Official Title:	A Phase 3 Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of Intravenous Infusions of ATB200 Co-Administered with Oral AT2221 in Adult Subjects With Late-Onset Pompe Disease
NCT Number:	NCT04138277
Document Date:	Amendment 3: 10 December 2024

CLINICAL STUDY PROTOCOL

A PHASE 3 OPEN-LABEL EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF INTRAVENOUS ATB200 CO-ADMINISTERED WITH ORAL AT2221 IN ADULT SUBJECTS WITH LATE-ONSET POMPE DISEASE

Protocol Number: ATB200-07

Amendment 3: 10 December 2024
(Supersedes Amendment 2: 26 April 2023)

EudraCT Number: 2019-000954-67
EU CTR # 2023-505170-15-00
US IND Number: 127,387

Compounds: ATB200 (cipaglucosidase alfa) and AT2221 (miglustat)

Sponsor
Amicus Therapeutics, Inc.
47 Hulfish Street
Princeton, NJ 08542, USA

DOCUMENT HISTORY

Protocol ATB200-07 Document History

Document Number	Document Date
Amendment 2	26 April 2023
Amendment 1	2 October 2020
Original Protocol	25 March 2019

SUMMARY OF CHANGES TO THE PROTOCOL

The previous version of this document (Amendment 2: 26 April 2023) was modified to create the current version (Amendment 3: 10 December 2024).

Table 1: Summary of Changes to the Protocol

Document History	
Version and Date of Document	**Comments**
Original Version: 25 March 2019	
Amendment 1: 2 October 2020	• Administrative updates • Update to number of study sites • Update to study objectives • Removal of text related to new subjects in Japan • Addition of COVID-19-related changes • Clarification to inclusion criteria • Clarification to duration of treatment • Addition of efficacy endpoint (6-minute walk distance predicted value) • PK endpoints revised • Summary of known and potential risks and benefits updated following HA request • Withdrawal criteria updated • Subjects of reproductive potential updated • New physical description of miglustat added • Temperatures for study drug storage revised • Clarification for weight collection for calculation of miglustat dose • Schedule of assessments updated • Separate PK sampling schedule included for Japanese subjects • Infusion visits and home infusion visits updated • Retrospective data collection removed • Clarification for how adverse events during Study ATB200-03 that are still ongoing in this study will be recorded • Clarification to overdose/underdose included • Informed consent text revised

Table 1: Summary of Changes to the Protocol (Continued)

Document History	
Version and Date of Document	**Comments**
Amendment 2: 26 April 2023	• Administrative updates • Study end date extended • Analysis population definitions updated • Statistical methods section updated to refer to the statistical analysis plan • Addition of text to comply with EU clinical trial regulation requirements • Duration of study updated • Addition of definition of study completer • Clarification to withdrawal criteria • Update to study drug storage for temperature incursions • Cipaglucosidase alfa section updated to clarify an inconsistency regarding the weight entry • Miglustat section updated to clarify inconsistency regarding weight entry and additional dosing instructions • Prohibited medications list updated • Schedule of assessments updated • Infusion visits and home infusion visits section updated • End of study and early termination section updated • Follow-up period section updated • Text added for data privacy regulations • Clarification added to immunogenicity assessments section • Adverse event assessment of severity updated to align with the electronic case report form • Clarification of overdose/underdose definitions • Clarification to missed dose section • Addition of text for EU general data protection regulation requirements

Table 1: Summary of Changes to the Protocol (Continued)

Document History	
Version and Date of Document	**Comments**
Amendment 3: 10 December 2024	The purpose of this amendment is to continue collecting long-term safety and efficacy data on LOPD subjects treated with cipaglucosidase alfa/miglustat while decreasing some of the burden on those subjects taking part, and continuing to provide treatment where regulatory approval has not yet been granted or the product is not yet commercially available. Subjects may continue in this study until commercial cipaglucosidase alfa/miglustat becomes available in their country as a treatment for Pompe patients. • Administrative updates • Removal of COVID-19-related procedures • Duration of treatment updated • Definition of the end of study updated to include that the CSR will be written based on a data cutoff date of 31 December 2024. Any data collected after the data cutoff date will be provided as an addendum to the final CSR. • Clarification to infusion visits and home infusion visits section • Appendix added for subjects who continue in the study after Amendment 3 is approved. Information includes: – Objectives to align with reducing the burden of participation for subjects – Reduced efficacy assessments updated to align with reducing the burden of participation for subjects – A new schedule of assessments for subjects who continue in the study – Data analysis and statistical considerations for subjects continuing in the study

Abbreviations: COVID-19 = Coronavirus disease 2019; CSR = clinical study report; HA = health authority; LOPD = late-onset Pompe disease; PK = pharmacokinetic

Table 2: Serious Adverse Event Contact Information

Role	**Contact Information**
Reporting of serious adverse events	**Safety FAX number:** +1 866-422-1278 **Email address:** safetyreporting@amicusrx.com

2. DECLARATIONS OF SPONSOR AND INVESTIGATOR

2.1. Declaration of Sponsor

This clinical study protocol is subject to critical review and has been approved by Amicus Therapeutics (Amicus).

The information it contains is consistent with the following:

- the current benefit-risk evaluation of ATB200 (cipaglucosidase alfa, recombinant human acid α-glucosidase) co-administered with AT2221 (miglustat, *N*-butyl-deoxynojirimycin)
- the moral, ethical, and scientific principles governing clinical research, as set out in the current version of Declaration of Helsinki and the principles of Good Clinical Practice (GCP) described in the United States (US) Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312 and in the International Council on Harmonisation (ICH) GCP E6 guidelines

The investigator will be supplied with details of any significant or new findings related to treatment with cipaglucosidase alfa co-administered with miglustat.

17 December 2024 | 09:03 EST

Date: _____ Signature: [redacted]

Amicus Therapeutics

2.2. Declaration of Investigator

I confirm that I have read this clinical study protocol. I understand it, and I will work according to the moral, ethical, and scientific principles governing clinical research, as set out in the Declaration of Helsinki and the principles of GCP described in the US CFR Parts 50, 54, 56, and 312 and in the ICH GCP E6 guidelines. I will also work in accordance with applicable local requirements.

Date: _____ Signature: _____

Printed Name: _____

3. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Amicus Therapeutics (Amicus)

Name of Investigational Products: ATB200 (cipaglucosidase alfa) and AT2221 (miglustat)

Name of Active Ingredients:

Cipaglucosidase alfa: Recombinant human acid α-glucosidase (rhGAA)

Miglustat: *N*-butyl-deoxynojirimycin

Cipaglucosidase alfa/miglustat: cipaglucosidase alfa co-administered with miglustat

Title of Study: A Phase 3 Open-label Extension Study to Assess the Long-term Safety and Efficacy of Intravenous ATB200 Co-administered with Oral AT2221 in Adult Subjects with Late-onset Pompe Disease

Study Sites: Up to approximately 59 sites globally

Phase of Development: 3

Objectives:

This amendment aims to continue collecting long-term safety and efficacy data on LOPD subjects treated with cipaglucosidase alfa/miglustat while reducing subject burden and providing treatment where regulatory approval or commercial availability is pending. The objectives for the study are presented here and the objectives for the amendment are provided in Appendix 1.

Primary

The primary objective of this study is to assess the long-term safety and tolerability of ATB200 (cipaglucosidase alfa)/AT2221 (miglustat) co-administration.

Secondary

The secondary objectives of this study are as follows:

- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on ambulatory function, as measured by the 6-minute walk test (6MWT)
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on pulmonary function, as measured by sitting forced vital capacity (FVC) (% predicted)
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on muscle strength
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on health-related patient-reported outcomes
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on motor function
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on overall clinical impression, as assessed by both physician and subject
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on measures of pulmonary function other than FVC (% predicted)
- to assess the long-term effect of cipaglucosidase alfa/miglustat co-administration on biomarkers of muscle injury and disease substrate
- to assess the immunogenicity of cipaglucosidase alfa/miglustat co-administration

- to characterize the pharmacokinetics (PK) of cipaglucosidase alfa and miglustat and using plasma total GAA protein level by signature peptide and plasma miglustat concentration assays in subjects at sites in Japan only

Methodology:

This is a multicenter, international open-label extension study of cipaglucosidase alfa/miglustat in adult subjects with late-onset Pompe disease (LOPD) who completed Study ATB200-03.

The final analysis of the complete data set will be performed for the final CSR based on a data cutoff date of 31 December 2024. Upon approval of this amendment, any subjects continuing in the study will follow an updated Schedule of Assessments (Appendix 1). An addendum to the final CSR will be produced once the remaining subjects have completed the study.

For subjects who participated in Study ATB200-03, the first infusion visit in this study should be scheduled approximately 2 weeks after the last visit in Study ATB200-03 in an effort to ensure continued administration of study drug on the same schedule with no gap between studies. Infusion visits for administration of study drug will be scheduled every 2 weeks throughout the study; assessments (eg, clinical laboratory tests) for monitoring of initial safety will be performed at these infusion visits for the first 6 weeks of the study. Subjects may be eligible for administration of study drug at their home after 3 months in the study if they have not had a moderate to severe infusion-associated reaction (IAR) during those 3 months. During the conduct of the study, the SARS-CoV-2 (COVID-19) pandemic emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. With the intention of maintaining regular infusions, home infusions will be allowed prior to completing Week 12 wherever possible for subjects who may be eligible. If infusions were missed near the scheduled assessments on Week 12, Week 26, or at any of the study visits scheduled every 26 weeks after Week 26, it should be communicated with Amicus on a case-by-case basis to determine whether catch-up infusions are needed and how many catch-up infusions are needed prior to the study assessments. Study visits that include efficacy, safety, and other assessments will be scheduled approximately every 3 months for the first 6 months, then every 6 months thereafter. These visits may occur over 2 days, provided all study assessments and procedures (with the exception of PK sample collection) are performed before administration of study drug.

Efficacy assessments (ie, functional assessments) include evaluation of ambulatory function (6MWT), motor function tests (Gait, Stairs, Gowers' maneuver, and Chair [GSGC] test and Timed Up and Go [TUG] test), muscle strength (manual muscle testing and quantitative muscle testing), and pulmonary function tests (forced vital capacity [FVC], slow vital capacity [SVC], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and sniff nasal inspiratory pressure [SNIP]). Patient-reported outcomes include the Rasch-built Pompe-specific Activity (R-PAct) Scale, EuroQol 5 Dimensions-5 Levels Instrument (EQ-5D-5L), Patient-reported Outcomes Measurement Information System (PROMIS®) instruments for physical function, fatigue, dyspnea, and upper extremity, and Subject's Global Impression of Change (SGIC). The Physician's Global Impression of Change (PGIC) will also be performed. Pharmacodynamic (PD) assessments include measurement of biomarkers of muscle injury (creatine kinase [CK]) and disease substrate (urinary hexose tetrasaccharide [Hex4]). Blood samples for PK assessment of total GAA protein and miglustat concentration in plasma will be collected from subjects at sites in Japan only. Safety assessments include monitoring of adverse events (AEs), including IARs, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, physical examinations including weight, electrocardiograms (ECGs), and immunogenicity. Concomitant medications and nondrug therapies will also be recorded.

