist of items to gather information on patient background, diagnostic history, family history, medical/surgical history, resource utilization, current symptomatology and functional status. The questionnaire administered during subsequent visits will assess interval history and resource utilization, as well as current symptomatology and functional status.
- Health-related productivity questionnaire is a validated, self-administered questionnaire that was developed to measure how treatment of disease impacts an individual's ability to participate in the workforce and complete daily household duties.

- The SF-36 is a 36-item, validated, multidimensional, generic health-related quality of life measure that has been validated for adults in numerous healthy and ill populations internationally (20). The SF-36 consists of 8 scales, including physical functioning, role physical, bodily pain, mental health, role emotional, social functioning, vitality, and general health and includes two summary measures of physical health and mental health derived from scale aggregates.
- The EQ-5D is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal. The EuroQol 5 dimension, 5 level (EQ-5D-5L) health status measure consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. Index-based values (ie, utilities) are a major feature of the EQ-5D-5L instrument, facilitating the calculation of quality-adjusted life years that are used to inform economic evaluations of health care interventions.
- The PGIS asks patients to rate abdominal problems, bodily pain, fatigue, and shortness of breath "over the past week." The PGIS will be used to assess the validity of some of the PRO measures used in patients with ASMD in this study.
- The PGIC asks patients to rate change in abdominal problems, bodily pain, fatigue, and shortness of breath "since beginning the study medication". The PGIC will be used to assess the validity of some of the PRO measures used in patients with ASMD in this study.
- Home infusion experience questionnaire may be added for patients who received home infusion treatment to ask patients about their experience of home treatment.

9.1.4.14 Treatment experience interviews

Qualitative semi-structured interviews will be conducted to understand patient experience living with ASMD and participating in this study. The interviews will be conducted over the telephone in patients receiving the study drug for at least last 2 years.

9.1.4.15 Physician's global assessment of change from baseline

The investigator will evaluate the patient's current clinical status according to the schedule provided in Section 1.2 as being mild, moderate, or severe and compare individual patient status made during different time points by indicating 1 of the following 7 categories: marked improvement, moderate improvement, mild improvement, no change, mild worsening, moderate worsening, or marked worsening.

9.2 SAFETY ENDPOINTS

Safety endpoints will include the following:

- Assessment of AEs, including SAEs, IARs (eg, cytokine release syndrome [CRS], APRs), and adverse events of special interest (AESIs)
- Clinical laboratory tests
- Vital signs
- Electrocardiogram
- Physical examinations
- Doppler echocardiography
- Biomarkers
- Immune response assessments
- Multiplex assay of inflammatory and vascular biomarkers (Meso Scale).
  Multiplex assay for vascular biomarkers will no longer be assessed after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.

9.2.1 Adverse events

All AEs diagnosed by the investigator will be reported per applicable regulations and guidelines. Definitions for AEs, SAEs, AESI; and instructions for AE monitoring and reporting, are provided in Section 10.4 through Section 10.6. All AEs will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) effective at the time of the planned database lock.

9.2.2 Laboratory safety variables

The clinical laboratory data consist of blood analyses, including hematology, clinical chemistry, and urinalysis. Values will be converted into standard international units and then analyzed. International units will be used in all listings and tables.

The following clinical laboratory tests will be assessed by the site as specified in Section 1.2. IARs, APRs, and CRS' are associated with changes in specific clinical laboratory parameters (see Section 9.2.1).

- Clinical Chemistry: sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, total protein, albumin, glucose, cholesterol, phosphorus, and creatine kinase
- Liver Function Tests: ALT, AST, ALP, gamma glutamyl-transferase, total bilirubin, and direct bilirubin

- Hematology: complete blood count with differential and platelet count, including hematocrit, hemoglobin, and red blood cell, white blood cell, platelet, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts
- Coagulation Studies: prothrombin time (Protime), partial thromboplastin time, INR, and D-dimer
- Urinalysis: dipstick for glucose, protein, hemoglobin, leukocytes, ketones, and bilirubin
- Additional Tests: hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus antibody, serum/urine β HCG pregnancy test (women of childbearing potential only)

Note: If a urine pregnancy test is positive, dosing of study drug will be withheld until results are confirmed with a serum β-HCG test.

Laboratory reports will be made available to the investigator in a timely manner to ensure appropriate clinical review.

9.2.3 Vital signs

Vital signs will include systolic and diastolic blood pressure (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°F or °C).

9.2.4 Electrocardiogram variables

Standard 12-lead ECGs will be conducted as described in Section 1.2.

Electrocardiograms will be performed while the patient remains in a supine position for approximately 5 to 10 minutes before and while conducting the ECG. The following parameters will be assessed: heart rate; cardiac rhythm; intervals for PR, QRS, QT and QTc; QRS axis; left ventricular hypertrophy criteria, right ventricular hypertrophy criteria, and repolarization changes. Interpretation will include an assessment of heart rate, cardiac rhythm, intervals, axis, conduction defects, and overall cardiac impression for each patient.

A specialist trained in the interpretation of this test at each study site will review the ECGs according to site-specific procedures for safety. If possible, the same examiner should perform all such reviews. Details for ECG procedures are provided in the vendor manual.

9.2.5 Doppler echocardiography

A standard 2-dimensional and M-mode Doppler echocardiogram will be conducted at time points specified in the schedule of assessments in Section 1.2.

Examination will include, but not be limited to, ventricular cavity size, valve characterization, ejection fraction, ventricular wall thickness, regional wall motion, diastolic function, and pericardium characterization. Pulmonary blood pressure and blood flow will be assessed using Doppler ultrasound.

A specialist trained in the interpretation of this test at each study site will review the echocardiograms according to site-specific procedures for safety. If possible, the same examiner will perform all such reviews.

Details for ECHO procedures are provided in the vendor manual.

9.2.6 Physical examination

A complete physical examination will be performed before infusion at the time points specified in Section 1.2 and will include a neurological examination (mental status, cranial nerves, muscle strength, sensation, deep-tendon reflexes, and coordination) and an assessment of the patient's general appearance; skin; head, eyes, ears, nose, and throat; and examinations of lymph nodes, heart, lungs, abdomen, and extremities/joints.

An abbreviated physical examination of the patient's general appearance only will be performed before and after infusion at the time points specified in Section 1.2.

Patients will be assessed for body mass and height at the time points specified in Section 1.2.

9.2.7 Biomarkers

Biomarkers collected for monitoring the safety of olipudase alfa will include, but not be limited to hsCRP, plasma ceramide, iron, ferritin, cardiac-specific troponin I, and calcitonin. The percent neutrophils (acute-phase reactants), total bilirubin, and direct bilirubin are considered safety biomarkers, although they are assessed as part of the routine clinical laboratory tests.

Samples will be collected as specified in Section 1.2.

9.2.8 Multiplex assays

Testing for inflammatory and vascular biomarkers using multiplex assay (Meso Scale) will be performed on blood samples taken before and after infusion during dose escalation as specified in Section 1.2 and in case of suspicion of cytokine release syndrome.

IL-6, IL-8, TNF alpha, and IFN gamma were identified as key safety biomarkers during the PAP; as the multiplex assay of proinflammatory panel captures all these biomarkers, this panel will only be maintained for exploratory safety endpoint after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.

Procedures for the collection, handling and shipment of all biomarker samples to be sent to the sponsor or central laboratory are in the vendor manual.

9.2.9 Immunogenicity assessments

Samples will be collected as specified in Section 1.2 for the evaluation of anti-olipudase alfa IgG antibodies. Patients found to be IgG seropositive will be subsequently assessed for neutralizing IgG antibodies to olipudase alfa. During the study period, [redacted]

[redacted] collection will be monthly for the first 6 months after starting the new update, and quarterly after that.

9.2.10 Infusion-associated reactions

In the event that a patient reports an IAR of moderate/severe intensity or recurrent that is suggestive of a hypersensitivity reaction (as defined in Section 10.4.1.3), 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 a hypersensitivity reaction is suspected.

- For IgE anti-olipudase alfa antibody testing the same pre-dose serum sample drawn for anti-olipudase alfa IgG testing may be used if the IAR occurs at that study visit. If a predose sample was not drawn on that day, the patient should return to the study site 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-specific IAR Sample Collection Process manual for guidelines on the collection and shipping of samples (IgG and IgE, antidrug antibody, tryptase, and complement activation testing). The sponsor's Biomarkers and Clinical Bioanalyses-Boston laboratory will be informed of sample shipments
- If necessary, skin testing may be performed in patients who experience an IAR that meets the following criteria following consultation between the investigator and the sponsor:
  - IAR has moderate or severe intensity or is recurrent

    and
  - The patient has persistent and intractable symptoms of hypersensitivity suggestive of an IgE-mediated hypersensitivity reaction as described in Section 10.4.1.3

See also study manual for skin testing procedures.

Cytokine release syndrome: If a patient experiences an AE of moderate or severe intensity that is suggestive of CRS (as described in Section 10.4.1.3), an additional blood sample for the multiplex assay (Meso Scale) and calcitonin will be drawn immediately (if a sample had not been obtained already within the past 30 minutes).

See the laboratory manual for a comprehensive list of tests and guidelines on the collection and shipment of samples.

9.3 PHARMACOKINETIC AND PHARMACODYNAMIC ENDPOINTS

9.3.1 Pharmacodynamic endpoints

The pharmacodynamic endpoints will be the following:

- Clearance of sphingomyelin accumulation from baseline to Week 52 in liver tissue
- Change from baseline to Week 52 in levels of sphingomyelin, ceramide, and other metabolites in plasma or dried blood spot

Analysis of sphingomyelin, ceramide and other metabolites (Sphingosine-1- phosphate) in plasma or DBS through 52 weeks of treatment has been completed for all patients. Lyso-sphingomyelin and ceramide which represent the most informative readouts for pharmacodynamic response to treatment will be maintained throughout the study to continue to monitor levels of substrate and its metabolic product. No further analysis of sphingomyelin or other metabolites will be conducted after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.

9.3.1.1 Sphingomyelin in liver tissue

Liver biopsy samples will be evaluated for sphingomyelin accumulation at baseline, Week 52 and Week 104 according to the schedule provided in Section 1.2. Sphingomyelin accumulation in liver will be quantified by computer morphometry of high-resolution light microscopy images. Sphingomyelin will also be quantified using liquid chromatography-tandem mass spectrometry (LC/MS/MS).

Liver tissue samples will also be evaluated using histopathological methods for safety purposes.

Some medications and/or herbal supplements can be hepatotoxic or cause/prolong bleeding and should not be taken within 10 days before and 3 days after the biopsy procedure (see the study manual for details).

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

9.3.1.2 Sphingomyelin and metabolites in plasma and dried blood spot

Blood samples for quantifying sphingomyelin, ceramide, and other metabolites in plasma or in dried blood spot (DBS) will be collected according to the schedule provided in Section 1.2. No further analysis of sphingomyelin or other metabolites in DBS will be conducted after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. Lyso-sphingomyelin and ceramide in plasma will be maintained to continue to monitor levels of substrate and its metabolic product.

9.3.2 Pharmacokinetic endpoints

Pharmacokinetic endpoints will include evaluation in plasma of the following parameters: C_{max}, t_{max}, AUC, $AUC_{(0\text{-last})}$, $t_{1/2}$, CL, and V_{ss}.

9.3.2.1 Pharmacokinetic sampling time

Pharmacokinetic sampling will occur during the PAP and ETP according to the time points provided in Section 1.2. During the study period, [redacted] samples for PK will be collected at the second dose that is administered after the switch following the same schedule in Section 1.2.3. If a patient receives only a partial infusion (eg, due to a safety concern), then sampling will be repeated at the next infusion of study drug.

Time windows for PK sampling are ±10 minutes for collection times <8 hours after the end of infusion and ±3 hours for collection times ≥8 hours after the end of infusion. Blood will be drawn using an indwelling catheter from an arm that was not used for study drug administration. The exact time/date of PK sampling, study drug administration (including infusion start and stop times), and infusion rate will be recorded.

9.3.2.2 Pharmacokinetic handling procedures

Procedures for collection, storage, and shipment of PK samples are provided in the laboratory manual.

9.3.2.3 Bioanalytical methods

Concentrations of olipudase alfa in plasma will be determined using a validated enzyme-linked immunosorbent assay method.

9.3.2.4 Pharmacokinetic parameters

The pharmacokinetic parameters listed in Table 2 will be calculated from single- and multiple-dose data, as appropriate, and analyzed by non-compartmental methods.

Table 2 - Pharmacokinetic parameters and definitions

Parameter	Parameter definition
C_{max}	Maximum plasma concentration observed
t_{max}	Time to reach C_{max}
$AUC_{0\text{-last}}$	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time
AUC	Area under the plasma concentration versus time curve extrapolated to infinity according to the equation: $AUC = AUC_{last} + \frac{C_{last}}{\lambda_z}$. Values with a percentage of extrapolation >20% will not be taken into account in the descriptive statistics.
$t_{1/2z}$	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.
CL	Total body clearance of a drug from the plasma calculated using the equation $CL = \frac{Dose}{AUC}$
V_{ss}	Volume of distribution at steady state using the equation $Vss = \frac{CL \times AUMC}{AUC}$

The analyte and matrix for all PK parameters are olipudase alfa and plasma, respectively.

9.4 PHARMACOGENETIC ASSESSMENTS

In addition to patients who have blood drawn for the baseline assessment of condition-related genotypes (See Section 9.6.3), for those patients who signed the optional pharmacogenetic informed consent form, a blood sample will be collected and stored for other pharmacogenetic analyses.