Number of Subjects (Planned):

The maximum sample size for this study is based on the number of subjects who complete Study ATB200-03, estimated to be approximately 110 subjects.

Diagnosis and Main Criteria for Inclusion:

Subjects Who Participated in Study ATB200-03

Inclusion Criteria

1. Subject must provide signed informed consent prior to any study-related procedures being performed. If the subject is under 20 years of age, the subject must provide written informed consent. In Japan, the subject's parental guardian (or legal representative) must also sign the informed consent form.
2. Subject must have completed Study ATB200-03.

   Note: Subjects who were forced to withdraw from Study ATB200-03 for a logistical reason not related to the efficacy or safety of cipaglucosidase alfa/miglustat (eg, hospitalization for a car accident, COVID-19 pandemic, or emergency surgery) and which resulted in several consecutive missed doses may be eligible to participate in this study upon approval by the Amicus medical monitor.
3. Female subjects of childbearing potential and male subjects must agree to use medically accepted methods of contraception during the study and for 90 days after the last dose of study drug.

Exclusion Criteria

1. Subject plans to receive gene therapy or participate in another interventional study for Pompe disease.
2. Subject has a hypersensitivity to any of the excipients in cipaglucosidase alfa or miglustat, or has a medical condition or any other extenuating circumstance that may, in the opinion of the investigator or medical monitor, pose an undue safety risk to the subject or may compromise his/her ability to comply with or adversely impact protocol requirements. This includes clinical depression (as diagnosed by a psychiatrist or other mental health professional) with uncontrolled or poorly controlled symptoms.
3. Subject, if female, is pregnant or breastfeeding.
4. Subject, whether male or female, is planning to conceive a child during the study.

Investigational Product, Dosage, and Mode of Administration:

Cipaglucosidase alfa/miglustat will be co-administered as follows: miglustat 260 mg (4 × 65-mg oral capsules) for subjects weighing ≥ 50 kg and 195 mg (3 × 65-mg oral capsules) for subjects weighing ≥ 40 kg to < 50 kg, followed approximately 1 hour later by cipaglucosidase 20 mg/kg (reconstituted lyophilized drug product, 105 mg/vial), administered over a 4-hour intravenous [IV] infusion. The cipaglucosidase alfa/miglustat combination regimen will be administered every 2 weeks.

Note: Subjects are required to fast at least 2 hours before and 2 hours after administration of miglustat.

Duration of Treatment:

Treatment with open-label cipaglucosidase alfa/miglustat will be administered within this study protocol until one of the following conditions apply:

- the product is approved and commercialized for use in the investigational study population, or
- cipaglucosidase alfa/miglustat is rejected by the regulatory authority in the subject's local country as an approved treatment for Pompe disease, or
- the sponsor decides to continue to provide cipaglucosidase alfa/miglustat via a post-trial access mechanism, or

- the subject is withdrawn or withdraws consent, or
- the sponsor decides to end the study.

Reference Therapy, Dosage, and Mode of Administration:

None.

Criteria for Evaluation:

The long-term safety profile of cipaglucosidase alfa/miglustat will be characterized using incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation of study drug, frequency and severity of immediate and late IARs, and any abnormalities noted in other safety assessments (eg, clinical laboratory tests, ECGs, vital signs). Immunogenicity to cipaglucosidase alfa will also be described.

Efficacy endpoints are as follows:

- change from baseline 6-minute walk distance (6MWD)
- change from baseline in 6MWD (% predicted)
- change from baseline in sitting FVC (% predicted)
- change from baseline in the manual muscle test score for the lower extremities
- change from baseline in the total score for the PROMIS – physical function
- change from baseline in the total score for the PROMIS – fatigue
- change from baseline in the following variables related to motor function:
  - GSGC total score
  - time to complete the 10-meter walk (ie, assessment of gait) of the GSGC test
  - time to complete the 4-stair climb of the GSGC test
  - time to complete the Gowers' maneuver of the GSGC test
  - time to arise from a chair as part of the GSGC test
  - change from baseline in the time to complete the TUG test
- change from baseline in the following variables related to muscle strength:
  - manual muscle test score for the upper extremities
  - manual muscle test total score (upper and lower extremities combined)
  - quantitative muscle test value (kg) for the upper extremities
  - quantitative muscle test value (kg) for the lower extremities
  - quantitative muscle test total value (kg) (upper and lower extremities combined)
- change from baseline in the following variables from patient-reported outcome measures:
  - total score for the PROMIS – dyspnea
  - total score for the PROMIS – upper extremity
  - R-PAct Scale total score
  - EQ-5D-5L health status
- actual value of the subject's functional status (improving, stable, or declining) pertaining to the effects of study drug in the following areas of life, as measured by the SGIC:
  - overall physical well-being
  - effort of breathing

  - muscle strength
  - muscle function
  - ability to move around
  - activities of daily living
  - energy level
  - level of muscular pain
- actual value of the subject's functional status (improving, stable, or declining), as measured by the PGIC
- change from baseline in the following measures of pulmonary function, as follows:
  - sitting SVC (% predicted)
  - MIP (cmH_2O)
  - MIP (% predicted)
  - MEP (cmH_2O)
  - MEP (% predicted)
  - SNIP (cmH_2O)

Pharmacodynamic endpoints are as follows:

- change from baseline in serum CK level
- change from baseline in urinary Hex4 level

Pharmacokinetic endpoints (applicable for subjects at sites in Japan only):

- sparse blood sampling for determination of total GAA protein levels and miglustat concentrations in plasma for a population PK analysis

Pharmacokinetic endpoints derived from a population PK analysis of total GAA protein and miglustat concentrations will be provided in a separate modeling and simulation plan.

Statistical Methods:

Analysis Populations

The open-label extension enrolled subjects (OLE-ES) is a subset of the ATB200-03 intent-to-treat (ITT) population, and it includes all subjects who satisfied the eligibility requirements (based on the inclusion and exclusion criteria) and entered Study ATB200-07. This population will be used for the analyses of all efficacy and pharmacodynamic endpoints involving Studies ATB200-03 and ATB200-07 integrated data.

The open-label extension full analysis set (OLE-FAS) includes all subjects who entered the OLE Study ATB200-07 who had both a valid baseline and at least one post-baseline assessment for at least 1 of these efficacy endpoints (6MWD, sitting % predicted FVC, MMT-lower extremities, PROMIS – physical function, PROMIS – fatigue, and GSGC). This analysis set will be used for the analyses of the main efficacy and pharmacodynamic endpoints involving Study ATB200-07 stand-alone data.

The open-label extension safety population includes all subjects who took at least 1 dose of cipaglucosidase alfa/miglustat co-administration in Study ATB200-07. This population will be used for the summaries of medical history, drug exposure, and any other specific safety-related summaries for Study ATB200-07 stand-alone data.

The safety population consists of all subjects who took at least 1 dose of study drug in either Study ATB200-03 or Study ATB200-07. This population will be analyzed per the actual treatment received and will be used for all integrated safety summaries.

The treatment switched population is defined as subjects who were randomized to and received alglucosidase alfa/placebo in Study ATB200-03 and subsequently received cipaglucosidase alfa/miglustat in Study ATB200-07. This population will be used for specific analyses involving these treatment-switched subjects.

Treatment Groups

Appropriate reporting treatment groups will be defined in the statistical analysis plan for all analyses involving ATB200-07 stand-alone data as well as ATB200-03 and ATB200-07 integrated data.

Efficacy Analyses

In general, continuous data will be summarized using descriptive statistics, and categorical data will be summarized using counts and percentages. Specific analysis details and display format will be described in the statistical analysis plan.

Ambulatory Function, Motor Function, Pulmonary Function, and Muscle Strength Endpoints

The OLE-FAS and OLE-ES populations will be used for the analysis of 6MWD, FVC % predicted, GSGC total score, other manual muscle tests, quantitative muscle tests, and other pulmonary function tests. The % predicted 6MWD will also be summarized, where the predicted value will be calculated using the reference equations from Enright and Sherill (Enright and Sherill 1998). These continuous endpoints will be summarized by treatment group and visit. The change from baseline will be similarly summarized by treatment group and visit, and the 95% confidence intervals for the mean change will be provided for each treatment group. In addition, these analyses will be conducted on the treatment switched population (where applicable) for 6MWD and FVC % predicted.

Patient-reported Outcomes and Physician's Global Impression of Change

The OLE-FAS and OLE-ES populations will be used for patient-reported outcome analyses. Summary of each item as well as total score (raw total score and change from baseline in total score) for the R-PAct Scale, EQ-5D-5L (domain scores are to be analyzed as both categorical and continuous variables), and PROMIS instruments will be summarized by treatment group and visit. The change from baseline in the total scores will be summarized by treatment group and visit, and the 95% confidence intervals for the mean change will be provided for each treatment group.

Each item/domain of the SGIC will be summarized by treatment group and visit. The scores will be analyzed as both categorical and continuous variables. Additionally, the response scale for each item will be divided into 3 categories (improving, stable, or declining) which reflect the functional status, and these will be summarized by treatment group.

Summary of response score for actual values for PGIC will be summarized by treatment group and visit.

Biomarker Analyses

The OLE-ES population will be used for biomarker analyses involving serum CK and urinary Hex4. These continuous endpoints will be summarized by treatment group and visit. Changes from baseline will be similarly summarized by treatment group and visit, and the 95% confidence intervals for the mean and/or median change will be provided for each treatment group.

Pharmacokinetic Analyses

Pharmacokinetic endpoints from a population PK analysis of total GAA protein and miglustat concentrations will be provided in a separate modeling and simulation plan.

Safety Analyses

Safety analyses will be based on the safety population (for ATB200-03 and ATB200-07 integrated data) as well as the open-label extension safety population (for ATB200-07 stand-alone data).

Safety data will be summarized using descriptive statistics for continuous data and using counts and percentages for categorical data.

The effect of immunogenicity results on efficacy and safety will be explored. Analysis of immunogenicity data will be described separately.