This blood sample will be transferred to a site that will, on behalf of the sponsor, extract DNA from the sample. This sample may be used to determine a possible relationship between genes and response to treatment with olipudase alfa, how the body processes olipudase alfa and possible side effects to olipudase alfa.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID (deidentification code) that is different from the patient identification (ID). This "double coding" is performed to separate a patient's medical information and DNA data.

The clinical study data (coded by patient ID) will be stored in the clinical data management system, which is a distinct database in a separate environment from the database containing the

pharmacogenetic data (coded by Genetic ID). The key linking patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored for up to 15 years from the completion of the clinical study report, in compliance with applicable country-specific regulations.

Special procedures for storage and shipping of pharmacogenetic samples are described in detail in the laboratory manual.

9.5 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 samples will be stored for 15 years after end of the study in compliance with applicable country-specific regulations.

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 as ones used during the study (ie, subject/patient ID) and will be transferred to a Sanofi site (or a subcontractor site), which may be located outside of the country where the study is conducted. Safeguards for protecting patient confidentiality and personal data have been included (see Section 14.3 and Section 14.5).

9.6 OTHER ASSESSMENTS

9.6.1 Demographic information and medical 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.

9.6.2 Acid sphingomyelinase enzyme activity

Acid sphingomyelinase activity will be measured as specified in Section 1.2 in peripheral leukocytes and dried blood spot. A central laboratory may conduct the analysis of the samples and provide reports.

9.6.3 Genotyping: SMPD1, CHIT1, UGT1A1

Genotyping of SMPD1 and uridine diphosphoglucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) mutations will be performed by central laboratories if historical results are not available, or if historical results are available, but mutations were not annotated using the guidelines of the Human Genome Variation Society (http://www.hgvs.org/). Genotyping of CHIT1 will be performed by the sponsor if historical results are not available. Mutations will be annotated according to the guidelines of the Human Genome Variation Society (http://www.hgvs.org).

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

9.7 APPROPRIATENESS OF MEASUREMENTS

Dose escalation is necessary to progressively reduce stores of accumulated sphingomyelin and to avoid a large release of ceramide. Clinical AEs and safety biomarkers identified in the Phase 1 single-dose and repeat-dose studies study will also be used to monitor treated patients for potential DLTs (as described in Section 8.1.4).

If a patient experiences an IAR suggestive of a hypersensitivity reaction (as defined in Section 10.4.1.3), blood samples for anti-olipudase alfa antibody (IgG and IgE), tryptase activity, and complement activation testing will be collected. For patients in whom IgG antibodies develop, neutralizing antibody testing will also be performed.

Efficacy parameters include improvements in spleen and liver volume (as measured by abdominal MRI), pulmonary imaging and function (HRCT, X-ray, PFTs), cardiopulmonary function by treadmill ergometry, bone disease infiltration, hematology parameters, and patient-reported health-related quality of life instruments.

The DL_{CO} was chosen as a primary efficacy endpoint because this PFT reflects the underlying pathophysiological infiltration manifested by disease foam cells and changes in DLco can objectively show the effect of olipudase alfa treatment on lung function and reducing local inflammation. Pulmonary involvement is common and progressive, although the extent and severity of involvement varies widely among patients (21). Foam cell infiltrates of the pulmonary alveoli block oxygen uptake through the alveolar wall into the blood vessels. This abnormal diffusing capacity is consistent with ILD (9) which may manifest with coughing, shortness of breath, and recurrent respiratory infections. With low partial pressure of oxygen (PO2) values, patients are affected by dyspnea upon exertion. In most patients with ASMD, decreased pulmonary diffusion secondary to alveolar infiltration becomes evident in childhood and progresses with age (22). Life-threatening bronchopneumonia may occur and cor pulmonale has been described; progressive pulmonary involvement is associated with higher morbidity and mortality (21). Severely affected patients may experience significant pulmonary compromise by age 15 to 20 years. The excess sphingomyelin and other lipids resulting from ineffective ASM clearance from macrophages result in secretion of inflammatory cytokines that lead to fibrosis and diminished lung capacity (23). Some patients develop chronic oxygen dependence with progressive pulmonary failure (21).

Changes in health-related quality of life after 52 weeks administration of study drug will be assessed with the instruments listed in Section 9.1.4.13.

Changes from baseline in spleen volume and DL_{CO}, separately, at Week 52 were selected as the primary efficacy endpoints in this Phase 2/3 study. Splenomegaly is a significant, consistently present manifestation of ASMD, and the degree of splenomegaly has been recognized as clinically relevant by disease experts and shown to be positively correlated with liver volume and triglyceride levels, and negatively correlated with white blood cell count, hemoglobin, high density lipoprotein, percent predicted FVC, and height Z score (24). In both ASMD and a similar lysosomal storage disorder, Gaucher disease, splenomegaly is central to the underlying pathophysiology and is usually the first presenting clinical sign. Furthermore, reduction in spleen volume is recognized as a clinically meaningful endpoint in Gaucher disease (25, 26).

Clinical manifestations common to both ASMD and Gaucher disease include hepatosplenomegaly, thrombocytopenia, and anemia. Both diseases primarily affect the monocyte/macrophage lineage of cells and thus are diseases that affect the reticuloendothelial system. The main sphingolipids that accumulate in Gaucher disease (glucosylceramide) and ASMD (sphingomyelin) are major components of the plasma membranes of red blood cells, white blood cells, and platelets, which cannot be broken down by macrophages. Accordingly, assessments have been planned to monitor changes in hematology.

Due to the known association of sphingomyelin with cholesterol, patients with ASMD often accumulate cholesterol, and subsequently are affected by dyslipidemia, characterized by a high atherogenic cardiovascular risk profile. Typically, the dyslipidemia is characterized by low concentrations of HDL and high concentrations of total cholesterol (27, 28) and recent case reports have described the occurrence of premature coronary artery disease (27). Accordingly, the fasting lipid profile will be assessed as an efficacy parameter and the NMR spectrum of HDL will be characterized (12, 13, 29). NMR lipid profiles analyzed for all patients through 52 weeks of treatment were not identified as an informative efficacy biomarker thus will be removed from the protocol after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021.

Because skeletal involvement can lead to osteopenia or osteoporosis, common manifestations of ASMD and splenomegaly have been shown to be inversely correlated with lumbar spine bone mineral density Z-scores (30), the severity of bone disease will be measured at baseline and once every year. A biomarker for bone resorption, C-telopeptide concentrations in serum have been shown to be decreased in patients with Gaucher disease.

Although hemoglobin level, platelet count, and white blood cell count will comprise part of the standard safety laboratory assessments, these parameters are often abnormal in patients with ASMD because many cells of the reticuloendothelial system originate in the bone marrow and it is one of the most extensively involved organs in ASMD (31, 32). Bone marrow involvement, combined with hypersplenism, contributes to the thrombocytopenia, anemia, and to the neutropenia sometimes observed in patients with ASMD.

Biomarkers will be measured that are known to be associated with macrophage proliferation (ACE), secreted by activated (NP cells) macrophages (chitotriosidase and CCL18), and

inflammatory background triggered in sphingolipidoses (bone-specific alkaline phosphatase, C-telopeptide). Changes in these biomarkers have supported the clinical responses observed with enzyme-replacement and substrate-reduction therapies in other sphingolipidoses such as Gaucher disease Type 1 and Fabry disease (33, 34, 35). The initial objective to monitor ACE changes through 52 weeks of treatment for all patients has been achieved; no further longitudinal analysis is required after the cutoff date for a planned second database lock of the study for purpose of regulatory submissions in 2021. CCL18 and chitotriosidase will continue to be monitored to assess overall disease burden.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The schedules of study assessments for all patients enrolled in this study are provided in Section 1.2. The individual evaluations are described in Section 9 and will occur before infusion with study drug, unless otherwise noted, and during approximately the same time for each visit (in reference to the screening/baseline visit). When multiple assessments are required, the order will be vital signs before ECG before blood draw.

Day 1 is the day the first infusion is administered. The study visit schedule will be calculated using the date of Day 1 of the dose escalation period as the reference.

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

Patients will complete the eDiary at these time points:

- Early in the screening period to verify inclusion criterion I06
- Before the first infusion to collect baseline data (see Section 9.1.4.4).
- At least 7 days before each quarterly visit of the PAP and ETP.
- At end of study (EOS)/early discontinuation

To collect patient responses to the composite endpoint, patients will enter responses in the eDiary device during the evening of the 7 consecutive days before Day 1 and each quarterly visit, separately, of the PAP and the ETP. Sites will distribute and collect the eDiary device according to the schedule presented in Section 1.2. Patients will make entries into the eDiary device at home according to the scheduled provided in Section 1.3.

Rescreening may be possible for patients who screen failed, but is subject to sponsor approval. Imaging, function tests (eg, PFTs, ergometry), and questionnaires performed within 12 weeks of the expected date of randomization can be used for rescreening. All labs will be repeated, except genotyping and ASM activity measurements. The eDiary will not be repeated.

In-patient hospitalization will be required before the start of the infusion and until at least 24 hours after the end of infusion during dose escalation (ie, through Week 16 [PAP]/Week 70 [ETP] if no dosing adjustments are necessary) and may be required during quarterly visits up through the end of Year 2; in-patient hospitalization may be necessary during quarterly and yearly study visits in Years 3 through 5. Blood will be collected and safety assessments performed 24 and 48 hours after the end of infusion. After the cut-off date for a planned second database lock of the study for purpose of regulatory submissions in 2021, the 48 hours post-infusion blood samplings will no longer be collected. For all other visits, patients will be observed after the end of infusion for at least 1 hour. Study drug infusions will occur once every 2 weeks (±3 days) in

reference to the date of the first infusion (Day 1) for each patient, at the site or at home during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic if agreed between the investigator and the sponsor for eligible patients, in compliance with applicable country-specific regulations. Quarterly visits will occur at the site. If site visits are not possible and home infusion is already approved for the eligible patient, quarterly visits will be done at home. In such a case, some of the quarterly visit assessments can be done by the site through the phone (eg, Health-related quality of life instruments). The rest of the missed quarterly visit assessments will be done as unscheduled, as soon as site visits become available.

Telehealth visits are an acceptable alternative to site visits during the COVID-19 pandemic, in accordance with institutional policy and with applicable country-specific regulations.

For the end of study/early discontinuation visit, assessments may vary depending on when discontinuation occurs.

- Patients who discontinue during the dose escalation period of the PAP or the ETP due to intolerability of 0.1 and/or 0.3 mg/kg olipudase alfa or placebo (ie, during study Weeks 0 through 6 [preinfusion]/Weeks 54 through 60 [preinfusion]) will only have:
  - Complete physical examination
  - Vital signs
  - Samples collected for the following assessments:
    - Clinical chemistry,
    - Coagulation
    - LFTs
    - Hematology
    - Urinalysis
    - hsCRP, iron, ferritin, plasma ceramide, cardiac specific troponin I, calcitonin
    - Multiplex assay
    - Anti-olipudase alfa IgG
    - β-HCG pregnancy test (if female of childbearing potential)
  - No other assessments will be performed, unless deemed necessary for safety reasons.
- Patients who discontinue during the dose escalation period of the PAP or the ETP after the Week 6/Week 60 infusion will only have:
  - Complete physical examination
  - Vital signs
  - ECG
  - Samples collected for the following assessments:
    - LFTs

- Hematology
- Urinalysis
- hsCRP, iron, ferritin, plasma ceramide, cardiac specific troponin I, calcitonin
- Multiplex assay
- Anti-olipudase alfa IgG
- β-HCG pregnancy test (if female of childbearing potential)
- Sphingomyelin, ceramide, and other metabolites in plasma
- Metabolites in dried blood spot
- Chitotriosidase, ACE, and CCL18
- Fasting lipid profile

- No other assessments will be performed, unless deemed necessary for safety reasons.

- For the EOS visit and for patients who discontinue after the dose escalation period of the PAP or the ETP, NPB Health Assessment, NPB-HAQ, PGIS questionnaires, abdominal MRI, liver echo Doppler, HRCT, chest X-ray, pulmonary function tests, treadmill ergometry, and echocardiogram with Doppler will not be repeated if they had been done within 3 months prior; DXA and bone MRI will not be repeated if they had been done within 6 months prior. All other assessments specified in Section 1.2.2.3 will be performed.

10.1.1 Home infusions

Home infusion may be given by trained home nurses during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic in the ETP every 2 weeks (±3 days), in compliance with applicable country-specific regulations. Patients must meet specific eligibility requirements outlined below. In addition, the investigator and the sponsor must agree that home infusion is appropriate for each patient.

For a patient to receive home infusions, the following criteria must be met.

- The investigator must agree in writing that home infusion is appropriate for the patient.
- The patient must be willing and able to comply with home infusion procedures.
- The patient must, in the investigator's (or designee's) opinion, have been clinically stable with no history of moderate or severe IARs for at least 6 months, that, in the opinion of the investigator, may affect the patient's ability to tolerate the infusion.
- No infusion rate increases will be allowed while a patient is receiving home infusions.
- The patient must have no ongoing (not yet recovered) SAEs that, in the opinion of the investigator, may affect the patient's ability to tolerate the infusion.
- Home infusion infrastructure, resources, and procedures must be established and available according to applicable country-specific regulations.

- In patients experiencing an IAR while being infused at home, the investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion or return to the site for the subsequent visit and when the patient would be ready to resume home infusion. In case home infusion continues, the investigator will guide the home infusion staff on the measures to be followed for subsequent infusion to manage the IAR (eg, infusion interruption, premedication, change the infusion rate, etc. (See Treatment of infusion-associated reactions in Section 8.8).
- If recurrent IARs or hypersensitivity reactions occur, the investigator should assess whether or not it is safe for the patient to continue to be treated via home infusion.
- If a severe hypersensitivity reaction or an anaphylaxis reaction occurs, during an infusion given at home, treatment will be discontinued immediately, and appropriate medical treatment will be initiated. The patient will return to the study site for further management until the investigator agrees with the sponsor that it is safe for the patient to continue to be treated via home infusion. See Section 8.8 for details on severe hypersensitivity and anaphylaxis management.
- Prior to beginning home infusions, the home infusion staff, including new staff members, must have been appropriately trained and/or licensed, if applicable, on proper procedures to prepare and administer infusions, monitor patients, document procedures, and report to site on a timely basis.
- The home infusion staff must have access to and be trained on proper use of safety equipment, including, but not limited to, cardiopulmonary resuscitation equipment.
- Home infusion staff must keep source documentation of the infusion, including documentation of any AEs, IARs, examinations/ assessments, sample collections and concomitant medication. Home infusion staff must be amenable to providing specific source documentation to Sanofi Genzyme and agree to be monitored. The Principal Investigator is still responsible for all study procedures and patient's safety even when delegating infusion responsibilities to the home care company.
- An additional questionnaire about home infusion experience may be added any time before end of the study for patients who received home infusion treatment.
- If the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, and home infusion already approved for the eligible patient, the investigator can decide whether reintroduction should occur at the hospital/study site or home visit.
- [redacted] if the site visit is not possible during a regional or national emergency declared by a governmental agency such as the COVID-19 pandemic due to site closure or extenuating circumstances that prevent an in-person site visit, the first infusion [redacted] is allowed during home infusion for eligible patients in agreement between the Sponsor and the Investigator in compliance with applicable country-specific regulations.

10.2 DEFINITION OF SOURCE DATA

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions 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, the laboratories, and other departments involved in the clinical study.

All protocol-required information collected during the study must be recorded by the investigator or other study personnel in the source documentation for the study. The source documentation will be used to enter the protocol-required information into the eCRF. No data should therefore be directly entered into the eCRF.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

Study drug will be continued whenever possible; however, if study drug is stopped, it will be determined if the stop can be made temporarily as permanent discontinuation will be a last resort. Any discontinuation will be fully documented in the source and eCRF. In any case, the patient should remain in the study as long as possible.

Pregnancy

Pregnancy will lead to 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. Urine β-HCG will be tested up to 24 hours before the first infusion of the study; then once every 4 weeks before infusion. In addition, these patients are required to have a negative serum or urine β-HCG pregnancy test during the PAP and ETP every 4 weeks after randomization before undergoing visit specific assessments and being infused with study drug. Patients must be willing to practice true abstinence or use 2 acceptable, effective methods of contraception while they are participating in the study. If a patient is no longer participating in the study, they must practice true abstinence or use 2 acceptable, effective methods of contraception for 15 days following their last dose of study drug. Every effort will be made to prevent pregnancy during this study.

In all cases, the sponsor must be notified of all terminations to treatment as soon as possible and, if applicable, the date of withdrawal from the study must be recorded in the eCRF and in the patient's medical record. If possible, all tests and evaluations listed for the end of study visit will be carried out. If a patient fails to return for the necessary visits, then every effort must be made to contact the patient and determine the reason(s), which will be recorded on the eCRF.

Alcohol consumption

Although blood alcohol testing will not be required, patients must be willing to abstain from the use of alcohol for 1 day before and 3 days after each study drug infusion (Section 7.2).

Patients will be counseled to limit alcohol consumption during the study:

- Male patients to a maximum of 30 g alcohol per day (2 drinks/day)
- Female patients to a maximum of 15 g alcohol per day (1 drink/day)

Patients who do not limit alcohol can be discontinued from the study, according to investigator's discretion.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation corresponds to more than 1 dose not administered to the patient as decided by the investigator after consultation with the sponsor.

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

Re-initiation of study drug administration will be done under close and appropriate clinical/and or laboratory monitoring after the investigator has considered to his/her best medical judgment that the responsibility of study drug in the occurrence of the concerned event was unlikely and if the study selection criteria are still met (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 will be required (see Section 8.1.3).

For all patients who have missed two or more doses that require reintroduction of olipudase alfa, the dose reintroduction will take place at the site. During the COVID-19 pandemic, if site visits are not possible and home infusion is already approved for the eligible patient, the investigator can decide whether reintroduction should occur at the hospital/study site or home visit.

Upon reintroduction of treatment, certain assessments will be repeated at infusions (Section 8.1.3.2). The investigator will decide if additional specific assessments may be required before the patient can begin the reintroduction regimen.

For all temporary treatment discontinuations, the duration will be recorded by the investigator in the appropriate screens of the eCRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent discontinuation of study drug is any discontinuation associated with the definitive decision from the investigator, sponsor, or the patient not to re-expose the patient to the study drug at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patient may withdraw from treatment if he/she decides to do so, at any time and irrespective of the reason; withdrawal may be the decision of the investigator or sponsor. All efforts will be made to document the reasons for discontinuation in the eCRF.

Patients should discontinue from treatment for the following reasons:

- The patient reported unacceptable toxicity (see Section 8.1.4)
- The patient required intervention or therapy precluded by the protocol that was deemed by the investigator to be medically necessary
- The patient was unable to comply with the requirements of the protocol
- The patient was noncompliant with study activities or wished to be withdrawn from treatment
- The patient was erroneously included in the study (failed to satisfy all study criteria in Section 7)
- The patient participated in another interventional investigational study while in ASCEND study
- Pregnancy

In addition, the sponsor may decide to discontinue the study early for any other reason.

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

Patients who received at least 1 dose of study drug and who are withdrawn from the study will be asked to complete all EOS/discontinuation assessments before withdrawal (as detailed in Section 1.2) and will receive a safety follow-up telephone call from the study site 30 to 37 days after the final administration of study drug.

The investigator will document the reason(s) for treatment discontinuation/study withdrawal on the eCRF.

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 eCRF and in the patient's medical record. If possible, all tests and evaluations listed for the end of study visit will be carried out. If a patient fails to return for the necessary visits, then every effort must be made to contact the patient and determine the reason(s), which will be recorded on the eCRF.

10.3.4 Handling of patients after permanent treatment discontinuation

Any patient who discontinues participating in the study will be contacted by the study investigator to obtain information about the reason(s) for discontinuation and collection of any potential AEs.

If possible, all tests and evaluations listed for the end of study/early discontinuation visit in Section 1.2 are to be carried out within 2 weeks of the last study drug infusion. If a patient fails to return for the necessary visits, then every effort must be made to contact the patient, determine the reason(s) for discontinuation, and record the reason(s) 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.

In addition, since the primary study comparison is based on intent to treat principle using all randomized patients with any study treatment, missing data, especially the key study assessments during the PAP (12 months) may potentially lead to biased results and challenges in assessing the treatment effect of the study drug. Therefore, all efforts should be made to continue to follow the patients for primary and key secondary endpoints, after the temporary or permanent discontinuation of treatment, in addition to the standard post study safety follow up. If possible, at the minimum, patients should be assessed at their regularly scheduled Week 52 visit (or as close as possible to Week 52) if treatment discontinuation occurred prior to that visit.

10.3.5 Procedure and consequence for patient withdrawal from study

Patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. Preferably the patient should withdraw consent in writing and, if the patient refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

The reason for withdrawal should be captured. Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Patients who withdraw should be asked to come back for the end of study visit and will receive the safety follow phone call.

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.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

The investigator is the primary person responsible for making all clinically relevant decisions on safety issues.

When necessary, a specialist will be consulted in a timely manner (eg, acute renal failure, convulsions, skin rashes, angioedema, cardiac arrest, electrocardiographic modifications, etc).

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An adverse event (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.

10.4.1.2 Serious adverse event

A serious adverse event (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 will 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 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 when a condition is to be considered a medically important event. The list is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)

  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
- Development of drug dependency 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
- Chronic neurodegenerative diseases (newly diagnosed) and not part of the ASMD spectrum

10.4.1.3 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. Reporting guidelines and follow-up instructions are provided below.

AESIs include the following:

- **Pregnancy** of a female patient entered in the study as well as pregnancy occurring in a female partner of a male patient entered in this study
- **Symptomatic overdose** (serious or non-serious) of study drug
  - An overdose (accidental or intentional) of study drug 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
  - An asymptomatic overdose will be reported as a standard AE
- **Laboratory values:** The following laboratory values and symptoms will be considered AESIs (see also Dose-limiting toxicities in Section 8.1.4, Reporting of adverse events of special interest with immediate notification in Section 10.4.4.1 and Summary of adverse event reporting instructions in Table 3), as follows:
  - Any increase in AST, ALT, total bilirubin, or AP >3x baseline (prior to 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 the ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN)

- **Infusion-associated reactions:** Some AEs may be manifestations of IARs, including hypersensitivity reaction, APR, and CRS; however, the original signs and symptoms may be reported as AEs. In the eCRF, investigators will be asked to identify if a specific AE represents a clinical manifestation of the IAR.

  Infusion-associated reactions are defined as AEs that occur during the infusion or within 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 by the investigator or the sponsor as an IAR. For this study, IARs may present as hypersensitivity reactions, APRs, and CRS.

  - **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. 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 include fever, hypotension, tachycardia, nausea, vomiting, pain, and headache.

  - **Acute phase reactions**

    Considered a type of IAR and specific to infusion with olipudase alfa, APRs were observed in the Phase 1 single-dose study and the Phase 1b repeat-dose study (6). Typically, APRs occurred within 12 to 72 hours after olipudase alfa infusion and were indicative of an inflammatory response as they were associated with elevations in hsCRP and changes in acute phase reactants including, but not limited to, neutrophils, iron, ferritin, fibrinogen, D-dimer, transferrin, albumin, Protime, and partial thromboplastin time.

    Typical AEs that were reported by the patient included, but were not limited to, pyrexia, nausea, vomiting, fatigue, and pain; and were concurrent with the changes in specific laboratory parameters. Accordingly, APRs will be determined based on combined significant laboratory findings and clinical symptoms.

  - **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 CRS. Increases were observed after a single dose of ≥0.3 mg/kg olipudase alfa in the Phase 1, single-dose study in IL-8 and IL-6; macrophage inflammatory protein 1, alpha component (MIP-1α); macrophage inflammatory protein 1, beta component (MIP-1β); and other cytokines and biomarkers (based Myriad Rules-Based Medicine Human Multi-Analyte Profile® antigen panel). 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), typical symptoms 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 will be determined based on combined significant laboratory findings and clinical symptoms.

10.4.1.4 Definitions for criteria of adverse events

Relationship to study treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting and will be made in blinded studies and also for known comparators. For each AE/SAE the investigator will determine if there is a reasonable possibility and 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: No evidence exists for a causal relationship between exposure and the AE; however, such a relationship cannot be excluded.
- Possibly Related: Some evidence exists that there is a possibility of a causal relationship between exposure and the AE.
- Related: Strong evidence exists that there is a causal relationship between exposure and the AE.

A relationship to the study drug 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 and amend the AE/SAE report accordingly.

Severity of adverse event scoring

Note that “severity” is not the same as “seriousness,” which is defined in Section 10.4.1.2.

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.

Outcome

The "outcome" describes the status of the AE, which will be provided by the investigator for each AE reported for each patient. 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.

Action taken regarding the study drug

The investigator will be required to provide the action taken on the study drug (eg, active, comparator) in response to the AE. Options include:

- Dose increased: increased the frequency, strength, or amount of study drug.
- Dose not changed: no change in administration of the study drug.
- Dose reduced: reduced the frequency, strength, or amount of study drug.
- Study drug is interrupted: temporary interruption in administration of the study drug.
- Study drug is withdrawn: administration of the study drug is terminated (no further dosing).
- Not applicable: applies when an event has occurred prior to initial dosing, after the last dose, or if the patient dies due to the event.
- Unknown: not known, not observed, not recorded, or refused.

10.4.2 General guidelines for reporting adverse events

See Table 3 for an overview of AE reporting instructions.

- All AEs, regardless of seriousness or relationship to study treatment spanning from the signature of the informed consent form until the end of the study will be recorded on the corresponding eCRF.
- Except for IARs, whenever possible, diagnosis or single syndrome will be reported instead of symptoms. For IARs, all symptoms must be recorded separately.
- The investigator will specify the date of onset, intensity, action taken with respect to study drug, corrective treatment/therapy given, additional investigations performed, outcome, and opinion as to whether a reasonable possibility exists that the AE was caused by the study drug.
- The investigator should take appropriate measures to follow all AEs until clinical recovery has completed and laboratory results have returned to normal, or until progression has been stabilized, or until death, 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 study drug discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI (see Section 10.4.1.3)

Table 3 - 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 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Symptomatic overdose	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Infusion associated reactions (IAR)/Hypersensitivity reactions	Yes	Yes	No
		Laboratory values per Section 10.4.1.3 and Section 10.4.4.1	Yes	Yes	No

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

10.4.3 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 eCRF.
- SEND (by email) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team.
- Care will 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 will be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) will be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, every effort will 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 case report form process) will be available and used when the eCRF 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 study drug with a reasonable possibility, will be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

10.4.4.1 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 10.4.3, even if the event does not fulfill a seriousness criterion, using the corresponding screens in the eCRF.