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5. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Definition of Term
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
AT2221	*N*-butyl-deoxynojirimycin (miglustat)
ATB200	recombinant human acid α-glucosidase (rhGAA) (cipaglucosidase alfa)
ATB200/AT2221	cipaglucosidase alfa co-administered with miglustat
CK	creatine kinase
COVID-19	Coronavirus disease 2019 caused by the SARS-CoV-2 virus
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5 Dimensions-5 Levels Instrument
ERT	enzyme replacement therapy
FSH	follicle stimulating hormone
FVC	forced vital capacity
Gaa	gene encoding acid α-glucosidase (mouse protein)
GAA	human acid α-glucosidase
GAA	gene encoding human acid α-glucosidase
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GSGC	Gait, Stairs, Gowers' maneuver, and Chair test
Hex4	hexose tetrasaccharide
IAR	infusion-associated reaction
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IND	Investigational New Drug
IRB	institutional review board

Abbreviation or Specialist Term	Definition of Term
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
KO	knockout
LOPD	late-onset Pompe disease
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
PD	pharmacodynamic
PGIC	Physician's Global Impression of Change
PK	pharmacokinetic
PROMIS®	Patient-reported Outcomes Measurement Information System
REB	research ethics board
rhGAA	recombinant human acid α-glucosidase
R-PAct	Rasch-built Pompe-specific Activity
SAE	serious adverse event
SGIC	Subject's Global Impression of Change
SNIP	sniff nasal inspiratory pressure
SUSAR	suspected unexpected serious adverse reaction
SVC	slow vital capacity
TEAE	treatment-emergent adverse event
TUG	timed up and go

6. INTRODUCTION

6.1. Pompe Disease

Pompe disease (Online Mendelian Inheritance in Man #232300, also known as acid maltase deficiency or glycogen storage disease type II) is an autosomal recessive genetic disorder caused by mutations in the gene encoding human acid α-glucosidase (*GAA*). These mutations may result in complete absence or partial loss of endogenous human acid α-glucosidase (GAA) activity, which is responsible for the breakdown of lysosomal glycogen. The enzyme deficiency results in accumulation of intracellular glycogen leading to progressive disruption of cellular function, particularly in the heart, skeletal muscles, and diaphragm. The age at onset of clinical manifestations, rate of progression, and severity, including degree of organ and/or muscular (skeletal, respiratory, and cardiac) involvement, largely depends on the severity of the mutations and consequently on the residual enzyme activity (Hirschhorn and Reuser 2001; Raben, Plotz et al. 2002). Lower enzyme activity is generally associated with a more severe clinical course of the disease (Kishnani, Steiner et al. 2006).

Pompe disease may be categorized into 2 classes: infantile-onset Pompe disease (classic and nonclassic) and late-onset Pompe disease (LOPD) (Leslie and Bailey 2017).

Late-onset Pompe disease can present at any age greater than 12 months and does not present with clinically apparent cardiac involvement (Leslie and Bailey 2017). Late-onset Pompe disease is often referred to as juvenile-onset Pompe disease when occurring in the pediatric subpopulation of the LOPD category. Late-onset Pompe disease has a slower rate of progression compared with infantile-onset Pompe disease, with most patients experiencing progressive limb-girdle weakness and respiratory failure due to involvement of muscles in the proximal lower and upper limbs, paraspinal muscles, and diaphragm. Clinical manifestations include difficulty walking, climbing stairs, and progressive limitations of motor activities of daily living with progression to a need for ambulatory support followed by wheelchair dependence (Hirschhorn and Reuser 2001). Clinical manifestations of the disease are compounded by respiratory involvement, initially as sleep-disordered breathing and orthopnea (shortness of breath in supine position). The progressive nature of Pompe disease generally results in the use of invasive mechanically assisted ventilation. Biochemical abnormalities include increased level of serum creatine kinase (CK), a biomarker of muscle injury, and urinary hexose tetrasaccharide (Hex4), a biomarker of disease substrate. Life expectancy for patients with LOPD can range from early childhood to late adulthood, depending on the age of onset, rate of disease progression, the extent of respiratory muscle involvement, and the presence of co-morbidities (Hagemans, Janssens et al. 2004).

Enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (rhGAA), alglucosidase alfa, became available for all patients in Europe and the US in 2006. While alglucosidase alfa provides initial benefit to many patients, the magnitude and duration of therapeutic response with continuing therapy vary among individual patients (van der Ploeg, Clemens et al. 2010; Schoser, Stewart et al. 2017). The current ERT, at best, may offer improvement in measures of muscle function, strength and respiratory function for a finite duration followed by slow decline in these parameters (Toscano and Schoser 2013; Wyatt, Henley et al. 2012).

The most serious tolerability issue with alglucosidase alfa is the occurrence of infusion-associated reactions (IARs), which, in some instances can include life-threatening anaphylaxis or other severe allergic responses (Lumizyme® Prescribing Information, August 2014; Myozyme® Summary of Product Characteristics, December 2018). Management of these events include dose reduction, reduced infusion rates and prolonged infusion times, and dose interruption or discontinuation. Premedication with antihistamines and steroids (prior to infusion) is also regularly used to prevent and reduce the occurrence and severity of IARs and hypersensitivities related to alglucosidase alfa infusion. Despite these measures, patients with Pompe disease may still experience IARs, and some cannot tolerate regular infusions of the currently approved ERT.

Co-administration of ATB200 (rhGAA, cipaglucosidase alfa) with AT2221 (miglustat; *N*-butyl-deoxynojirimycin) (cipaglucosidase alfa/miglustat) is designed to address the limitations of alglucosidase alfa relating to duration of effect and tolerability issues with regard to IARs. Cipaglucosidase alfa has been approved in combination with miglustat in the EU, Great Britain, and other countries around the world for treatment of adults with LOPD, and in the US for the treatment of adults with LOPD who are not improving on their current ERT.

6.2. Cipaglucosidase Alfa/Miglustat

Cipaglucosidase alfa/miglustat is a novel first-in-class co-administered product approach for the treatment of adult and pediatric patients with LOPD. Cipaglucosidase alfa/miglustat is being developed for co-administration for which (1) cipaglucosidase alfa is the main active substance (enzyme) that is engineered for optimal targeting to lysosomes, the site of glycogen catabolism in affected tissues, and (2) miglustat is a co-administered enzyme stabilizer that stabilizes cipaglucosidase alfa from denaturation in systemic circulation, which enhances the delivery of the active component cipaglucosidase alfa to lysosomes.

6.2.1. Cipaglucosidase Alfa

Cipaglucosidase alfa is a next-generation rhGAA enzyme. Cipaglucosidase alfa differs structurally from currently approved rhGAA (alglucosidase alfa) enzyme. Based on the published literature, cipaglucosidase alfa matches the sequence for human alpha glucosidase but has important differences on its post-translational glycan structures that enable more rapid cellular uptake and lysosomal targeting of the enzyme.

6.2.2. Miglustat

Miglustat is an iminosugar that functions as an enzyme stabilizer of cipaglucosidase alfa. Because cipaglucosidase alfa is a recombinant lysosomal enzyme, it is most stable at lysosomal acidic pH and thus is susceptible to denaturation and enzyme inactivation at neutral blood pH when administered intravenously (IV). Miglustat binds to cipaglucosidase alfa and protects cipaglucosidase alfa from denaturation in blood. This interaction of miglustat with cipaglucosidase alfa results in stabilization of the cipaglucosidase alfa enzyme in the blood and enhancement of the pharmacokinetics of the cipaglucosidase alfa leading to a more efficient percentage of active enzyme being delivered to key disease-relevant tissue (ie, muscles).

Miglustat capsules contain the same active ingredient, *N*-butyl-deoxynojirimycin (miglustat), as that in Zavesca® (Actelion Pharmaceuticals US Inc.), which is approved for the treatment of

adults with type I Gaucher disease (in the US and EU) and for treatment of adult and pediatric patients with Niemann Pick-C disease (in EU and Japan). Miglustat is administered at a lesser frequency (1 dose every 2 weeks) in contrast to dosing with miglustat for Gaucher disease and Niemann Pick-C disease (3 times daily) (see Section 11.5 for dosing for this study).

6.3. Human Dosing Rationale

The doses and regimen selected for evaluation in this study, 20 mg/kg cipaglucosidase alfa + 260 mg miglustat for subjects weighing ≥ 50 kg or 195 mg miglustat for subjects weighing ≥ 40 kg to < 50 kg every 2 weeks, is the same as that evaluated in Study ATB200-03, the study preceding this study. Dose selection was based on a body of evidence that includes in vitro data demonstrating the stabilizing effects of miglustat on the cipaglucosidase alfa enzyme, nonclinical pharmacokinetic (PK)/pharmacodynamic (PD) data from studies conducted in the murine gene encoding acid α-glucosidase (mouse protein) (ie, *Gaa*) knockout (KO) model, and clinical PK/PD, efficacy, and safety data from Phase 1/2 Study ATB200-02.

6.3.1. Cipaglucosidase Alfa

Dose selection of cipaglucosidase alfa 20 mg/kg was based on providing a comparable total protein dose for cipaglucosidase alfa as that approved for alglucosidase alfa, as determined by spectrophotometric analysis (ultraviolet absorbance 280 nm, A280), which showed comparable specific activity (GAA enzyme activity/mg protein/hour). Despite similar specific activities, an equivalent dose of 20 mg/kg administered to *Gaa* KO mice showed a PK profile of cipaglucosidase alfa distinct from alglucosidase alfa, as indicated by lower exposures. These lower exposures were due to faster clearance of cipaglucosidase alfa from plasma, which resulted in more efficient targeting and delivery of cipaglucosidase alfa into the disease-relevant muscles. At 20 mg/kg cipaglucosidase alfa, glycogen reduction was most effective and significantly improved compared with 20 mg/kg alglucosidase alfa in *Gaa* KO mice and was thus chosen as the dose to be tested in patients with Pompe disease.

Cipaglucosidase alfa is the primary active agent with an enzymatic mechanism of action that specifically reduces intramuscular glycogen, the primary lysosomal storage material in LOPD. Cipaglucosidase alfa differs structurally from the currently approved rhGAA (alglucosidase alfa) based on both its amino acid sequence and post-translational glycan structures and phosphorylation. One of the key features that distinguishes cipaglucosidase alfa from alglucosidase alfa is that substantially more (~95%) of the initial cipaglucosidase alfa dose binds cation-independent mannose 6-phosphate receptor (CI-MPR) compared with only ~27% of alglucosidase alfa at equivalent enzyme concentrations. The substantially higher binding of cipaglucosidase alfa to the CI-MPR receptor is due to the greater bis-M6P content of cipaglucosidase alfa compared with alglucosidase alfa, which has 10 times higher affinity to bind to the receptor compared with M6P. As a result, a significantly greater amount of cipaglucosidase alfa is internalized into the disease-relevant muscles compared with alglucosidase alfa and therefore, the former is more potent. In vitro studies have demonstrated this by improved uptake of cipaglucosidase alfa into muscle cells as well as by substantially greater glycogen reduction in disease-relevant muscles of *Gaa* KO mice with 20 mg/kg cipaglucosidase alfa compared with 20 mg/kg alglucosidase alfa. In addition, in vivo studies have indicated that the co-administration of miglustat with cipaglucosidase alfa shows even greater trends in glycogen reduction compared with either cipaglucosidase alfa alone or

alglucosidase alfa. Therefore, a 20 mg/kg dose of cipaglucosidase alfa with miglustat is expected to provide improved uptake into muscle tissue than even higher doses at 40 mg/kg of alglucosidase alfa.