- Pregnancy
  - Pregnancy occurring in a female patient or the partner of a male patient included in the clinical trial. 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 will be discontinued
  - Follow-up of the pregnancy is mandatory until the outcome has been determined
- Infusion-associated reaction (see Section 10.4.1.3), which include:
  - Hypersensitivity reaction
  - Acute-phase reaction
  - Cytokine release syndrome
- Symptomatic overdose of study drug

  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. See Section 10.4.1.3.
- The following laboratory values and symptoms (see also Dose-limiting toxicities in Section 8.1.4), as follows:
  - Any increase in AST, ALT, total bilirubin, or AP >3x baseline (prior to 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 the ULN combined with an increase in ALT or AST >2x baseline (prior to olipudase alfa therapy) with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, 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

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to study drug (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 study drug 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.

10.6 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

11.1 GENERAL CONSIDERATIONS

The PAP analysis will be performed after all patients have completed the Week 52 assessments (ie, at the completion of the 52-week PAP treatment period) and will include a formal database lock, unblinding of the study treatment arms, and analyses of efficacy, safety, pharmacodynamic, and pharmacokinetic data.

11.2 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the 2 primary efficacy endpoints of percentage change from baseline in spleen volume (expressed in MN) at Week 52 and the percentage change from baseline in DL_{CO} (expressed as % predicted of normal) at Week 52. The assumptions for the spleen volume endpoint are the following:

- An 11.8% common standard deviation based on data from previous ASMD and Gaucher disease type 1 studies
- A 30% mean difference from baseline to Week 52 between 3.0 mg/kg olipudase alfa and placebo in percentage change in spleen volume MN
- An expected exclusion rate from the modified intent-to-treat (mITT) population of 11%

Based on the above assumptions, a comparison between 3.0 mg/kg olipudase alfa and placebo would have over 95% power using a t-test at a 2-sided 5.0% significance level with 36 patients randomized 1:1 to placebo or 3.0 mg/kg olipudase alfa. At a 2.5% significance level, the power would still be over 95%.

The following assumptions for the DL_{CO} endpoint are based on results obtained from the olipudase alfa Phase 1b Study DFI13412:

- A 20% common standard deviation
- A 25% mean difference from baseline to Week 52 between 3.0 mg/kg olipudase alfa and placebo in percentage change in DL_{CO} (in % predicted)
- An expected exclusion rate from the mITT population of 11%

Based on these assumptions, a comparison between the 3.0 mg/kg treatment arm and the placebo arm will have 93% power using a t-test at a 2-sided 5.0% significance level and with 36 patients randomized 1:1 to placebo or 3.0 mg/kg.

The assumptions for the splenomegaly-related score endpoint came from the Sanofi-sponsored clinical trial in myelofibrosis (JAKARTA, NCT# 01437787). The assumptions for the power calculations are:

- A common standard deviation of 9.4
- A mean difference of 8.0 from baseline to Week 52 between 3.0 mg/kg of olipudase alfa and placebo in the splenomegaly-related score
- An expected exclusion rate from the mITT population of 11%

Based on the above assumptions, a comparison between 3.0 mg/kg of olipudase alfa and placebo will have 82% power using a t-test to detect a statistical trend, defined as 2-sided p-value ≤0.15, with 36 patients randomized 1:1 to placebo and 3.0 mg/kg of olipudase alfa.

For the US protocol, in which a combination spleen endpoint is used, using the simplifying assumption that the 2 components of the combination spleen endpoint (spleen volume and SRS) are independent, the likelihood that statistical significance (spleen volume significance based on Hochberg procedure and SRS p-value ≤0.15) will be declared for the combination spleen endpoint is greater than 80%.

11.3 DISPOSITION OF PATIENTS

Screened patients will be defined as any patient who has signed the informed consent form. Screened patients who completed screening and met all eligibility criteria will be eligible for randomization. Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

Randomized patients include any patient who had been allocated to a randomized treatment arm by IXRS regardless of whether the study drug has been administered.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.4 ANALYSIS POPULATIONS

The **randomized population** will include any patient who had been allocated to a randomized treatment arm regardless if study drug was administered.

The **safety population** is a subset of the randomized population and will include randomized patients who received at least 1 infusion (partial or total). This is the primary population for the safety analysis.

The **mITT population** is the same as the safety population, and is used as the primary population for the efficacy analysis.

The **per protocol** population will be a subset of the mITT population who have no major protocol deviations that are expected to interfere with assessments of the 2 primary efficacy endpoints.

The **extension treatment population** will consist of patients who completed the PAP and who continue into the extension treatment period.

The **PK population** will consist of mITT patients who have evaluable drug concentration data.

The **PD population** will consist of mITT patients who have at least 1 evaluable PD marker data available post-baseline.

Patients who are included in the safety population and have rescue therapy initiated are included in the **rescue therapy population**. Since in the ETP all subjects get olipudase alfa, the rescue therapy is relevant only for the PAP.

11.5 STATISTICAL METHODS

11.5.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure will be assessed and summary statistics will be presented for the safety population.

11.5.2 Analyses of efficacy endpoints

Efficacy endpoints and assessments are provided in Section 9.1.

11.5.2.1 Primary efficacy analysis

The 2 primary efficacy endpoints (percentage change in spleen volume in MN from baseline to Week 52 [combined with change in SRS from baseline to Week 52 in the US only, and is referred to as the "combination spleen endpoint"]) and percentage change in DL_{CO} in percent predicted from baseline to 52 weeks) will be analyzed in the mITT population using the mixed model for repeated measures.

For percent change in DLco (% predicted) from baseline, the mixed model for repeated measures (MMRM) will include baseline DLco (% predicted), baseline age, treatment arm, study visit (Week 26, Week 52), and study visit by treatment arm interaction as covariates; have an unstructured variance-covariance matrix; and be fit using restricted maximum likelihood estimation. Comparisons between treatment arms will be made using least-square mean contrasts at the 52 week visit.

The analysis will include all DLco observations after baseline in the first 12 months of the study regardless of the treatment discontinuation status, with the exception that measurements made after the switch of treatment (eg, placebo patients switch to olipudase alfa after meeting the rescue criteria) will not be considered. For the primary analysis, missing data will not be imputed and will be assumed as Missing at Random (MAR).

Similar analyses will be performed for the spleen volume (MN) and the splenomegaly-related symptom score (SRS), when baseline value of the spleen volume (or SRS) will be used as covariate.

Descriptive assessment of MAR assumption and sensitivity analyses to assess the impact of missing data are described in the SAP.

Hypothesis tests will be 2-sided and adjusted for multiple comparisons to maintain a family-wise Type 1 error rate of 5%. The details of multiplicity adjustments are provided in Section 11.5.4.

11.5.2.2 Secondary efficacy analyses

The secondary efficacy endpoints include the following:

- Percentage change in liver volume (in MN) from baseline to Week 52
- Percentage change in platelet counts from baseline to Week 52
- Week 52 change from baseline in fatigue severity as measured by Item 3 of the BFI scale
- Week 52 change from baseline in pain severity as measured by Item 3 of the BPI-SF scale
- Week 52 change from baseline in dyspnea severity as measured by the FACIT dyspnea tool
- Change in SRS from baseline to Week 52 (except US, where it is part of the primary "combination spleen endpoint") (Section 9.1.4.4)

The secondary efficacy endpoints will be analyzed in the mITT population using the mixed model for repeated measures and 2 sided hypothesis tests. The multiplicity adjustment for the secondary endpoints using a hierarchical, closed testing principle is described in Section 11.5.4. Handling of the missing data for secondary efficacy endpoints will be described in the SAP.

11.5.3 Extension treatment period

Long-term efficacy will be summarized for all efficacy endpoints using data collected during the ETP.

11.5.4 Multiplicity considerations

The hypothesis testing for the primary efficacy endpoints and secondary efficacy endpoints will be adjusted for multiplicity using a 2-stage gatekeeping strategy to maintain the 5% familywise error rate. A Hochberg method will be used to test the 2 primary endpoints followed by sequential, closed hypothesis testing for the secondary efficacy endpoints. The primary efficacy endpoint testing will proceed as follows:

Compare olipudase alfa to placebo on DLco and spleen volume: The overall 5% significance level for the two hypothesis tests will be maintained using the Hochberg method (MTP2 is maintained for 2-sided, 2-endpoint testing):

- The p-values associated with the 2 primary endpoint comparisons will be ranked and the higher of the 2 p-values will be compared to 0.05. If the higher p-value is ≤0.05, the primary efficacy testing stops, and both primary endpoints are considered statistically significant.
- If the higher p-values is ≥0.05, the primary endpoint associated with the higher p-value is not significant and the lower p-value is compared to 0.025. If the lower p-value is ≤0.025, the primary endpoint associated with this p-value is considered statistically significant.
- In the US, the combined spleen endpoint will be considered statistically significant if, from Steps 1 and 2, the spleen volume endpoint is significant and the SRS p-value ≤0.15.

The hypothesis testing for the secondary efficacy endpoints will proceed in a hierarchical fashion using the closed testing principle, and will stop if there is a nonsignificant comparison. From sponsor perspective, the study is declared positive if either DLco or combination spleen endpoint is significant.

For Europe and the rest of world, from sponsor perspective, the study is declared positive if at least one of the primary endpoints is statistically significant by the above method.

If statistical significance is reached on both the DLco and spleen volume using the Hochberg method (and the trend in splenomegaly-related score is established in case of USA), then hypothesis testing of the secondary efficacy endpoints will proceed using sequential testing at 5% level with the order as specified below. At any step when the endpoint is not significant at 5% level, the formal testing in subsequent steps will stop; the p-values for the subsequent endpoints in the sequence will be considered exploratory and hence interpreted at the nominal level. This controls the overall type I error level at 5%, using the closed testing principle. If either of the primary endpoints is not significant, then hypothesis testing for the secondary endpoints will be considered exploratory, and p-values will be interpreted at the nominal level. Testing will proceed according to the following sequence:

1. Percentage change in liver volume (in MN) from baseline to Week 52
2. Percentage change in platelet counts from baseline to Week 52
3. Week 52 change from baseline in fatigue severity as measured by Item 3 of the BFI scale
4. Week 52 change from baseline in pain severity as measured by Item 3 of the BPI-SF scale
5. Week 52 change from baseline in dyspnea severity as measured by the FACIT dyspnea tool
6. Change in SRS from baseline to Week 52 (except US, where it is part of the primary "combination spleen endpoint") (Section 9.1.4.4)

11.5.5 Analyses of safety data

Safety analyses will be performed using the safety population by the actual treatment received, irrespective of the treatment to which the patient has been randomized. The actual treatment received is defined as:

- PAP analysis: olipudase alfa if any infusion in the PAP contains olipudase alfa (including any rescued placebo patient); placebo if all infusions in the PAP contain only placebo
- ETP analysis: olipudase alfa

Additional summaries may be conducted using the most recent dose the patient received before the event of interest.

The summary of safety results will be presented by treatment arm. All safety analyses will be performed using the following common rules:

- The baseline value is defined generally as the last available value before randomization, except hematology and ECG parameters. Baseline for hematology parameters is derived as the mean of all available results before the start of first infusion. Baseline for ECG parameters is derived as the mean of all available results on the Day 1/Week 0 visit before the start of first infusion.
- The following definitions will be applied to laboratory parameters, ECGs and vital signs.
  - 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 and vital signs.
  - The PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.5.5.1 Adverse events

Pretreatment AEs will be listed and presented separately from treatment-emergent AEs.

All AEs will be coded using the most recent version of the MedDRA. Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order) and preferred term (PT), and the number 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 within each treatment arm.

All treatment-emergent adverse events (TEAEs), all TEAEs potentially related to study drug, all TEAEs leading to treatment discontinuation and/or study discontinuation, all TEAEs that are IARs, all TEAEs that are SAEs (including those potentially related to treatment), and all AEs with fatal outcome (including fatal TEAEs) will be summarized. The TEAE observation period will be defined as the time from the first infusion of study drug through the end of study visit or 30 to 37 days after the last infusion of study drug, whichever one occurs later.

Detailed listings of TEAEs, SAEs, AESIs, related AEs, and discontinuations due to AEs will be provided and include the randomized treatment arm and olipudase alfa dose of the infusion or placebo before or during the occurrence of the AE, when applicable.

The number of TEAEs and annualized rate, and the number and proportion of patients reporting specific AEs will be tabulated for the overall analyses of AEs.

Separate analyses of AEs may also be conducted by demographic characteristics (eg, age and sex). Adverse events of special interest, such as IARs, and SAEs will be analyzed similarly.

Adverse events of special interest

Detailed listings for AESIs will be provided.

Deaths

The following deaths summaries will be generated:

- Death in nonrandomized patients or randomized and not treated patients
- Treatment-emergent AE leading to death (death as an outcome on the AE CRF page as reported by the investigator) by primary SOC and PT

11.5.5.2 Physical examinations, vital signs, electrocardiograms, and echocardiograms

Observed values and changes from baseline (as applicable) will be summarized. Outlier summaries for the ECG parameters (eg, QTc) and vital signs will be created for the safety population.

The ECG data will be analyzed using the Bazett's and Fridericia's QT correction methods (36). All ECG variables will be summarized for each randomization dose group/dose and time point. Change from baseline will also be calculated and summarized using descriptive statistics.

11.5.5.3 Clinical laboratory tests

Observed values and changes from baseline to study time points will be summarized. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. Frequencies of clinically significant abnormal values and shifts from baseline to study time points will be summarized. Patient listings of biomarkers will be provided.