6.3.2. Miglustat

Dose selection for miglustat 260 mg was based on in vitro stability studies showing that miglustat at 17 μM preserves cipaglucosidase alfa catalytic activity in blood of neutral pH at 37°C. In *Gaa* KO mice, oral co-administration of a dose approximating 17 μM concentration (10 mg/kg) administered 30 minutes before IV administration of 20 mg/kg cipaglucosidase alfa showed most effective glycogen reduction in skeletal muscles compared with either cipaglucosidase alfa alone or alglucosidase alfa. Notably, miglustat at a concentration of 17 μM approximates the resultant plasma concentration after oral dosing of 260 mg miglustat in the ongoing clinical study, ATB200-02, being conducted in patients with LOPD. Importantly, 260 mg miglustat provided maximal duration of binding and stabilization in plasma for up to 18 hours, with minimal duration of inhibition for up to only 4 hours in tissues (Modeling and Simulations to Support Dosing of cipaglucosidase alfa and miglustat for a First-In-Human Study in Patients with Late-Onset Pompe Disease, AMIC-PCS-102, September 2015).

For patients who weigh ≥ 40 kg to < 50 kg, miglustat dose modification is necessary. Patients in this body weight category will receive 195 mg miglustat (3 × 65-mg capsules). Exposure-matching modeling and simulations for body weights of ≥ 40 kg to < 50 kg for the 195 mg dose were similar to body weights of 70 kg at the 260 mg dose (ATB200 and AT2221 Population Pharmacokinetic Simulations and Exposure Matching for Pediatric Subjects, February 2019). Patients who have a baseline body weight of < 50 kg, but gain weight during the study and reach a weight of 55 kg, will have the dose of miglustat increased to 260 mg (4 × 65-mg capsules). If their body weight subsequently decreases and returns to a level below 50 kg, then the miglustat dose would be reduced to 195 mg (3 × 65-mg capsules).

Additional information is provided in the Investigator's Brochure.

6.4. Nonclinical Studies

Nonclinical single-dose gross tolerance and toxicokinetic studies and repeat-dose toxicology and toxicokinetic studies in rats and nonhuman primates with cipaglucosidase alfa alone, miglustat alone, and co-administered cipaglucosidase alfa/miglustat did not reveal any significant or adverse treatment-related changes in a variety of parameters including body weight, food consumption, hematology, clinical chemistry, central nervous system (rats), cardiovascular (nonhuman primates), and electrocardiogram (ECG) evaluation. In addition, no treatment-related microscopic findings were detected on histologic evaluation. Notably, in the single-dose gross tolerance and toxicokinetic study of miglustat in nonhuman primates, emesis was observed following treatment at the mid and high doses of 250 and 1000 mg/kg, but was not observed at the low dose of 25 mg/kg, and food consumption was not affected. In the 13-week co-administration toxicity study of cipaglucosidase alfa/miglustat in nonhuman primates, no treatment-related emesis was observed at any dose of miglustat, including the highest tested dose of 175 mg/kg. No other overt signs of toxicity were noted in any of the single- or repeat-dose toxicity studies.

6.5. Clinical Studies

Study ATB200-02 is an ongoing Phase 1/2 first-in-human study of safety, tolerability, PK, PD, and efficacy of cipaglucosidase alfa/miglustat in subjects with LOPD. The study is being conducted in 4 stages: single-ascending doses of cipaglucosidase alfa (Stage 1, 6 weeks), multiple-ascending doses of miglustat co-administered with cipaglucosidase alfa (Stage 2, 12 weeks), extended treatment at the selected doses (Stage 3, 2 years), and long-term extension (Stage 4, until approval).

Refer to the current Investigator's Brochure (IB) for updated clinical information.

6.6. Summary of Known and Potential Risks and Benefits

Based on efficacy and safety information in the Investigator's Brochure, the benefit-risk balance of cipaglucosidase alfa/miglustat remains positive overall. Cipaglucosidase alfa/miglustat has demonstrated clinically significant benefits in the treatment of Pompe disease, and no important risks have been identified that would preclude the use of cipaglucosidase alfa/miglustat. Mild to moderate IARs have been identified in ongoing clinical studies and are manageable with reduction or temporary stopping of infusion and premedication with corticosteroids, antihistamines, and acetaminophen. No life-threatening or fatal IARs have been observed in clinical studies to date. As with any investigational new drug (IND) or research study procedure, there are risks that are not known that may be serious and may even cause death. The most up to date information regarding efficacy, safety, and benefit-risk assessment for cipaglucosidase alfa/miglustat can be found in the current Investigator's Brochure.

Cipaglucosidase alfa/miglustat has proven overall to be generally safe and relatively well tolerated. Alternative treatments provide initial benefit to patients with Pompe disease. The magnitude and duration of therapeutic response with continuing therapy varies among individual subjects and, at best, may offer improvement in measures of muscle function, strength, and respiratory function for a finite duration, ie, 2 to 3 years in most subjects, followed by a slow decline in these parameters. These alternative treatments may themselves be associated with significant risks. A monthly review for safety signals is part of routine pharmacovigilance.

The strength of the current benefit-risk analysis is based on the safety pool of data from a variety of sources (clinical study, literature, and independent registries) and in various geographies (eg, EU, Australia, and US) while the mean duration of treatment is approaching 36 months.

Weakness of the data is primarily based on the small number of subjects in the clinical study described. There are no specific studies that target specific subpopulations of patients such as elderly, or subpopulations. Uncertainties exist over the long-term safety profile.

Study participants may not experience any benefit from participating in this study. However, potential benefits include stabilization or improvement in the signs and symptoms of Pompe disease and the positive health effects of regular surveillance by a physician. In addition, study participation provides the opportunity to contribute data relevant and necessary for continued advancement in the treatment of Pompe disease. In light of the progressive nature of Pompe disease and the benefits observed in adults with LOPD to date, the potential benefits justify the risks and inconveniences of clinical trial participation. The sponsor acknowledges that these inconveniences include frequent travel to the study site with associated impact on attendance at work and/or school; the discomfort of study procedures, such as blood draws; and the need to

follow other study requirements, such as adequate birth control for females of child-bearing potential. However, the sponsor has made efforts to limit this impact by allowing for at-home administration of study medication (if permitted locally and deemed clinically appropriate based on criteria outlined in the protocol) and minimizing the number of visits with full study assessments. Finally, study participants are informed at the time of consent that if at any time they do not wish to continue with the study, eg if the risks or inconveniences become too onerous, they may withdraw without any adverse impact on their ongoing care by their physician.

Refer to the current IB for updated information.

6.7. Study Population

This is an open-label extension study for adult subjects with LOPD who completed Study ATB200-03. For this amendment, subjects may continue in this study until commercial cipaglucosidase alfa/miglustat becomes available in their country as a treatment for Pompe patients.

7. STUDY OBJECTIVES

The final analysis will be performed for the final CSR based on a data cutoff date of 31 December 2024 with the study objectives below. The study objectives upon approval of this amendment are presented in Appendix 1, Section 7.

7.1. Primary Objective

The primary objective of this study is to assess the long-term safety and tolerability of cipaglucosidase alfa/miglustat co-administration.

7.2. Secondary Objectives

The secondary objectives of this study are as follows:

- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on ambulatory function, as measured by the 6-minute walk test (6MWT)
- to assess the long-term efficacy cipaglucosidase alfa/miglustat co-administration on pulmonary function, as measured by sitting forced vital capacity (FVC) (% predicted)
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on muscle strength
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on health-related patient-reported outcomes
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on motor function
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on overall clinical impression, as assessed by both physician and subject
- to assess the long-term efficacy of cipaglucosidase alfa/miglustat co-administration on measures of pulmonary function other than FVC (% predicted)
- to assess the long-term effect of cipaglucosidase alfa/miglustat co-administration on biomarkers of muscle injury and disease substrate
- to assess the immunogenicity of cipaglucosidase alfa/miglustat co-administration
- to characterize the pharmacokinetics of cipaglucosidase alfa and miglustat using plasma total GAA protein level by signature peptide and plasma miglustat concentration assays in subjects at sites in Japan only

8. INVESTIGATIONAL PLAN

8.1. Study Design

This is a multicenter, international, open-label extension study of cipaglucosidase alfa/miglustat in adult subjects with LOPD who completed Study ATB200-03.

The purpose of this amendment is to continue collecting long-term safety and efficacy data on LOPD subjects treated with cipaglucosidase alfa/miglustat while decreasing some of the burden on those subjects taking part, and continuing to provide treatment where regulatory approval has not yet been granted or the product is not yet commercially available. Subjects may continue in this study until commercial cipaglucosidase alfa/miglustat becomes available in their country as a treatment for Pompe patients. The final analysis will be performed for the final CSR based on a data cutoff date of 31 December 2024. Upon approval of this amendment, any subjects continuing in the study will follow the updated Schedule of Assessments in Table 10.

For subjects who participated in Study ATB200-03, the first infusion visit in this study should be scheduled approximately 2 weeks after the last visit in Study ATB200-03 in an effort to ensure continued administration of study drug on the same schedule with no gap between studies. Infusion visits for administration of study drug will be scheduled every 2 weeks throughout the study; assessments (eg, clinical laboratory tests) for monitoring of initial safety will be performed at these infusion visits for the first 6 weeks of the study. During the conduct of the study, the SARS-CoV-2 (COVID-19) pandemic emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. With the intention of maintaining regular infusions, home infusions will be allowed prior to completing Week 12 wherever possible for subjects who may be eligible (see Section 12.2.2). Study visits that include efficacy, safety, and other assessments will be scheduled approximately every 3 months for the first 6 months, then every 6 months thereafter. These visits may occur over 2 days, provided all study assessments and procedures (with the exception of PK sample collection) are performed before administration of study drug. If a visit was missed due to COVID-19-related quarantines, travel restrictions, and risk of infection, it should be recorded as such in the Interactive Response Technology (IRT) system and electronic data capture (EDC) system. A reason for the missed visit should be entered into the EDC as COVID-19 related. The relevant institutional review boards (IRBs), independent ethics committees (IECs), and REBs should be notified of any deviations from the protocol. If infusions were missed near the scheduled assessments at Week 12, Week 26, or at any of the study visits scheduled every 26 weeks after Week 26, it should be communicated with Amicus on a case-by-case basis to determine whether catch-up infusions are needed and how many catch-up infusions are needed prior to the study assessments.

Efficacy assessments (ie, functional assessments) include evaluation of ambulatory function (6MWT), motor function tests (Gait, Stairs, Gowers' maneuver, and Chair [GSGC] test and timed up and go [TUG] test), muscle strength (manual muscle testing and quantitative muscle testing), and pulmonary function tests (FVC, slow vital capacity [SVC], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and sniff nasal inspiratory pressure [SNIP]). Patient-reported outcomes include Rasch-built Pompe-specific Activity (R-PAct) Scale, EuroQol 5 Dimensions-5 Levels Instrument (EQ-5D-5L), Patient-reported Outcomes Measurement Information System (PROMIS®) instruments for physical function, fatigue,

dyspnea, and upper extremity, and Subject's Global Impression of Change (SGIC). The Physician's Global Impression of Change (PGIC) will also be performed. Pharmacodynamic assessments include measurement of biomarkers of muscle injury (CK) and disease substrate (urinary Hex4). Blood samples for PK assessment of total GAA protein and miglustat concentration in plasma will be collected from subjects at sites in Japan only. Safety assessments include monitoring of AEs, including IARs, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, physical examinations including weight, ECGs, and immunogenicity. Concomitant medications and nondrug therapies will also be recorded.

For subjects continuing in the study after approval of this amendment, updated efficacy and safety assessments are provided in Appendix 1, Section 8.1.

8.2. Duration of Study

The study will consist of a treatment period that lasts until one of the following conditions apply:

- the product is approved and commercialized for use in the investigational study population, or
- cipaglucosidase alfa/miglustat is rejected by the regulatory authority in the subject's local country as an approved treatment for Pompe disease, or
- the sponsor decides to continue to provide cipaglucosidase alfa/miglustat via a post-trial access mechanism, or
- the subject is withdrawn or withdraws consent, or
- the sponsor decides to end the study.

8.3. Criteria for Termination of the Study

The study may be terminated by the sponsor if there is evidence suggesting that safety risks associated with cipaglucosidase alfa/miglustat treatment outweigh the potential benefits.

8.4. Definition of the End of Study

End of study is defined as the date of the last subject's last visit. The final analysis will be performed for the final CSR based on a data cutoff date of 31 December 2024. Any data collected after this date will be provided as an addendum to the final CSR when all subjects have completed the study or have been withdrawn from the study. Upon approval of this amendment, subjects who remain in the study will follow the Schedule of Assessments in Appendix 1 (Table 10).

8.5. Definition of Study Completer

A study completer is defined as a subject who has fulfilled both of the following requirements:

- completion of study treatment, defined as continuing to receive treatment as a participant in the ATB200-07 study until the study ends or until the subject transitions to locally approved and commercially available cipaglucosidase alfa/miglustat or another post-trial access mechanism

8.6. Discussion of Study Design, Including Choice of Control Groups

This is an open-label extension study to assess the long-term safety of cipaglucosidase alfa/miglustat and has no control group. Although efficacy will be assessed, it is not a primary objective.

9. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

9.1. Number of Subjects

The maximum sample size for this study is based on the number of subjects who complete Study ATB200-03, estimated to be approximately 110 subjects at up to approximately 59 sites globally.

9.2. Eligibility Criteria

9.2.1. Subjects Who Participated in Study ATB200-03

Subjects who participated in Study ATB200-03 must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

9.2.1.1. Inclusion Criteria

1. Subject must provide signed informed consent prior to any study-related procedures being performed. If the subject is under 20 years of age, the subject must provide written informed consent. In Japan, the subject's parental guardian (or legal representative) must also sign the informed consent form.
2. Subjects must have completed Study ATB200-03.

   Note: Subjects who were forced to withdraw from Study ATB200-03 for a logistical reason not related to the efficacy or safety of cipaglucosidase alfa/miglustat (eg, hospitalization for a car accident, COVID-19 pandemic, or emergency surgery) and which resulted in several consecutive missed doses may be eligible to participate in this study upon approval by the Amicus medical monitor.
3. Female subjects of childbearing potential and male subjects must agree to use medically accepted methods of contraception during the study and for 90 days after the last dose of study drug.

9.2.1.2. Exclusion Criteria

1. Subject plans to receive gene therapy or participate in another interventional study for Pompe disease.
2. Subject has a hypersensitivity to any of the excipients in cipaglucosidase alfa or miglustat, or has a medical condition or any other extenuating circumstance that may, in the opinion of the investigator or medical monitor, pose an undue safety risk to the subject or may compromise his/her ability to comply with or adversely impact protocol requirements. This includes clinical depression (as diagnosed by a psychiatrist or other mental health professional) with uncontrolled or poorly controlled symptoms.
3. Subject, if female, is pregnant or breastfeeding.
4. Subject, whether male or female, is planning to conceive a child during the study.

9.3. Withdrawal Criteria

Subjects may withdraw or be withdrawn from the study for any reason, including, but not limited to, the following:

- at their own request
- if, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being

  Note: Subjects with serious adverse events (SAEs) of anaphylaxis to cipaglucosidase alfa must be withdrawn from the study.
- if, in the investigator's opinion, there is a lack of efficacy for the subject
- persistent noncompliance with study requirements, such as failure to comply with the study visit schedule, in the judgment of the investigator and/or medical monitor
- persistent noncompliance with study drug or failure to return to the study site for infusion visits, in the judgment of the investigator and/or medical monitor
- inability to contact subject (ie, subject is lost to follow-up)
- pregnancy (female subjects)
- planning to conceive a child (male or female subjects)
- sponsor decision to terminate the study

In all cases, the reason for withdrawal and the date of withdrawal must be recorded in the electronic case report form (eCRF) and in the subject's medical records.

Subjects who withdraw will be requested to complete the Early Termination Visit. The investigator will make every effort to contact withdrawing subjects and schedule the early termination assessments. Upon study completion or subject discontinuation, subjects who are confirmed positive for anti-rhGAA antibodies will complete follow-up immunological testing for up to 12 months after the last dose of study drug (ie, at 6 months and 12 months) or until they begin treatment with an investigational therapy or an ERT that is approved by the local health authority and is commercially available (see 12.2.6).

9.4. Subjects of Reproductive Potential

Subjects must be willing to apply highly effective contraception during the study and through the duration as defined below and for 90 days after the final dose of study treatment.

The allowed methods of contraception described in the following text are only effective when used consistently, correctly, and in accordance with the product label. For Japanese subjects, only approved contraceptive measures in Japan are considered as effective measures. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception. A highly effective birth control is defined as one that results in a low failure rate (ie, < 1% per year) when used consistently and correctly.

Women of child-bearing potential are defined as all women physiologically capable of becoming pregnant, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Highly effective methods of contraception include the following:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal*, transdermal*
- progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable*, implantable*
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Note: * Indicates products not approved in Japan.

Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Note: Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhea with a serum FSH level > 40 mIU/mL and estradiol < 20 pg/mL, or have had surgical bilateral oophorectomy, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment and she is considered not of child-bearing potential.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Male subjects and their partners must use highly effective methods of contraception (ie, condom in male subjects and highly effective contraception, as listed previously in this section, in their female partners) for the entire duration of the study and continue to use contraception and refrain from fathering a child for 90 days following the study treatment.

In the event of pregnancy in a female subject, study drug must be discontinued. Pregnancies occurring during study participation (female subject or a female partner of a male subject) must be reported to Amicus and followed as described in Section 13.4.

10. TREATMENT OF SUBJECTS

Subjects will receive cipaglucosidase alfa/miglustat as follows: miglustat 260 mg (4 × 65-mg oral capsules) for subjects weighing ≥ 50 kg or miglustat 195 mg (3 × 65-mg oral capsules) for subjects weighting ≥ 40 kg to < 50 kg, followed approximately 1 hour later by cipaglucosidase alfa 20 mg/kg (reconstituted lyophilized drug product, 105 mg/vial), administered over a 4-hour IV infusion. The cipaglucosidase alfa/miglustat combination regimen will be administered every 2 weeks. Subjects are required to fast at least 2 hours before and 2 hours after administration of miglustat.

Study drug will be administered every 2 weeks at the study site. After 3 months in the study without any moderate to severe IARs, subjects may be eligible for administration of study drug at their home (see Section 12.2.2). In countries or at sites where the administration of alglucosidase alfa is reserved for hospital use, however, all study drug will be administered in a hospital setting.

Cipaglucosidase alfa and miglustat will be administered under the supervision of study site personnel; therefore, treatment compliance will be calculated using study drug administration records.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

Study drug is defined in this protocol as cipaglucosidase alfa/miglustat, cipaglucosidase alfa/miglustat, and a combination of these.

Cipaglucosidase alfa (rhGAA) functions as ERT. Miglustat (*N*-butyl-deoxynojirimycin) is an iminosugar that functions as an enzyme stabilizer of rhGAA. Table 3 provides details on the investigational products.

Table 3: Investigational Products

Product Name	**Cipaglucosidase Alfa**	**Miglustat**
Dosage Form	Lyophilized powder for IV infusion	Hard gelatin capsule
Unit Dose	15 mg/mL	65 mg
Route of Administration	IV infusion	Oral
Physical Description	Sterile, nonpyrogenic, white to off-white lyophilized cake or powder supplied in single-use, clear 20-mL (cc) glass vials	White, size 2, hard gelatin capsules supplied in 40-cc HDPE bottles or size 2, hard gelatin capsules with a gray opaque cap, white opaque body, printed with "AT2221" in black ink on the body, supplied in 40-cc HDPE bottles
Excipients	Sodium citrate dihydrate, citric acid monohydrate, mannitol, polysorbate-80	Microcrystalline cellulose, pregelatinized starch, sucralose, magnesium stearate, colloidal silicon dioxide
Manufacturer	WuXi Biologics Co., Ltd 108 Meiliang Rd Mashan, Binhu District, WuXi, China	Alcami 1726 N 23rd St Wilmington, NC 28405 USA

Abbreviations: HDPE = high density polyethylene; IV = intravenous; USA = United States of America

11.2. Study Drug Packaging and Labeling

Miglustat (65 mg oral capsule) will be supplied by Amicus to sites or the central pharmacy used for the home infusion program as hard gelatin capsules in high density polyethylene bottles and will be administered orally.

Cipaglucosidase alfa (105 mg/vial) will be supplied by Amicus to sites or the central pharmacy used for the home infusion program as a lyophilized powder in glass vials and will be administered by IV infusion upon reconstitution with sterile water for injection and followed by dilution with 0.9% sodium chloride for injection prior to administration. Sterile water for injection and 0.9% sodium chloride for injection will be supplied by the study sites or central pharmacy used for the home infusion program.

Each container will be labeled in conformance with regulatory requirements and, where applicable, local laws. All labels will be printed with the following information at a minimum: study identifier, identity of drug and dosage, sponsor name and contact details (and/or details of a local designee contact), dosing instructions, storage information, and other applicable local law statements. All labels will comply with legal requirements of each country.

11.3. Study Drug Storage

Sites and the central pharmacy used for the home infusion program will be instructed to store miglustat 65-mg oral capsules according to the conditions identified on the labels of each study drug, at room temperature (15°C to 25°C or 59°F to 77°F), with excursions permitted down to 2°C or 36°F and up to 40°C or 104°F for up to 20 days in a secure area, free from environmental extremes, and with restricted access.