11.5.5.4 Immune response assessments

Immune response assessments will be analyzed in the safety population. The presence, absence, and titers of serum anti-olipudase alfa IgG antibodies and routine levels of acute phase reactants will be summarized over time overall and by the dose level of the infusion before or during the evaluation. Levels of acute phase reactants, serum tryptase, complement activation, neutralizing

antibodies, and anti-olipudase alfa antibodies (IgG and IgE) obtained in response to an IAR, and skin testing results (if available), will be presented in patient listings, if applicable.

11.5.6 Pharmacokinetic and pharmacodynamic analyses

11.5.6.1 Pharmacokinetic analyses

Plasma concentration-time data will be analyzed using actual dosing and sampling times by non-compartmental methods.

As data permit, the following PK parameters as specified in Section 9.3.2.4 will be calculated for each patient and each dose of olipudase alfa.

Pharmacokinetic parameters will be assessed as a function of time (upon repeat dosing) and in relation to immunogenicity. If data do not lend to non-compartmental analysis, or for additional analyses, model based approaches such as nonlinear mixed effects modeling may be used.

11.5.6.2 Pharmacodynamic analyses

Pharmacodynamic endpoints are defined in Section 9.3.1. The analysis of these endpoints will use the PD population.

Concentration-time data for sphingomyelin and metabolite levels will be summarized.

All other PD parameters will be summarized using descriptive statistics. Change from baseline will be calculated and summarized. Exploratory correlation analyses will be attempted to evaluate relationships between different PD markers and between sphingomyelin and/or lyso-sphingomyelin levels from different sources.

11.5.6.3 Pharmacokinetics - pharmacodynamics

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

11.5.7 Analyses of quality of life variables

Scoring for the quality of life assessments (eg, BPI, BPI-SF, etc) will be conducted as stated by the developers of the questionnaires, if available.

12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

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 a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international guidelines, and national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. See also Section 13.3.

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 of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB/IEC). All participants will be informed to the fullest extent possible about the study in language and terms they are able to understand.

Before a patient’s participation in the clinical trial, the informed consent form will be signed, name entered, and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form and optional pharmacogenetic informed consent form used by the investigator for obtaining the patient's informed consent must be reviewed and approved by the sponsor before submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

As required by local regulation, the investigator or the sponsor must submit this clinical trial protocol to the appropriate ethics committee (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 ethics committee (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, etc) and the date of the review will be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Study drug 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 must be submitted to the ethics committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC will 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 ethics committee (IRB/IEC).

A progress report is sent to the ethics committee (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(s) and delegated investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice (E6), and the applicable regulatory requirements.

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).

All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Guidance on completion of CRFs will be provided in the eCRF completion guide.

Particular attention will 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.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor

13.2 RESPONSIBILITIES OF THE SPONSOR

The sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded in the eCRFs. Thus, the main duty of the monitoring team is to ensure that the safety, well-being, and rights of all study patients are observed, and to assist the investigator and the sponsor in maintaining a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical trial.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

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 ensure that patient safety, well-being, and rights are observed, and 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, study drug allocation, patient compliance with the study drug regimen, study drug accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the 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 eCRFs (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 laws and rules).

13.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the investigator to maintain adequate and accurate 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.

Should a correction be made, the corrected information will be entered in the eCRF 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 eCRF.

The computerized handling of the data by the sponsor when available in the eCRF may generate additional requests (Discrepancy Resolution Form) 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 eCRF.

13.4.1 Use of computerized systems

The following computerized systems may be used during the different steps of the study:

- For data management activities, Medidata Rave
- For PK activities, PKDMS Version 2.0 incorporating WinNonlin Enterprise, Version 5.2.1, Pharsight
- For statistical activities, SAS
- For pharmacovigilance activities, AWARE
- For monitoring activities, IMPACT
- For medical writing activities, VEEVA VAULT
- For MRI activities, WebSend and BioPACS
- For the eDiary, Exco Engage Portal
- For ECGs, Cami 7
- For echocardiograms, Digiview
- For pulmonary function tests, EasyDataCentral
- For central laboratory tests, Covance Lablink

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 before the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

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

The investigator should retain the study documents at least 25 years after the completion or discontinuation of the clinical trial.

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

The investigator must notify the sponsor before 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, the eCRFs, the investigator's brochure and the results obtained during the course of the clinical trial, is confidential, before 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 committees (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.

Furthermore, the investigator and the sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, investigator and its collaborators involved in the study.

14.4 PROPERTY RIGHTS

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

The investigator shall not 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, and shall be treated by both the sponsor and the investigator in compliance with all applicable laws and regulations.

Patient race will be collected in this study because these data are required by several health authorities including the US Food and Drug Administration. The following options will be listed for race on the eCRF: American Indian or Alaska Native; Asian; Black; Native Hawaiian or Other Pacific Islander; White; Japanese; plus the additional options of Not Reported and Unknown.

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 maintaining their own liability insurance policy. An insurance certificate will be provided to the ethics committees (IECs/IRBs) or health 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 are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The investigator must make every effort to assist 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/she must inform the sponsor and authorize the sponsor to participate in this inspection.

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

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

The investigator must take appropriate measures required by the sponsor to take corrective actions for all issues identified during the audit or inspections.

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

14.8.1 Decided 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.
- Noncompliance of the investigator or subinvestigator, 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 Decided by the Investigator

The investigator must notify (30 days prior notice) the sponsor of his/her decision and give the reason in writing.

In all cases (decided by the sponsor or by the investigator), the appropriate ethics committee(s) (IRB/IEC) and Health Authorities will 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. A full clinical study report (CSR) will be prepared when the PAP data becomes available. At study completion (ie, at the end of ETP), the CSR for the entire study, including the ETP, will be prepared.

14.10 PUBLICATIONS AND COMMUNICATIONS

The investigator agrees not to publish or release data or information pertaining to the study before 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, the first presentation or publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. However, if no multicenter publication has occurred within 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 to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the study 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 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 to 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 ethics committee (IRB/IEC) and also by regulatory authorities if substantial before 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 before implementation of the change and patient signature will be re-collected if necessary.

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy.
2. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
  - Refrain from donating sperm

    and
  - At least 1 of the following conditions applies:
    - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

or

- Agree to use a male condom plus an additional contraceptive method with a failure rate of < 1% per year (see table for female subjects)

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol

Highly effective contraceptive methods that are user dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] - oral - injectable
Highly effective methods that are user independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. *b* Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least [XX, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Female subjects:

Highly effective contraceptive methods that are user dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[b]

- oral - injectable
Highly effective methods that are user independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. *b* Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 15 days after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Male subjects with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner’s pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to

the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Appendix B Country-specific requirements

Summaries of country-specific protocol amendments are included in Appendix C.

Appendix C Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located after the "Names and Addresses of Coordinating Investigator and directly before the Clinical Trial Summary.

The primary reasons for each protocol amendment are summarized below.

AMENDED CLINICAL TRIAL PROTOCOL 12 (15-Apr-2020)

This amended protocol (12) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is made to provide option of home infusion during the COVID-19 pandemic for eligible patients during the extension treatment period (ETP) in compliance with applicable country-specific regulations and in case of multiple missing infusions, to clarify the process of dose reintroduction, and change the reintroduction starting dose. Previous omissions and errors were corrected.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary-Study design, Sections 1.2.2.2, 1.2.2.3 Schedule of Assessments, 6.1 Description of the protocol, 8.1.1 Treatments administered, 8.1.3.2 Dosing delays or missed doses, 10.1 Visit schedule	Provide option for home infusion during COVID-19 pandemic	Home infusion is necessary for patients to continue treatment in case of procedure taken during COVID-19 pandemic
Clinical Trial Summary-Study design, Sections 1.2.2.2, 1.2.2.3 Schedule of Assessments, 6.1 Description of the protocol, 10.1 Visit schedule	Change hospitalization requirements in quarterly and yearly visits during ETP to be at investigator discretion	Update hospitalization requirements to be more flexible at PI discretion regarding quarterly and yearly visits in ETP
Clinical Trial Summary- Study design, Section10.1 Visit schedule	Update observation period after infusion to 1 hour instead of 3 hours	Match observation period in other studies
Section 1.2 Schedule of Assessments	Weight at previous on-site quarterly visit or home visit (during COVID-19 pandemic, if ≥3 months passed since last on-site quarterly visit) may be used to calculate drug dosage at current visit. In tables where new footnotes were added, the footnote numbers were updated.	To allow dose calculation to be done based on quarterly visit weight during ETP

Section # and Name	Description of Change	Brief Rationale
Section 8.1.3.2 Dosing delays or missed doses	Reduce the dose when reintroduction from 0.6 mg/kg to 0.3 mg/kg in case patient was on a dose of ≥ 0.6 mg/kg and missed ≥3 infusions	To allow safer reintroduction at a lower level in case of missing ≥3 infusions
Section 8.1.3.2 Dosing delays or missed doses	List of assessments needed during dose reintroduction. Reformatting of language and remove redundant language	Clarify rules of dose reintroduction and needed assessments
Section 8.8 Concomitant medication-treatment of infusion associated reaction	In case of anaphylaxis, language updated to reflect immediate discontinuation of the infusion	Clarification of anaphylaxis management
Sections 9.1.3 Tertiary and exploratory efficacy endpoints, 9.1.4.13 Health-related quality of life questionnaires,	An additional questionnaire about home infusion experience may be added for patients who received home infusion treatment	Record patient experience
Section 10.1.1 Home infusions	List of eligibility requirements for home infusion	Provide details of who are eligible for home infusion and guidance on safety measures
Section 10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)	Addition of home infusion during COVID-19 pandemic and guidance for reintroduction assessment	Provide details guidance in case of COVID-19 Pandemic and assessment during reintroduction
Sections 9.5 Future use of samples, 14.2 Record retention in study site	Change document retention to 25 years and clarify that left over samples will be stored for future use for 15 years, in compliance with country specific regulations.	To comply with the standard procedures and match the approved informed consent

Amended Clinical Trial Protocol 11 (12-Aug-2019)

This amended protocol (11) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is made to indicate the different assessments that will be done after manufacturing process update as per regulatory authorities' requirements. Previous omissions and errors were corrected.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary, Main selection criteria Exclusion Criteria	Corrected an error in platelet count number superscript	Correct a previous error
Clinical Trial Summary, 6.2.1 Duration of study participation for each patient	Corrected the duration of ETP to 4 years	Correct an error. The total duration of the study is correct but the ETP duration was to be corrected.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary, 6.3 Interim Analysis	Updated to specify that a formal summary of data or interim CSR may be produced to support regulatory approval(s) and/or other submission/application requirement(s)	Clarify the plans for interim CSR (s)
Clinical Trial Summary, 7.2 Exclusion Criteria	Modified E 10: The patient is unwilling or unable to avoid 10 days before and 3 days after the protocol scheduled liver biopsies, that are required at screening/baseline, at Week 52 and at Week 104, the use of medications or herbal supplements that are potentially hepatotoxic (eg, 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, erythromycin, valproic acid, anti-depressants, kava, echinacea) and/or may cause or prolong bleeding (eg, anti-coagulants, ibuprofen, aspirin, garlic supplements, ginkgo, ginseng).	Assessment to be done after manufacturing process update
1.2.1.2 Schedule of Assessments: Year 1 - PAP Week 18 through Week 52	Correction of footnote reference for anti-olipudase alfa IgG (footnote 'k' instead of footnote 'j')	Correct a previous error
1.2.2.1 Schedule of assessments: ETP - Year 2 Week 54 to Week 70	Correction of footnote reference for eDiary (footnote 'm' instead of 'l') and study drug infusion (footnote 'n' instead of 'm')	Correct a previous error
1.2.2.2 Schedule of assessments: ETP - Year 2 Week 72 to Week 104	Footnote 'h' has been updated to include language for hematology assessments in cases where drug product from an updated manufacturing process will be administered. Correction of footnote reference for study drug infusion (footnote 'p' instead of 'o')	Clarification and correction of a previous error
1.2.2.3 Schedule of assessments: ETP - Year 3 until end of study	Footnote 'i' has been updated to include language for hematology assessments in cases where drug product from an updated manufacturing process will be administered. Correction of footnote reference for β-HCG pregnancy test (footnote 'k' instead of 'j')	Clarification
1.2.3 Pharmacokinetic sampling during the primary analysis and extension treatment periods	Updated to include details of sampling in cases where drug product from an updated manufacturing process will be introduced. Added footnote 'c' to specify that during the study period, if drug product from an updated manufacturing process is administered, samples for PK will be collected at the second dose that is administered after the switch following the same schedule in other PK sampling weeks	Assessment to be done after manufacturing process update
9.1.2	Added a reference to Section 9.1.4.13 for change in SRS from baseline to Week 52	Clarification
9.3.2.1 Pharmacokinetic sampling time	Updated to include details of sampling in cases where drug product from an updated manufacturing process will be introduced	Assessment to be done after manufacturing process update
10.3.3 List of criteria for permanent treatment discontinuation	Updated the reason for patient discontinuation from treatment : The patient participated in another investigational study	Clarify that patient will be discontinued if participated in another interventional investigational study
11.5.4 Multiplicity consideration	Update language to match multiplicity rules planned	Clarify statistical consideration of multiplicity of primary and secondary end points

Section # and Name	Description of Change	Brief Rationale
15 Clinical Trial Protocol Amendments	Updated to state that any amendment to the clinical trial protocol requires written approval/favorable opinion by the ethics committee (IRB/IEC) and also by regulatory health authorities if substantial before its implementation, unless there are overriding safety reasons	Clarify language regarding the approvals needed in case of protocol amendment to adhere to Sanofi policy
17 Appendices Appendix C - Protocol Amendment History	Updated to include the summary of changes from Amended protocol 10	This change was made to adhere to Sanofi policy.