Sites and the central pharmacy used for the home infusion program will be instructed to store cipaglucosidase alfa lyophilized powder vials according to the conditions identified on the study drug label, at cold temperature (2°C to 8°C or 36°F to 46°F), with excursions of up to 7 days permitted down to -20°C or -4°F and up to 25°C or 77°F in a secure area, free from environmental extremes, and with restricted access.

Temperature logs must be maintained for the duration of the study. The temperature of the refrigerator where cipaglucosidase alfa is stored and the temperature of the storage room (or cabinet) where the miglustat are stored must be recorded for each working day of the week the pharmacy personnel (or designated study personnel) is available. Temperature is required to be recorded using a standard min-max thermometer that has calibration records available (details usually contained within the device leaflet) and is maintained according to the institution's standard maintenance policy.

The study drugs are to be stored only at the site(s) listed on Form FDA 1572 or Statement of Foreign Investigator form for non-US sites. Study drug is to be dispensed only to subjects who have provided written informed consent and have met all entry criteria.

11.4. Study Drug Preparation

Instructions for preparation of oral product and infusion as well as the volume and rate of infusion will be provided in the pharmacy manual.

11.5. Administration

11.5.1. Cipaglucosidase Alfa

The dose of cipaglucosidase alfa, 20 mg/kg, is based on body weight and will be based on the last available body weight value in the IRT system. Weight will be entered into the IRT system at the Baseline Visit, Week 12, Week 26, and every 26 weeks thereafter for calculation of cipaglucosidase alfa dose.

Cipaglucosidase alfa does not contain any preservatives. Vials are single-use only. Reconstituted vials should be retained at the site or the central pharmacy for the home infusion program until the monitor checks accountability.

Cipaglucosidase alfa is to be administered every 2 weeks as an approximate 4-hour IV infusion. Changes in any premedications, dose, rate, or duration of infusion due to safety or tolerability issues will be documented. The total volume of infusion is determined by the subject's body weight. Instructions for preparation for infusion and the volume and rate of infusions will be provided in the pharmacy manual. Reconstitution of cipaglucosidase alfa should be performed by qualified study personnel (eg, pharmacist or pharmacy technician or nurse under physician supervision). Intravenous administration of cipaglucosidase alfa should be performed by qualified study personnel. Subjects should be carefully monitored during and after the first 3 infusions (Section 12.2.2). Any delegation of this responsibility must follow Section 16.3.5. Rate and duration of infusion must be constant for each infusion.

11.5.2. Miglustat

The dose of miglustat is 260 mg (4 × 65-mg oral capsules) for subjects weighing ≥ 50 kg and 195 mg (3 × 65-mg oral capsules) for subjects weighing ≥ 40 kg to < 50 kg.

Miglustat is administered orally, approximately 1 hour before cipaglucosidase alfa infusion. Subjects will take 3 or 4 capsules of miglustat, depending on their body weight. Subjects should fast for at least 2 hours before and 2 hours after administration of miglustat. Fasting is defined as nothing by mouth except water; this includes prescription or over-the-counter medications, vitamins, or herbal supplements other than premedications for administration of cipaglucosidase alfa. If a medication is considered necessary for the health of the subject, approval must be obtained from the medical monitor unless in case of emergency. Therefore, subjects should arrive at the clinic at least 1 hour prior to the start of the cipaglucosidase alfa infusion to receive miglustat.

If a subject has received miglustat on a dosing day but then is unable to receive the infusion of cipaglucosidase alfa, the subject may be re-dosed with miglustat at least 24 hours later, prior to their rescheduled infusion of cipaglucosidase alfa.

11.6. Randomization and Blinding

This is an open-label study with no randomization. However, treatment assignment from Study ATB200-03 must remain blinded until that study is complete and treatment assignments are unblinded for analysis. Therefore, an unblinded monitor will be employed to review select laboratory results that could potentially unblind a subject's treatment assignment.

11.7. Study Drug Accountability

In accordance with local regulatory requirements, the investigator, designated site personnel, head of the medical institution (where applicable), or certified mobile research nurse for home infusions must document the amount of study drug dispensed and/or administered to study subjects, and the amount received from and returned to Amicus (or designee), where applicable. Product accountability records must be maintained throughout the course of the study.

11.8. Study Drug Handling and Disposal

The investigator must keep an accurate record/log of the quantities of study drug dispensed and administered to each subject. The monitor will periodically check the supplies of study drugs held at the site or central pharmacy used for the home infusion program to verify accountability of all study drugs used and to verify the drug accountability logs are completed and maintained in the investigator study file. The monitor will return all original containers of study drugs, whether empty or containing used or unused study drugs, to Amicus or their designee for destruction. Sites and certified mobile research nurses for home infusions may not destroy study drugs on site unless Amicus has provided prior written approval.

11.9. Prohibited Medications

Use of the following medications is prohibited during treatment with study drug:

- miglitol (eg, Glyset®)
- nonstudy miglustat (eg, Zavesca)
- approved ERT (eg, alglucosidase alfa or avalglucosidase alfa) after treatment with cipaglucosidase alfa/miglustat has begun
- acarbose (eg, Precose® or Glucobay®)
- voglibose (eg, Volix®, Vocarb®, or Volibo®)
- oral anabolic steroid or derivative
- any investigational/experimental drug

Subjects who are taking β_2-receptor agonists or nonselective β-blockers (eg, propranolol, nadalol, carvedilol) before Day 1 must maintain the same dose as was received during Study ATB200-03 for the duration of this study. Use of inhaled β-2 agonists and/or single uses of epinephrine (eg, for treatment of an infusion-associated reaction) are permitted.

12. STUDY PARAMETERS AND PROCEDURES

12.1. Schedule of Assessments

A Schedule of Assessments showing each study assessment and procedure along with the scheduled time of occurrence is provided for subjects who participated in Study ATB200-03 (Table 4). All study assessments should be conducted by the investigator and/or a suitably qualified designee. Information will be recorded in the source documents and, where appropriate, the eCRF.

For subjects continuing in the study after approval of this amendment, an updated Schedule of Assessments is provided in Appendix 1 (Table 10).

Visits may occur over 2 days; if assessments are not able to be completed in 2 days, an additional day may be scheduled. Once established, every effort should be made to maintain the order of procedures, approximately at the same time of day, at each study visit throughout the study, regardless of the number of days that are used for the visit.

Table 4: Schedule of Assessments for Subjects Who Participated in Study ATB200-03

		Treatment					Follow-up
Study Visit	**Baseline[a]**	**Day 1[b]**	**Infusion Visits (Every 2 Weeks Through EOS/ET)**	**Weeks 2, 4, 6**	**Weeks 12, 26, and then Every 26 Weeks[c]**	**EOS/ ET**	**≥ 30 Days After Last Dose**
Visit Window (Days)	—	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Administrative							
Informed consent (12.2.1)	X						
Eligibility criteria (9.2.1)	X	X					
Demographics (12.3.1)	X						
Schedule next visit	X	X	X	X	X	X	
Clinical Assessment							
Medical history (12.3.2)	X						
Prior/concomitant medications and nondrug therapies (12.3.3)	X	X	X	X	X	X	X
Complete PE (12.3.4)	X					X	
Brief PE (12.3.4)				X	X		
Vital signs (12.3.6)	X	X	X	X	X	X	
Weight[d] (12.3.5)	X				X	X	
Height (12.3.5)	X						
AEs/SAEs, including IARs (13)	X	X	X	X	X	X	X

Table 4: Schedule of Assessments for Subjects Who Participated in Study ATB200-03 (Continued)

		Treatment					Follow-up
Study Visit	**Baseline[a]**	**Day 1[b]**	**Infusion Visits (Every 2 Weeks Through EOS/ET)**	**Weeks 2, 4, 6**	**Weeks 12, 26, and then Every 26 Weeks[c]**	**EOS/ ET**	**≥ 30 Days After Last Dose**
Visit Window (Days)	—	± 3	± 3	± 3	± 3	± 3	± 3
Subject/Physician-reported Outcomes[e]							
R-PAct Scale (12.3.8)	X				X	X	
PROMIS instruments for physical function, fatigue, dyspnea, upper extremity (12.3.8)	X				X	X	
EQ-5D-5L (12.3.8)	X				X	X	
PGIC (12.3.9)					X	X	
SGIC (12.3.8)					X	X	
Laboratory Assessments							
12-lead ECG (12.3.10)	X				X	X	
Serum chemistry, hematology (12.3.11.1)	X			X	X	X	
Anti-rhGAA antibodies (total and neutralizing) (12.3.12)	X			X	X	X	
IgE (12.3.12)	X		See Section 12.3.12.				
Urine pregnancy test[f] (12.3.11.2)	X	X	X	X	X	X	
Urinary Hex4 (12.3.14)	X			X	X	X	
Urinalysis (12.3.11.1)	X			X	X	X	

Table 4: Schedule of Assessments for Subjects Who Participated in Study ATB200-03 (Continued)

		Treatment					Follow-up
Study Visit	**Baseline[a]**	**Day 1[b]**	**Infusion Visits (Every 2 Weeks Through EOS/ET)**	**Weeks 2, 4, 6**	**Weeks 12, 26, and then Every 26 Weeks[c]**	**EOS/ ET**	**≥ 30 Days After Last Dose**
Visit Window (Days)	—	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Pulmonary Function Tests							
MIP, MEP, SNIP (12.3.16)	X				X	X	
FVC, SVC (sitting, supine) (12.3.16)	X				X	X	
Motor Function Assessments							
TUG (12.3.17)	X				X	X	
GSGC (12.3.17)	X				X	X	
6MWT (12.3.18)	X				X	X	
Muscle Strength							
Manual muscle strength (MRC) (12.3.19)	X				X	X	
Quantitative muscle strength (hand-held dynamometer) (12.3.19)	X				X	X	

Table 4: Schedule of Assessments for Subjects Who Participated in Study ATB200-03 (Continued)

		Treatment					Follow-up
Study Visit	**Baseline[a]**	**Day 1[b]**	**Infusion Visits (Every 2 Weeks Through EOS/ET)**	**Weeks 2, 4, 6**	**Weeks 12, 26, and then Every 26 Weeks[c]**	**EOS/ ET**	**≥ 30 Days After Last Dose**
Visit Window (Days)	—	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Study Drug Administration							
Miglustat (10)		Every 2 weeks 1 hour before infusion of cipaglucosidase alfa					
Cipaglucosidase alfa (10)		Every 2 weeks					

Abbreviations: 6MWT = 6-minute walk test; AE = adverse event; ECG = electrocardiogram; EOS = end of study; EQ-5D-5L = EuroQol 5 Levels-5 Dimensions Instrument; ERT = enzyme replacement therapy; ET = early termination; FVC = forced vital capacity; GAA = human acid α-glucosidase; GSGC = Gait, Stairs, Gowers' maneuver, and Chair test; Hex4 = hexose tetrasaccharide; IAR = infusion-associated reaction; IgE = immunoglobulin E; IRT = interactive response technology; MEP = maximal expiratory pressure; MIP = maximum inspiratory pressure; MRC = Medical Research Council; PE = physical examination; PGIC = Physician's Global Impression of Change; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; rhGAA = recombinant human acid α-glucosidase; R-PAct = Rasch-built Pompe-specific Activity; SAE = serious adverse event; SGIC = Subject's Global Impression of Change; SNIP = sniff nasal inspiratory pressure; SVC = slow vital capacity; TUG = timed up and go

[a] Baseline Visit is for subjects who did not complete Week 52 in Study ATB200-03.