Amended Clinical Trial Protocol 10 (05 Dec 2018)

This amended protocol (10) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is made to include the immunogenicity schedule of analysis to be followed in case of drug product from an updated manufacturing process is administered. Also it is made to clarify language regarding the assessments done during dose reescalation.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.2 Schedule of assessments. Flow chart # 1.2.1.2 foot note k, 1..2.2.2 footnote j, 1..2.2.3 footnote l All footnotes to the assessment of Anti-olipudase alfa IgG	During the study period, if drug product from an updated manufacturing process is administered, collection will be monthly for the first 6 months after starting the new update, and quarterly after that.	Describe the schedule of immunogenicity (anti olipudase alfa IgG) assessment in case of manufacturing update to the process
8.1.3.2 Dosing delays or missed doses	Outside a dose escalation period, or if the patient has already reached his/her maximum tolerated dose, a patient who has missed 2 consecutive doses and whose last dose was 0.3 mg/kg or 0.6 mg/kg should receive the same dose at the next scheduled infusion and for the rest of the study period. If the last dose was 1, 2, or 3 mg/kg, the first reintroduction dose should be 1 level below the last dose. During this dose re-escalation, the schedule of assessments (except PK) will be similar to dose escalation period starting from the corresponding dose. If this dose re-escalation happened during the PAP, re-escalation of 0.6 mg/kg will correspond to week 6, repetition of 0.6 mg/kg will correspond to week 8, 1 mg/kg to week 10, 2 mg/kg to week12 and 3 mg/kg to week 14 assessments. If the	Clarify language of dose re-escalation

Section # and Name	Description of Change	Brief Rationale
	dose re-escalation happened during the ETP, re-escalation of 0.6 mg/kg will correspond to week 60, repetition of 0.6 mg/kg will correspond to week 62, 1 mg/kg to week 64, 2 mg/kg to week 66 and 3 mg/kg to week 68 assessments. For the following infusions, the dose will be escalated up to the dose the patient had reached prior to the infusion interruption (target dose or maximum tolerated dose) following the standard escalation process described in Table 1. Outside a dose escalation period, or if the patient has already reached his/her maximum tolerated dose, a patient who has missed 3 or more consecutive doses and whose last dose was 0.3 mg/kg will receive a dose of 0.3 mg/kg at the next scheduled infusion and for the rest of the study period. If the last dose was 0.6, 1, 2, or 3 mg/kg), the first reintroduction dose will be 0.6 mg/kg. During this dose re-escalation, the schedule of assessments (except PK) will be similar to dose escalation period starting from the corresponding dose. If this dose re-escalation happened during the PAP, re-escalation of 0.6 mg/kg will correspond to week 6, repetition of 0.6 mg/kg will correspond to week 8, 1 mg/kg to week 10, 2 mg/kg to week12 and 3 mg/kg to week 14 assessments. If the dose re-escalation happened during the ETP, re-escalation of 0.6 mg/kg will correspond to week 60, repetition of 0.6 mg/kg will correspond to week 62, 1 mg/kg to week 64, 2 mg/kg to week 66 and 3 mg/kg to week 68 assessments.	
9.2.9 Immunogenicity assessments	During the study period, if drug product from an updated manufacturing process is administered, collection will be monthly for the first 6 months after starting the new update, and quarterly after that.	Describe the schedule of immunogenicity (anti olipudase alfa IgG) assessment in case of manufacturing update to the process.

Amended Clinical Trial Protocol 09: 18-Sep-2018

Reason for Amendment:

This amendment was made to clarify that portal hypertension would be detected for all patients using already existing liver ultrasound echo parameters and also to clarify language in statistical analysis and pharmacokinetic assessments.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary- Study design	The PAP will include a screening/baseline period and a treatment period. During the screening/baseline period, from day -60 to day 1 preinfusion, approximately 36 patients will provide informed consent and undergo screening assessments to determine trial eligibility and undergo baseline measurements.	Clarification and correction
Clinical Trial Summary- Study design	Note: a Schedule does not account for rechallenge. ~~a~~ Study drug includes olipudase alfa and placebo	Correction
Clinical Trial Summary- Study	If a patient is discontinued due to inability to tolerate rechallenge (ie, a second dose of 0.3 mg/kg olipudase alfa), then an additional patient ~~will~~ may be	Clarification and correction

Section # and Name	Description of Change	Brief Rationale
design	randomized.	
Clinical Trial Summary- Study design	For treatment periods during the PAP and the ETP, dose-limiting toxicity criteria ~~and study stopping rules~~ will apply.	Clarification
Clinical Trial Summary- Statistical considerations	Patients who are included in the safety population and have rescue therapy initiated are included in the **rescue therapy population**.	Clarification and correction
Clinical Trial Summary- Statistical considerations	Adverse event (AE) incidence tables will present by system organ class (SOC) (sorted by internationally agreed order) and preferred term (PT) ~~sorted alphabetically for each treatment arm,~~ and the number and percentage of patients experiencing an AE.	Correction
Clinical Trial Summary- Statistical considerations	Exploratory correlation analyses will be attempted to evaluate relationships between different pharmacodynamic markers and between sphingomyelin and/or lysosphingomyelin levels from different sources.	Clarification and correction
Clinical Trial Summary- Statistical considerations	The PK-PD relationships ~~will~~ may be explored graphically and if a relationship is apparent, PK-PD modeling ~~will~~ may l be attempted and results reported, as appropriate.	Clarification and correction
6.1 DESCRIPTION OF THE PROTOCOL	Patients will be randomly and centrally assigned in a 1:1 ratio across sites using blocks of fixed size into 1of 2 arms, placebo, saline 0.9% sodium chloride solution, or 3.0 mg/kg olipudase alfa target dose. Dose-escalation during the PAP to the randomized target doses will occur according to the schedule provided in Section 8.1.3 and Table 1. To maintain the double-blind, all patients will dose-escalate ~~in the same manner.~~ using the schedule provided (true dose escalation for patients who were in the placebo arm during the PAP and mock dose escalation for patients in the active arm during the PAP).	Clarification and correction
	If a patient is discontinued due to inability to tolerate rechallenge (ie, a second dose of 0.3 mg/kg olipudase alfa), then an additional patient ~~will~~ may be randomized.	Clarification
	For treatment periods during the PAP and the ETP, dose-limiting toxicity (DLT) criteria ~~and study stopping rules~~ will apply.	Correction
8.1.1. Treatments administered	If a patient is discontinued due to inability to tolerate rechallenge (ie, a second dose of 0.3 mg/kg olipudase alfa), then an additional patient ~~will~~ may be randomized.	Clarification
	For treatment periods during the PAP and the ETP, DLT criteria ~~and study stopping rules~~ will apply.	Clarification and remove repetition
8.1.3.3 Escalation schema	The following criteria will determine the next dose of study drug to be administered, provided the patient does not experience an AE that meets the ~~patient stopping criteria~~ DLT (Section 8.1.4).	Correction
	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~~ DLT criteria (Section 8.1.4), then study drug infusion may be withheld or administered at the discretion of the investigator.	Correction
8.3 Blinding Process	~~Patients, investigators, and the sponsor will be blinded to the identity of placebo and olipudase alfa for all study drug infusions during the entire PAP and the first part of the ETP.~~	Clarification

Section # and Name	Description of Change	Brief Rationale
8.3.1 Methods of blinding	This study has a double-blind, placebo-controlled design. During both the PAP and the first part of the ETP, patients, investigators, and the sponsor will be blinded to the identity of study treatment. ~~for all study infusions~~ Also, patients and investigators will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2, until after the database lock ~~after the last patient in the~~ for PAP and dose escalation in ETP has completed ~~the 52-week assessments and results have been analyzed~~ (sponsor will be blinded ~~until last patient in~~ the database lock for PAP). To maintain the double-blind, all patients regardless of treatment assignment will undergo dose escalation (true or mock) in the same manner in both the PAP and ETP.	Clarification that liver ultrasound with Doppler parameters will be used to detect the likelihood of portal hypertension and severe portal hypertension
8.3.1 Methods of blinding	The investigators and the sponsor will also be blinded to the PK data. Genzyme Clinical Supplies will remain unblinded throughout the study to provide the appropriate study drug to patients~~. A pharmacokineticist will receive reports of olipudase alfa plasma concentrations.~~	Clarification and correction
	At the facilities where the PK measurements, ADA, and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team and a process will be set up to prevent any potential unblinding.	Clarification and correction
9.1.4.10 Liver ultrasound with Doppler	Some of the above mentioned parameters will be used to detect the likelihood of portal hypertension, and if detected whether it was severe, as described in the vendor's manual.	Clarification
	Liver ultrasound will be performed as described in the vendor's manual.	
Table 2	~~Apparent total~~ Total body clearance of a drug from the plasma calculated using the	Clarification
	~~Apparent volume~~ Volume of distribution at steady state using the equation	Clarification
10.3.4 Handling of patients after permanent treatment discontinuation	In addition, since the primary study comparison is based on intent to treat principle using all randomized patients with any study treatment, missing data, especially the key study assessments during the PAP (12 months) may potentially lead to biased results and challenges in assessing the treatment effect of the study drug. Therefore, all efforts should be made to continue to follow the patients for primary and key secondary endpoints, after the temporary or permanent discontinuation of treatment, in addition to the standard post study safety follow up. If possible, at the minimum, patients should be assessed at their regularly scheduled Week 52 visit (or as close as possible to week 52) if treatment discontinuation occurred prior to that visit.	Clarification and correction
11.4 ANALYSIS POPULATIONS	Patients who are included in the safety population and have rescue therapy initiated are included in the rescue therapy population. Since in the ETP all subjects get olipudase alfa, the rescue therapy is relevant only for the PAP.	
11.5.2.1 Primary efficacy analysis	For percent change in DLco (% predicted) from baseline, the mixed model for repeated measures (MMRM) will include baseline DLco (% predicted), baseline age, treatment arm, study visit (week 26, week 52), and study visit by treatment arm interaction as covariates; have an unstructured variance-covariance matrix; and be fit using restricted maximum likelihood estimation. Comparisons between treatment arms will be made using least-square mean contrasts at the 52 week visit.	Clarification and correction
	The analysis will include all DLco observations after baseline in the first 12 months of the study regardless of the treatment discontinuation status, with the exception that measurements made after the switch of treatment (eg, placebo patients	

Section # and Name	Description of Change	Brief Rationale
	switch to olipudase alfa after meeting the rescue criteria) will not be considered. For the primary analysis, missing data will not be imputed and will be assumed as Missing at Random (MAR). Similar analyses will be performed for the spleen volume (MN) and the splenomegaly-related symptom score (SRS), when baseline value of the spleen volume (or SRS) will be used as covariate. Descriptive assessment of MAR assumption and sensitivity analyses to assess the impact of missing data are described in the SAP.	
11.5.2.2 Secondary efficacy analyses	Handling of the missing data for secondary efficacy endpoints will be described in the SAP.	Clarification
11.5.5.1 Adverse events	Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order) and preferred term (PT) ~~sorted in alphabetical order for each treatment arm,~~ and the number and percentage of patients experiencing an AE. The number of ~~AEs~~TEAEs and annualized rate, and the number and proportion of patients reporting specific AEs will be tabulated for the overall analyses of AEs.	Clarification and correction
11.5.6.1 Pharmacokinetic analyses	As data permit, the following PK parameters as specified in Section 9.3.2.4 will be calculated for each patient and each dose of olipudase alfa ~~≥0.3 mg/kg~~.	
11.5.6.2 Pharmacodynamic analyses	Exploratory correlation analyses will be attempted to evaluate relationships between different PD markers and between sphingomyelin and /or lyso-sphingomyelin levels from different sources.	
11.5.6.3 Pharmacokinetics - pharmacodynamics	The PK-PD relationships may be explored graphically~~. If~~ and if a relationship is apparent, PK-PD modeling may be attempted and results reported, as appropriate. ~~If appropriate, the following parameters will also be assessed: Cmax and area under the effect-time curve.~~	Clarification and correction

Protocol Amendment 10 Version number: 1 (electronic 1.0) Date: 26-Jan-2018

This amendment is associated with Amended Clinical Trial Protocol 08.

Reason for Amendment:

1. Change in patient selection criteria to remove cirrhosis from Exclusion Criteria

In section(s): Clinical Trial summary- Study Population- Main selection Criteria- (Exclusion criteria); 1.2.1.1 Schedule of assessments: year 1 - PAP screening to Week 16, Selection of Patients; 7.2 Exclusion Criteria

Rationale: Cirrhosis was initially included as an exclusion criterion in olipudase alfa trials based on the spectrum of natural history of cirrhosis in ASMD patients.

Liver biopsies were included in these trials to monitor the potential acceleration of inflammatory disease from fibrosis to cirrhosis upon exposure to olipudase alfa, since known biologically active

intermediates, the direct catabolites of acid sphingomyelin are released upon treatment. This is also the key for the dose escalation process applied to all trials with olipudase alfa. However, unpublished data (on file) available from Year 3 biopsy of the long-term, open-label, treatment (extension study LTS13632, of phase 1b DFI13412 study) did not show evidence suggestive of a progressive worsening of fibrosis to cirrhosis in patients treated with olipudase alfa (see details in the table below).

Patient	Phase 1b Base Q2 2013	Phase 1b EOS Q4 2013 –Jan14	LTS (Year 3) Q1-Q3 2017
250-001-001	Changes are most consistent with stage 3 fibrosis Specimen <1.5 cm minimum length in SOM recommended to minimize sampling error	Changes are most consistent with stage 4 fibrosis (cirrhosis) Specimen <1.5 cm minimum length in SOM recommended to minimize sampling error	Changes compatible with stage 4 fibrosis (cirrhosis) NOTE: specimen length this time compliant with SOM Q3 2017
826-001-001	Changes are most consistent with stage 1 fibrosis Liver pathology **very similar to observed Phase I trial** (2007-2008). Little to no interval change is appreciated	Changes are most consistent with stage 1 fibrosis	Changes are most consistent with stage 2 fibrosis (Q2 17)
840-001-002	**No** cirrhosis present. Liver pathology very similar to observed Phase I trial (2007-2008)	Changes are most consistent with **stage 1** fibrosis Current liver pathology very similar to baseline	Changes are most consistent with **stage 1** fibrosis (Q2 17)
840-001-003	Changes are most consistent with stage 2 fibrosis Specimen <1.5 cm minimum length Liver pathology very similar to observed Phase I trial	Changes are most consistent with stage 3 fibrosis	Changes are most consistent with stage 3 fibrosis (Q1 17)
840-001-004	Changes are most consistent with **stage 2** fibrosis Liver pathology very similar to observed Phase I trial	Changes are most consistent with **stage 2** fibrosis	Changes are most consistent with **stage 3** fibrosis (Q2 17)

The DMC is regularly consulted and presented the updates results of the 5 adult patients in Trial LTS13632 and these results were presented in the listing.

Therefore, Sanofi Genzyme does not plan to conduct a liver biopsy at Year 5 in the Trial LTS13632 as it corroborated with the recommendation of the Liver Ad Board in April 2015.

Currently there is one patient treated in the extension study LTS13632 whose liver biopsy fibrosis stage is 4 (cirrhosis) with no reported issues.

As such, Sanofi Genzyme is proposing to remove the cirrhosis exclusion criterion from study DFI12712.

Removal of the cirrhosis exclusion criterion from this study will not impact the current schedule of safety assessments and liver biopsies will continue to be performed at baseline, Week 52, and Week 104 for documentation of entry status and disease progression.

Additionally, liver function tests criteria at entry and DLTs and stopping rules will remain unchanged. Patients with cirrhosis will still need to be in a compensated state, and must have liver functions, platelets, coagulation tests and other safety parameters values within the protocol acceptable ranges in order to enroll into study DFI12712.

While keeping all provisions in place to monitor patients' safety, it is important to evaluate the benefit of olipudase alfa in the population of ASMD patients with grade 4 fibrosis (cirrhosis) as part of the disease natural history in absence of safety risk.

Patient with liver biopsy diagnosed cirrhosis have not shown to have increased risk of adverse events from liver biopsy procedures versus patients without cirrhosis (Seeff et al, Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2013 September 12). Therefore, patients diagnosed with cirrhosis during screening liver biopsy will go through the subsequent protocol scheduled liver biopsy assessments at Week 52 and Week 104, unless there is other safety concern that can be discussed with the sponsor.

DMC recommendation on this proposed change:

This proposed change and rational was presented to DFI12712 DMC as it is presented in this document.

DMC chairman and members unanimously approved removing of cirrhosis for exclusion criteria for the reasons mentioned above.

2. Remove liver biopsy from assessments beyond Week 104

In section(s): 1.2.2.3 Schedule of assessments: ETP - year 3 until end of study;
9.3.1.1 Sphingomyelin in liver tissue

Rationale: Liver biopsy assessment is scheduled at the main study time points; baseline, Week 52, and Week 104. Liver biopsy assessment in these time points is set to follow the changes at histopathological and histochemical levels comparing olipudase alfa and placebo in PAP and one year thereafter in ETP. Beyond Year 2 assessments, there would be no need for further biopsy assessments every year based on the recent long term study results (LTS13632).

DMC recommendation on this proposed change:

This proposed change and rationale was presented to DFI12712 DMC as it is presented in this document.

DMC chairman and members unanimously approved removing of liver biopsy assessments beyond Week 104 of study participation for the rational mentioned above.

3. Change the secondary endpoints hierarchical order

In section(s): Clinical Trial summary- (Endpoints); 9.1.2 Efficacy Endpoints; 11.5.2.2 Secondary Efficacy Analysis; 11.5.4 Multiplicity Considerations

Rationale: SRS is included as a co-primary endpoint for US. For the rest of the world, it is among the secondary endpoints. The hypothesis testing for the secondary efficacy endpoints will proceed in a hierarchical fashion using the closed testing principle, and will stop if there is a nonsignificant comparison.

The study design was based on clinically important and meaningful change in most of the ASMD manifestations. While spleen size is standing as a primary endpoint as an important clinical assessment, liver size could follow as the next important organ change. Listed thereafter, are the clinical assessment of changes in platelet count, fatigue, pain and dyspnea. Then at the end, SRS would be sought as an expression of impact in organ size change.

It is not expected that SRS change would be significant, but only rather expected to show (as per protocol) a "trend" ($p \leq 0.15$). While a significant change would be expected for liver size change, followed by the other clinical changes. These important significant changes should not be missed in case SRS is not significant. Therefore, hierarchy is accordingly rearranged.

4. Clarify language of exclusion criteria

In section(s): Clinical Trial summary- Study Population- Main selection Criteria- (Exclusion criteria); 7.2, Exclusion Criteria

Rationale: correct previous omission of mentioning that cardiac valve dysfunction should be clinically significant to have the patient excluded.

In addition, other minor changes are listed in the description of changes (next section).

Protocol Amendment 09 Version number: 1 (electronic 1.0) Date: 24-Aug-2017

This amendment is associated with Amended Clinical Trial Protocol 07.

Reason for Amendment:

1. Change in 7.2 Exclusion Criteria to include patients with non-melanoma skin cancer and simplify language

In section(s): Clinical Trial summary; 7, Selection of Patients

Rationale: The original intention was to exempt patients with superficial skin cancer from exclusion due to malignancy diagnose in the past 5 years. This change is to correct having this exemption only limited to basal cell carcinoma and to include all types of non-melanoma skin cancer. In addition, language of exclusion criterion due to other medical conditions was simplified.

2. Add Lab Values that already are part of Adverse Events of Special Interest (AESIs) to the relevant sections and table

In section(s): 10.4.1.3 Adverse event of special interest; 10.4.2, General guidelines for reporting adverse events; Table 3, Summary of adverse event reporting instructions

Rationale: correct previous omission to include these lab values in corresponding sections describing AESIs.

3. Correct discrepancy of PK Collection

In section(s): 9.3.2.1, Pharmacokinetic sampling time

Rationale: correct previous omission as the sampling time was changed in the previous amendment to be ±3 hours for those samples taken ≥ 8 hours after infusion ends in the PK samples table, however this was omitted from change in the corresponding PK section and stayed as ±1 hour for those samples taken ≥ 8 hours after infusion ends.

4. Replace all instances of "after infusion" text with "after the end of infusion" where applicable.

In section(s): Clinical Trial summary; 1.2, Schedules of Assessments in multiple footnotes of multiple assessment flow chart tables; 9.3.2.1, Pharmacokinetic sampling time; 10.1, Visit Schedule

Rationale: Clarify that "after infusion" is intended to mean "after the end of infusion."

5. Delete an instructional text from an appendix.

In section(s): Appendix A, Guidance on contraceptive methods and collection of pregnancy information

Rationale: Correct previous omission

In addition, other minor changes are listed in the description of changes (next section).

Protocol Amendment 08 Version number: 1 (electronic 2.0) Date: 08-Feb-2017

This amendment is associated with Amended Clinical Trial Protocol 06.

1. Changes in objectives and endpoints

In section(s): Synopsis; 5, Study objectives; 9, Study endpoints,11, Statistical considerations

Rationale: Food and Drug Administration (FDA) request

2. Addition of Patient Global Impression of Symptom Severity (PGIS) of ASMD and Patient Global Impression of Change (PGIC)

In section(s): Synopsis; 1.2, Schedules of assessments; 9.1.3, Tertiary and exploratory efficacy endpoints; 9.1.4.13, Health-related quality of life questionnaires; 10.1, Visit schedule

Rationale: FDA request

3. Changes in statistical analysis

In section(s): Synopsis: 11, Statistical considerations

Rationale: Based on discussions with FDA to include the splenomegaly-related score (SRS) in the combination spleen endpoint and to show the results as a "trend" when relevant. Therefore, the analysis was changed from truncated Hochberg to Hochberg.

4. Clarification of time points at which vital signs should be taken

In section(s): 1.2, Schedules of assessments

Rationale: Correction of error in the previous version.

5. Addition of rules on how to resume study drug administration in patients who have missed infusion

In section(s): 8.1.3.2, Dosing delays or missed doses

Rationale: Rules were omitted in the previous protocol version (but were provided in the Interactive [Voice or Web] Response System [IXRS] documents).

6. Change in some of the dose limiting toxicity (DLT) conditions

In section(s): 8.1.4, Dose-limiting toxicities; 10.4.4.1, Reporting of adverse events of special interest with immediate notification

Rationale: The new rules take into account that patients may enter the study with abnormal liver function tests (LFTs) due to their ASMD. As a result, these patients could meet a DLT condition due to normal fluctuation in LFTs that would not otherwise be indicative of DLT. The new rules have been approved by the Data Monitoring Committee.

7. Change in assessments to be done before rescue treatment is applied

In section(s): 8.1.6, Rescue treatment

Rationale: Correction of error in the previous version.

8. Addition of recommendation on usage of cationic amphiphilic antihistamines in rules on concomitant medications

In section(s): 8.8, Concomitant medication

Rationale: These medications are commonly used.

9. Addition of tobacco use monitoring

In section(s): 1.2, Schedules of assessments

Rationale: To assess the possible effect on ASMD-related lung disease

Protocol Amendment 07 Version number: 02 (electronic 2.0) Date: 01-Feb-2016

This amendment is associated with Amended Clinical Trial Protocol 05**.**

Reasons for the Amendment:

1. Remove 1.0 mg arm from the primary analysis period (PAP)

In section(s): Clinical trial summary (Study design, Statistical considerations), 6.1, 8.1.3.3, 8.4, 11.2, 11.5.4

Rationale: The planned number of patients randomized to the 3mg/kg olipudase alfa and placebo arms was increased from 14 per arm to 18 per arm. To accommodate this increase while not substantially enlarging the planned sample size, the 1mg/kg olipudase alfa arm was removed from the study design. The rationale for this change is to increase the likelihood that a clear demonstration of efficacy or lack of efficacy is achieved with respect to the primary and secondary efficacy endpoints and to avoid ambiguous results related to underpowered endpoints. The assumptions used to determine the sample size for the spleen volume endpoint were informed by the results from several clinical trials conducted in patients with lysosomal storage disorders (ie, Gaucher disease). This is in contrast to the assumptions used to determine the power of the other primary endpoint, DLco, and important secondary efficacy endpoints such as splenomegaly-related symptoms where minimal information was available. In situations where insufficient information exists for robust sample size determination, an increase in sample size is warranted.

While efficacy and safety information from the 1 mg/kg olipudase alfa arm is of interest, it does not outweigh the importance of enabling the study to achieve the primary efficacy objective should olipudase alfa be as effective as the results from the Phase 1b study suggest. In addition, the increase in the number of patients treated with 3 mg/kg olipudase alfa in the primary analysis period and in the extension study will improve the understanding of the safety profile of the dose that is intended for use assuming regulatory approval.

2. Remove 1.0 mg arm from the extended treatment period (ETP)

In section(s): Clinical trial summary (Study design, Statistical considerations), 6.1, 8.1.3.3, 8.4, 11.2, 11.5.4

Rationale: To maintain consistency with the PAP

3. Remove "dose comparison."

In section(s): Title page, Clinical trial summary (Title, Study design)

Rationale: The 1.0 mg arm is no longer part of the study and hence the study is no longer designed to compare doses.

4. Remove "of different doses."

In section(s): Clinical trial summary (Study objectives, Primary objective), 5.1

Rationale: The 1.0 mg arm is no longer part of the study

5. Change randomization ratio from 2:1:2 to 1:1 during the PAP.

In section(s): Clinical trial summary (Statistical considerations [sample size determination]), 6.1, 8.4, 11.2

Rationale: Removing the 1 mg/kg arm in the PAP resulted in a necessary change in the randomization to 1:1. During the 4 year ETP, all patients will receive olipudase alfa.

6. Add inclusion criterion for mean splenomegaly-related symptoms score

In section(s): Clinical trial summary (Study population [Inclusion criteria]), 7.1

Rationale: To increase the statistical power of the evaluation of the secondary endpoint, "Change in splenomegaly-related symptom score from baseline to week 52".

7. Add contraception requirements following the last olipudase alfa infusion.

In section(s): Clinical trial summary (Study population, Main selection criteria, Inclusion criteria), 7.1, 10.3

Rationale: Conventionally, true abstinence or contraception is required during the treatment period and following the last administration for at least 5 multiples of the investigational product's half-life. Based upon the 24-hour half-life of olipudase alfa, the minimum duration for requiring contraception use is 5 days following the last infusion. To be conservative, the period of time that each patient will be required to either practice true abstinence or use 2 acceptable, effective methods of contraception was expanded to include 15 days after the patient's last olipudase alfa infusion.