[b] Day 1 Visit is to be scheduled approximately 2 weeks after the last administration of study drug in Study ATB200-03. Except for study drug administration and scheduling the next visit, all study procedures/assessments at the Day 1 Visit are to be performed only if results are not available from the last study visit in Study ATB200-03. If a subject has a change in the use of an assistive device that was used to perform the 6MWT during Study ATB200-03, then the 6MWT must be repeated at the Visit.

[c] After Week 26, study visits will be scheduled every 26 weeks until 31 December 2027 or until study termination by the sponsor.

[d] Weight will be entered into the IRT system at the Baseline Visit, Week 12, Week 26, and every 26 weeks thereafter for calculation of cipaglucosidase alfa dose.

[e] Subjects are to complete patient-reported outcome questionnaires before any other study assessment, if the questionnaires are available in that subject's language.

[f] Urine pregnancy tests are performed only for female subjects of childbearing potential. If the urine pregnancy test has a positive result, study drug will not be administered and a confirmatory serum pregnancy test will be performed.

Table 5: Schedule of PK Assessments for Subjects at Sites in Japan

Study Visit	Screening/Baseline (Day –30 to Day –1)[a]		Treatment					Follow-up
	Day –15[b]	Day –14	Day 1	Infusion Visits (Every 2 Weeks Through Week 52)	Weeks 2, 4, 6	Weeks 12, 26, 52, and then Every 26 Weeks[c]	EOS/ ET	≥ 30 Days After Last Dose
Visit Window (Days)	—	—	—	± 3	± 3	± 3	± 3	± 3
PK Assessments								
PK blood sampling (total GAA protein, miglustat)[d] (Section 12.3.13)					X	X		

Abbreviations: EOS = end of study; ET = early termination; GAA = human acid α-glucosidase; PK = pharmacokinetic

[a] Baseline efficacy assessments will be performed during screening, and baseline safety assessments will be performed on Day 1.

[b] For ERT-experienced subjects, Day –15 of the Screening Visit will be scheduled 1 to 2 days before the subject's next alglucosidase alfa infusion. For ERT-naïve subjects, the Screening Visit may be scheduled anytime between Day –30 and Day –15.

[c] After Week 52, study visits will be scheduled every 26 weeks until 31 December 2027 or until study termination by the sponsor.

[d] PK samples will be collected only in subjects at Japanese sites at either Week 2, 4, or 6 and at Week 52 only. Sparse blood samples will be collected for PK analysis at the time points specified in Section 12.3.13.

12.2. Additional Details on Study Visits

For subjects continuing in the study after approval of this amendment, please refer to Appendix 1 for additional details on study visits.

12.2.1. Day 1 for Subjects who Participated in Study ATB200-03

For subjects who participated in Study ATB200-03, the Day 1 Visit should be scheduled approximately 2 weeks after the last visit in Study ATB200-03 in an effort to ensure continued administration of study drug on the same schedule with no gap between studies and may occur over 2 days.

Administration of informed consent and confirmation of eligibility criteria will occur at the final visit in Study ATB200-03. Study personnel must confirm that these procedures were performed before any other study assessments are performed.

Subjects will also be registered using an IRT system at the last study visit in Study ATB200-03 to allow sufficient lead time for the first drug shipment. All subsequent shipments will be sent automatically through IRT system. Refer and comply with detailed guidelines in the IRT manual.

Any subjects who participated in Study ATB200-03, signed informed consent for this study, but did not receive at least 1 dose of study drug will have the following information entered into the electronic data capture system: reason for not being started on study drug, demographic information, informed consent, and inclusion/exclusion pages.

Day 1 is the first day of open-label study drug administration. Results from the last visit in Study ATB200-03 will serve as baseline values for this study. If a result from Study ATB200-03 is missing, that assessment will be performed at the Baseline Visit before open-label study drug is administered.

Japanese subjects who have undergone PK sample collection at the Week 52 visit in Study ATB200-03 will have their initial PK sample in this study collected at any of the Week 2, 4, or 6 visits.

12.2.2. Infusion Visits and Home Infusion Visits

Infusion visits will be scheduled every 2 weeks for administration of open-label study drug, with the option to have infusions administered at the home of the subject after 3 months if they have not had a moderate to severe IAR during those 3 months. Changes in the protocol-prescribed duration of study drug infusion due to safety or tolerability issues will be documented in the eCRF. In addition to the assessments noted in Table 4 (subjects who participated in Study ATB200-03), the site should follow their facility guidelines for performing infusions to monitor vital signs or other safety procedures that may be in place.

At each visit through Week 6, additional safety assessments (eg, clinical laboratory tests) will be performed for monitoring of initial safety. In addition, subjects will be monitored for 3 hours after the end of the first 3 infusions (ie, Day 1 and Weeks 2 and 4) by study personnel who are trained in diagnosing and treating acute hypersensitivity reactions and who have immediate access to medication and equipment to treat such reactions. Any additional monitoring according to standards at individual sites should also be performed. Any signs or symptoms noted during or

after the infusion should be reported as an AE. All assessments will be performed before infusion of study drug. No efficacy assessments will be performed at these visits.

If consistent with local laws and regulations, subjects may be considered eligible for administration of cipaglucosidase alfa/miglustat at their home. Eligible subjects may request participation in the home infusion program with requests granted on a case-by-case basis following discussion between the Amicus medical monitor and investigator with prior approvals from the relevant IRBs, IECs, or REBs, and regulatory authorities.

Home infusions of cipaglucosidase alfa will be performed by a certified mobile research nurse provided by an Amicus-designated home infusion service provider. Certified mobile research nurses will be trained to recognize and manage subjects in the event of an IAR (see Section 13.1.3) and will be equipped with emergency medicines and devices to treat subjects who have an IAR. Details regarding the infusion (eg, dose, flow rate) and observations will be documented by the certified mobile research nurse and promptly communicated to the investigator.

All subjects participating in the home infusion program will be required to complete all functional assessments at the protocol-specified site visits.

Subjects who participate in the home infusion program must meet all of the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria for home infusion program:

- Subject resides in a country where it is permissible to administer alglucosidase alfa outside of a hospital setting.
- Home site meets the following requirements regarding feasibility for ERT infusion:
  - Availability of sufficient space to prepare and administer cipaglucosidase alfa infusion
  - Availability of utilities and equipment required for storage of study drug upon receipt
  - Accessibility for delivery of study drug and associated supplies
  - Accessibility of trained certified mobile research nurse for preparation/administration
  - Ability to prepare cipaglucosidase alfa lyophilized drug product for reconstitution
  - Sufficient space to administer cipaglucosidase alfa infusion
  - Ability to properly dispose of waste and discard used medical supplies
- Amicus/designee deems the home site to be appropriate for home infusion following home assessment.
- Investigator agrees to collaborate with the home infusion agency/certified mobile research nurse with respect to providing advice and support as needed by the certified mobile research nurse.

Exclusion criteria for home infusion program:

- Subject experiences a moderate or severe IAR, or a mild IAR that is not controlled with medication after receiving study drug during this study, or with a history of a recurrent severe or life-threatening IAR including anaphylaxis at any time.

12.2.3. Post-baseline Assessment Visits

Assessments may occur over 2 days for each post-baseline visit, provided all assessments are performed before administration of study drug.

If infusions were missed close to the scheduled assessments, it should be communicated with the Amicus Medical Monitor to determine on a case-by-case basis whether catch-up infusions are needed and how many catch-up infusions are needed prior to the study assessments.

12.2.4. Unscheduled Visits

Unscheduled visits may be conducted at any time at the investigator's discretion for medical reasons (eg, evaluation of AEs, local laboratory tests for safety, other safety assessments).

12.2.5. End of Study/Early Termination

Subjects who complete the study or discontinue study drug for any reason will be asked to return for the End of Study/Early Termination Visit. The End of Study visit is performed as the final full assessment visit for a subject who has completed the study as defined in Section 8.5. The Early Termination visit is performed as the final full assessment visit for a subject who ends treatment with the study drugs prior to completing study treatment.

If infusions were missed close to the scheduled assessments on the last week of the study, it should be communicated with Amicus to determine on a case-by-case basis whether catch-up infusions are needed and how many catch-up infusions are needed prior to the study assessments.

12.2.6. Follow-up Period

A 30-day safety follow-up visit for monitoring of any AEs that were ongoing at end of study should be conducted.

12.3. Description of Study Assessments

All assessments will occur according to the Schedule of Assessments displayed in Table 4 for subjects who participated in Study ATB200-03.

For subjects continuing in the study after approval of this amendment, please refer to Appendix 1 for the updated Schedule of Assessments (Table 10).

Any study procedures that involve supine positions may be deferred if the subject is unable to complete them in a supine position.

If a subject is ill or injured at a scheduled visit, functional assessments (ie, 6MWT, motor function tests, muscle strength tests, and pulmonary function tests) may be deferred to an unscheduled visit when the subject's condition has improved, in consultation with the medical monitor.

Significant findings for vital signs, physical examinations, clinical laboratory tests, or ECGs that were not present prior to start of treatment and meet the definition of an AE must be recorded on the AE eCRF page.

12.3.1. Demographic Data Collection

Demographics (date of birth, sex, and race) will be recorded for any subject who signs informed consent to participate in this study. This information is required for interpretation of key efficacy (eg, % predicted FVC) and safety (laboratory parameters with age/gender-specific normal ranges) outcomes.

12.3.2. Medical History

For subjects who participated in Study ATB200-03, medical history findings reported for Study ATB200-03 will also be recorded for this study.

12.3.3. Prior/Current Medications

For subjects who participated in Study ATB200-03, any concomitant medications reported during Study ATB200-03 that have not been stopped before the Baseline Visit for this study will be recorded as prior medications.

All subjects will be asked to report any medications (including, to the extent possible, dosage, frequency, start dates, and stop dates) that they are currently taking. All prescription and nonprescription medications will be recorded. In addition, any nondrug therapies (including physiotherapy and occupational therapy) that a subject is undergoing are to be recorded. Details regarding use of ambulatory aids such as a cane or walker as well as respiratory support such as continuous positive airway pressure or bi-level positive airway pressure should also be recorded.