8. Clarify that the longest study duration per patient will be for at least 3 years and up to 5 years and 3 months dependent upon continued regulatory approval of the protocol.

In section(s): Clinical trial summary (Duration of study period [per patient]), 6.2.1

Rationale: Previous text can be interpreted as allowing patients to be in the study for only 3 years, so clarification was added.

9. Changed interim analysis wording from "interim analysis may be conducted" to "no interim analysis is planned."

In section(s): Clinical trial summary (Statistical considerations, Interim analysis), 6.3

Rationale: An interim analysis was initially planned for when 20 patients completed the primary analysis period. The purpose of such an interim analysis was to potentially accelerate regulatory approval of olipudase alfa. Given the numerous operational and statistical challenges associated with such a strategy, and given the need for a robust benefit risk determination, it was decided that an interim analysis strategy was not justified.

10. Clarify patient stopping criteria

In section(s): 8.1.5

Rationale: The role of the DMC in an emergency is to review safety data and recommend stopping the study if necessary to ensure patient safety. However, this does not limit the ability of investigators to make an immediate decision to discontinue dosing in an individual patient due to an any AE that raises significant concern regarding the safety of olipudase alfa, as described in Section 8.1.4 of the protocol.

Protocol Amendment 06 - DE Version number: 01 (electronic 1.0) Date 28-Sep-2015

This amendment applies to Germany and is related to Amended Clinical Trial Protocol 05-DE.

Reasons for the Amendment:

The change to the procedures reflects the removal of the conventional chest X-ray performed simultaneously with the Pulmonary HRCT Scan as requested by the Radiation Board of Germany (BfS).

Protocol Amendment 05 - GB Version number: 1 (electronic 1.0) Date: 22-Jul-2015

This amendment applies to the United Kingdom and is related to Amended Clinical Trial Protocol 05-GB.

REASON FOR AMENDMENT

- **Clarification to the length of the trial**

In section(s): Summary [Study Design section], Sections 6.1 and 6.2.1 of the protocol

Rationale: According to Medicines & Healthcare products Regulatory Agency (MHRA), patients may only be included for 3 years so clarification was added to the protocol

- **Patient stopping criteria updated to include timing of reporting to regulatory authority**

In section(s): Section 8.1.5

Rationale: According to Medicines & Healthcare products Regulatory Agency (MHRA), timing of reporting needed to be clarified.

- **Addition of contraception requirements following the last olipudase alfa infusion**

In section(s): Synopsis, Section 7.1 Inclusion criteria, and Section 10.3 of the protocol

Rationale: Conventionally, true abstinence or contraception is required during the treatment period and following the last administration for at least 5 multiples of the investigational product's half-life. Based upon the 24 hour half-life of olipudase alfa, the minimum duration for requiring contraception use is 5 days following the last infusion. To be conservative, the period of time that each patient will be required to either practice true abstinence or use 2 acceptable, effective methods of contraception was expanded to include 15 days after the patient's last olipudase alfa infusion.

Actual changes to text are shown in the description of changes.

Protocol Amendment 04 Version number: 1 (electronic 1.0) Date: 31-Mar-2015

This amendment is associated with Amended Clinical Trial Protocol 04.

Reason for Amendment:

- **Addition of a splenomegaly-related symptom efficacy endpoint**

In section(s): Clinical trial summary, study flow charts, Section 5.2, Section 9.1.2, Section 9.6

Rationale: Per the FDA's guidance, for reduction in spleen volume to be considered clinically meaningful and considered a primary endpoint, it would need to be combined with improvements in splenomegaly-related symptoms (eg, abdominal pain, early satiety, etc) in the subset of patients with these symptoms

- **Change in the tools used to collect information for the composite secondary efficacy endpoint and include use of an eDiary**

In section(s): Clinical trial summary, study flow charts, Section 4, Section 5.2, Section 9.1.2, Section 9.1.4

Rationale: According to the FDA, for reduction in spleen volume to be considered clinically meaningful and considered a primary endpoint, it would need to be combined with improvements in splenomegaly-related symptoms (eg, abdominal pain, early satiety, etc) in the subset of patients with these symptoms; The FDA also considers the CRQ-SAS to be too broad and suggests using the FACIT-dyspnea short form. Per the FDA's guidance, select questions from the myelofibrosis symptom assessment form, the FACIT-dyspnea Short form, and additional questions on abdominal body image and ability to bend down will be asked in an eDiary.

- In the composite endpoint, replace the dyspnea questions from CRQ-SAS with the FACIT-dyspnea Short form
- In the composite endpoint, replace the Niemann-Pick Health Assessment questionnaire with splenomegaly-related symptoms from a modified myelofibrosis symptom assessment form
- Include only items 3 of the Brief Pain Inventory – Short form and the Brief Fatigue Inventory in the composite endpoints

- **Clarify that abdominal MRIs and pulmonary imaging by HRCT will be evaluated by readers blinded to patient, treatment arm, and timepoint.**

In section(s): Section 9.1.4 Assessment of efficacy endpoints

Rationale: Ensure efficacy endpoint assessment will be nonbiased

- **Demote to tertiary the secondary efficacy endpoint percentage change in liver function tests ALT and total bilirubin**

In section(s): Clinical trial summary, Section 5.2, Section 9.1.2, Section 9.1.3

Rationale: To restrict the number of secondary efficacy endpoints

- **Remove requirement that inpatient hospitalization is necessary during quarterly visits of years 3 through 5**

In section(s): Clinical trial summary, study flow charts, Section 6.1, Section 8.1.1, Section 10.1

Rationale: Reduce patient burden

- **Added a provision for future use of samples**

In section(s): Section 9.5

Rationale: To allow for other research analyses to be used on left over samples from consenting patients.

- **Correct reporting requirements for pregnancy**

In section(s): Section 10.4.2

Rationale: To instruct clinical sites to complete the AE form and safety complementary form as well as other specific forms in the event of pregnancy.

- **Clarify the "Not applicable" taken regarding action to study drug for an adverse event**

In section(s): Section 10.4.1.4

Rationale: Sites were misusing the "not applicable" field of the eCRF when reporting action taken regarding the study drug.

- **Change from the Wilcoxon Mann Whitney test to the ANCOVA method for primary and secondary efficacy endpoint analyses**

In section(s): Section 11.5.2 and clinical trial summary

Rationale: Based on feedback from FDA and the CHMP advice letter, the protocol has been modified so that the mITT population includes patients who were randomized and treated.

Protocol Amendment 03 Version number: 1 (electronic 1.0) Date: 28-Jan-2015

This amendment is associated with Amended Clinical Trial Protocol 03.

Reason for Amendment:

- **New EudraCT number**

In section(s): Cover page

Rationale: Upon feedback from countries that use the EudraCT system, a new CTA based on protocol amendment 3 is being submitted with a new EudraCT number.

Protocol Amendment 2 Version number: 1 (electronic 1.0) Date: 05-Dec-2014

This amendment is related to Amended Clinical Trial Protocol 02.

Reason for Amendment:

- **Change in rhASM nomenclature**

In section(s): All sections

Rationale: The WHO recommends the INN name olipudase alfa for recombinant human acid sphingomyelinase deficiency.

- **The primary endpoint was modified to include change from baseline to week 52 in infiltrative lung disease as measured by the diffusing capacity of carbon monoxide (DL_{CO})**

In section(s): Clinical trial summary, Section 4, Section 5.1, Section 9.1.1, Section 9.6, Section 11.2, Section 11.5.2.1

Rationale: The clinically relevant pulmonary function test, DL_{CO}, was added to the pharmacodynamic marker change in spleen volume. The primary analyses of the 2 primary endpoints were adjusted accordingly.

- Inclusion criterion #04 has been adjusted to allow patients with more severe infiltrative lung disease to be enrolled in the study.
- Added Exclusion criteria #12 and #13 around ventilatory support to ensure patients can participate in the DLCO assessment

- **Removal of the key secondary endpoint and reorganize the secondary endpoints**

In section(s): Clinical trial summary, Section 5.2, Section 9.1.2, Section 9.6, Section 11.5.2.2

Rationale: With the promotion of change in DL_{CO} to primary endpoint, the secondary endpoints, including the key secondary endpoint, were reorganized. The analyses of secondary endpoints were adjusted accordingly.

- **Added a PK sampling timepoint**

In section(s):

Rationale: A PK sampling at 168 hours postinfusion has been added to more fully characterize AUC.

- **Increase the number of enrolled patients from approximately 24 to approximately 35**

In section(s): Clinical trial summary, Section 1.1.1, Section 6.1, Section 8.4, Section 11.2

Rationale: The sample size was increased to provide the power necessary to see a treatment effect for the DLCO primary endpoint

- Remove the 0.3 mg/kg treatment arm.
- Randomization ratio in the PAP changed from 1:1:1:1 (placebo, 0.3, 1.0, 3.0 mg/kg olipudase alfa) to 2:1:2 (placebo, 1.0 mg/kg, 3.0 mg/kg olipudase alfa)
- Remove patient stratification by baseline spleen volume

- **Remove requirement to stratify patients based on baseline spleen volume**

In section(s): Clinical trial summary, Section 6.1, Section 6.3, Section 8.4, Section 11.5.2.1, Section 11.5.2.2

Rationale: Simplify statistical calculations.

- **Patients assigned to the placebo arm in the PAP will be rerandomized 1:1 in the ETP to 1.0 mg/kg or 3.0 mg/kg olipudase alfa.**

In section(s): Clinical trial summary, Section 1.1.2, Section 6.1

Rationale: To more fully characterize the safety and efficacy of the 1.0 mg/kg olipudase alfa dose.

- Remove the olipudase alfa target dose selection in the ETP

- **Add an interim analysis of the primary endpoint after approximately 20 patients complete 52 weeks of treatment with study drug**

In section(s): Clinical trial summary, Section 6.3

Protocol Version number: 1 (electronic 1.0) Date: 05-Sep-2014

This amendment is related to Amended Clinical Trial Protocol 01.

- **Modification of study title**

In section(s): Title page; Synopsis; page headers.

Rationale: The protocol title has been changed to reflect the new study design and objectives.

- **Modification of study organization**

In section(s): All sections

Rationale:

- The 1 treatment period of 52 weeks in the original protocol has been increased to 2 treatment periods in the amended protocol: a primary analysis period (PAP) of 52 weeks, which will be followed by an extended treatment period (ETP) lasting for total study duration of up to 5 years.
- The dose escalation scheme has been updated to include a second 0.6 mg/kg dose to mitigate possible toxicity from sphingomyelin degradation that occurs too quickly. In the phase 1b study, DFI13412, infusion-associated reactions were more frequent when starting this dose and required dose-repetition or dose-reduction at next scheduled study infusions of higher doses. Accordingly, patients randomized to the 3.0 mg/kg treatment arm will not be fully dose escalated until study week 16. Consequently, study procedures scheduled for the week 12 quarterly visit have been shifted to week 14.
- In the original protocol, patients were to be randomized to a target dose 0.3, 1.0, or 3.0 mg/kg rhASM after the second 0.3 mg/kg infusion. In the amended protocol, patients will be randomized before the patient's first infusion with study drug.

- **Modification of study design**

In section(s): All sections

Rationale: All sections have been updated to the new study design.

- The original protocol was open-label. The amended protocol is double-blinded during the entire primary analysis period and initially during the extended treatment period.
- The original protocol did not include a placebo arm and was to enroll at least 15 patients 1:1:1 into 1 of 3 treatment arms: 0.3, 1.0, or 3.0 mg/kg rhASM. The number of patients in

the amended protocol has increased to approximately 24 patients who will be equally randomized to placebo, 0.3, 1.0, or 3.0 mg/kg rhASM.

- The original protocol did not have a crossover feature. In the amended protocol, patients randomized to the placebo arm during the PAP will crossover to the 3.0 mg/kg treatment arm during the ETP.
- Patients will be stratified based on baseline spleen volume into 1 of 2 groups before randomization in the amended protocol.
- Rescue criteria have been included for patients who experience clinical decline.

- **Modification of study objectives**

In section(s): tabulated clinical trial summary, Section 5 of the protocol

Rationale: The primary objective has been changed to an efficacy objective. A key secondary objective has been added.

- **Changes to the assessments**

In section(s): Section 1.2, Section 5, Section 9

Rationale: Because no serious adverse events or adverse events with severe intensity were observed in a prior clinical trial (DFI13412), the intensive monitoring for safety has been reduced. Other assessments have been added and those not relevant to characterizing the effect of study drug treatment based on past experience have been eliminated:

- The time spent hospitalized during quarterly visits as an in-patient was reduced from 48- to 24 hours after study drug infusion.
- 24-hour Holter monitoring and heart rate monitoring by telemetry have been eliminated.
- Electrocardiograms were reduced from triplet to singlet measurements 4, 12, and 24 hours after study drug infusion during quarterly visits.
- CRIM testing and X-rays of lumbar spine have been deleted.
- The following health-related quality of life questionnaires have been added: Chronic Respiratory Questionnaire - Self Administered - Standard Activities, Health-related productivity questionnaire, Short Form-36 Health Survey, Brief Fatigue Inventory, and Brief Pain Inventory - Short Form.
- Cycle ergometry has been changed to treadmill ergometry to accommodate sites that do not have a cycle ergometer.

Signature Page

dfi12712-16-1-1-amended-protocol13

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