Medications/procedures will be reviewed at each study visit in order to capture any changes that occurred during the study period.

Concomitant medications and nondrug therapies (eg, procedures, surgery, physical therapy, or assistive devices) specifically associated with an AE or IAR should be entered into the corresponding eCRFs.

12.3.4. Physical Examination

Complete physical examinations will include assessment of head, ears, eyes, nose, throat (HEENT), respiratory, cardiovascular, lymphatic, gastrointestinal, and neurologic systems.

Brief examinations will be targeted towards any abnormal findings noted at the previous visit and/or review of ongoing AEs.

All body systems with no abnormal findings must be noted so in the source documents.

12.3.5. Body Weight and Height

Body weight will be entered into the IRT system for calculation of dose. Calibration or standardization of the scale used to measure body weight should be performed on a monthly basis or according to scale specifications.

For subjects who participated in Study ATB200-03, height will be measured at the Baseline Visit only if height is not available in the records for that study.

12.3.6. Vital Signs

Vital signs include blood pressure (systolic and diastolic), respiration rate, heart rate, and temperature. Blood pressure measurements should be obtained using the same arm. Measurements will be taken with the subject in sitting position after having rested for a 5-minute period. The same position should be used at all visits.

12.3.7. Adverse Events

Reporting of AEs begins after the first dose of open-label study drug in this study. As required by their institutions, investigators will be responsible for reporting AE information to their IRB, IEC, or REB (see Section 13). If the start date of an AE is before the first dose of open-label study drug, it should be captured as medical history.

12.3.8. Patient-reported Outcomes

Patient-reported outcomes include the R-PAct Scale, EQ-5D-5L, PROMIS instruments for physical function, fatigue, dyspnea, and upper extremity, and SGIC, as available.

The R-PAct scale is an 18-item questionnaire to measure limitations in activities and restriction in social participation. Possible responses to questions are as follows: unable to perform, able to perform, but with difficulty, and able to perform without difficulty. A raw score ranging from 0 to 36 points is generated.

The EQ-5D-5L comprises 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. Subjects are asked to indicate their health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. The subject's self-rated health is also recorded on a vertical visual analogue scale, where the endpoints are labeled "The best health you can imagine" and "The worst health you can imagine."

Short forms for the PROMIS instruments for physical function (20 items) and upper extremity (7 items) measure signs and symptoms using general questions without a temporal reference. Short forms for the PROMIS instruments for fatigue (8 items) and dyspnea severity (10 items) measure signs and symptoms over the past 7 days. A 5-point scale is used for each instrument (though responses may vary within or among instruments), and a total score is generated for each instrument.

The SGIC is designed to record the subjects' impression of their functional status since starting open-label study drug using a 7-point scale ranging from "very much worse" to "very much improved." The administrator of the SGIC will read the questions to the subject and record the answers.

Subjects are to complete patient-reported outcome questionnaires before any other study assessment, if the questionnaires are available in that subject's language. Separate detailed instructions will be provided in the study functional assessment manual.

12.3.9. Physician's Global Impression of Change

The PGIC is designed to record the physician's assessment of the subject's status, taking into account the subject's signs and symptoms and other neuromuscular symptoms, and signs relative to their status at the Baseline Visit.

12.3.10. Electrocardiogram

A standard 12-lead ECG will be performed after subjects have rested for approximately 5 minutes prior to the start of the ECG recording. Subjects will be in the supine position throughout the ECG evaluation. A central ECG vendor will be used.

12.3.11. Clinical Laboratory Tests

12.3.11.1. Chemistry, Hematology, and Urinalysis

Clinical laboratory tests for safety monitoring include serum chemistry (Table 6), hematology (Table 7), and urinalysis (Table 8). Clinical laboratory tests will be performed prior to administration of study drug. The collection, processing, and shipment of all biological samples will be fully described in the study laboratory manual.

The investigator (or his/her designee) will review each laboratory report from the central laboratory and assess any out-of-range laboratory results as "not clinically significant" or "clinically significant" (see Appendix 3). Any results that are considered clinically significant should be confirmed in a repeat test at the investigator's discretion. The investigator should consider repeat testing of persistent clinically significant results until the analyte returns to normal or until an etiology is determined. The investigator (or his/her designee) will sign and date all laboratory reports. Results for CK, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) will be blinded to investigators and reviewed by an unblinded medical monitor until treatment assignments in Study ATB200-03 are unblinded to maintain consistency.

After approval of this amendment, clinical laboratory tests will be performed locally at site.

Table 6: Serum Chemistry Parameters

ALT	Creatinine
Alkaline phosphatase	GGT
AST	Glucose
Albumin	LDH
Bilirubin, total	Magnesium
BUN	Phosphorous
Calcium, total	Potassium
Carbon dioxide, total (bicarbonate)	Protein, total
Chloride	Sodium
CK	Uric acid

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase

Table 7: Hematology Parameters

Platelet count	Automated white blood cell differential:
Red blood cell count	Neutrophils
White blood cell count (absolute)	Lymphocytes
Hematocrit	Monocytes
Hemoglobin	Eosinophils
	Basophils

Table 8: Urinalysis Parameters

Color	Ketones
Appearance	Blood
Specific gravity	White blood cells
pH	Nitrite
Protein	Bilirubin
Glucose	Microscopy of sediment

12.3.11.2. Pregnancy Tests

All female subjects of childbearing potential will have a urine pregnancy test performed at infusion visits. If the urine pregnancy test has a positive result, study drug will not be administered and a confirmatory serum pregnancy test will be performed. Any pregnancy that occurs during the study period must be reported, and that subject must be withdrawn from the study (see Section 13.4).

12.3.12. Immunogenicity Assessments

Blood samples for measurement of anti-rhGAA antibodies (total and neutralizing) will be collected predose along with the clinical safety laboratory samples.

Neutralizing antibody assays may include the following:

- inhibition of rhGAA-mediated hydrolysis of 4-methylumbelliferyl-glucoside
- inhibition of rhGAA-mediated hydrolysis of glycogen
- inhibition of rhGAA binding to cation-independent mannose 6-phosphate receptor

Subjects who are confirmed to have a positive result for anti-rhGAA antibodies from the 30-day safety follow-up visit will continue to have follow-up immunological testing as long as they have a positive result for up to 12 months after the last dose of study drug (ie, at 6 months and 12 months) or until they begin treatment with an investigational therapy or an ERT that is approved by the local health authority and is commercially available or they start receiving cipaglucosidase alfa/miglustat through a post-trial access program.

If a subject experiences anaphylaxis or a moderate to severe IAR (in the opinion of the investigator) as outlined in Section 13.1.3, 3 blood draws will be required for measurement of

immunoglobulin E (IgE) levels. The first blood draw should be obtained 6 to 8 hours after onset of the infusion reaction, the second blood draw at 24 hours, and the third immediately before the next administration of study drug. Because anti-rhGAA or IgE results could potentially reveal a subject's treatment assigned in Study ATB200-03, these results will not be included on laboratory test reports.

Total GAA protein concentration will also be measured from the same blood sample since assay sensitivity for both anti-rhGAA antibodies and IgE can be affected by GAA protein levels.

An unblinded medical monitor not involved in the operational aspects of the study will manage review of all immunogenicity results, until Study ATB200-03 is unblinded.

12.3.13. Sample Collection for Pharmacokinetic Assessments (Sites in Japan Only)

Japanese subjects who participated in Study ATB200-03 will have sparse blood samples collected just prior to initiation of cipaglucosidase alfa infusion (time 0) and at 1, 4, 6, 12, and 24 hours after the start of cipaglucosidase alfa infusion at either Week 2, 4, or 6, and at Week 52 (Table 5) for plasma total GAA protein signature peptide T09 and plasma miglustat. Collection of the 12-hour sample will be optional.

Vital signs may be measured after each PK blood sample for monitoring of safety, as per local clinical guidelines, but results will not be recorded in the eCRF.

Pharmacokinetic assessment in Japanese subjects is necessary to fulfill local regulatory requirements for marketing applications.

12.3.14. Creatine Kinase and Urinary Hexose Tetrasaccharide

Creatine kinase is a type of enzyme found within muscles. Injury to the membrane surrounding muscle cells allows CK to leak into the bloodstream; therefore, increased levels of CK can be indicative of muscle injury. Creatine kinase levels will be measured as part of the serum chemistry panel and results will be blinded until treatment assignments in Study ATB200-03 are unblinded.

Levels of urinary Hex4, a biomarker of disease substrate, will be measured. The assay specifically targets one hexose tetrasaccharide, the glucose tetrasaccharide Glc4, which is a biomarker of glycogen storage. Glc4 is separated from other hexose tetrasaccharides in urine by ultra performance liquid chromatography and quantified by stable isotope dilution. The reported Hex4 value is actually a measure of Glc4. Concentrations of Glc4 are compared with age-matched control ranges.

12.3.15. Biological Specimens

Any biological specimens remaining at the end of the study may be used for future exploratory assays to improve the understanding of Pompe disease and its management. The retention of samples is optional; subjects will have the option to agree or refuse to have their samples retained. The retained samples will not be used for any future genetic testing.

These activities are in line with the EU General Data Protection Regulation (GDPR) and any other local applicable regulations.

12.3.16. Pulmonary Function Tests

Pulmonary function tests to be performed include FVC (sitting and supine), SVC (sitting and supine), MIP, MEP, and SNIP. These tests should be performed in the same position and in the same order at each study visit. If possible, the tests should be administered by the same person at each visit. The identity and qualification of the test administrator will be recorded. Training will be provided for site personnel.

Pulmonary function tests must be performed as detailed in a separate manual. A central vendor for pulmonary function tests will be used for this study.

12.3.17. Motor Function Tests

Motor function tests to be performed include the GSGC test and the TUG test.

The GSGC consists of a 10-meter walk for evaluation of gait, a 4-stair climb, Gowers' maneuver, and arising from a chair. Results of the GSGC include the time required to complete the individual tests, individual scores for each of the tests (1 to 7 points for each of gait, 4-stair climb, and Gowers' maneuver and 1 to 6 points for arising from a chair), and a total score. The total score ranges from a minimum of 4 points (normal performance) to a maximum of 27 points (worst score).

For the TUG test, the time it takes for the subject to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down will be recorded.

These assessments should be performed without an assistive device (eg, cane, walker). If at any time during the study, it is unsafe for a subject to perform an assessment without an assistive device, that test should not be performed and a comment should be entered on the source document indicating why the assessment was not completed.

The motor function tests will be performed in the same order at each study visit. If possible, the tests should be administered by the same person at each visit. The identity and qualification of the test administrator will be recorded. Training will be provided for site personnel by a central vendor.

Separate detailed instructions for these tests will be provided in the study functional assessment manual.

12.3.18. 6-Minute Walk Test

The 6MWT is an assessment of ambulatory function that involves the skeletal muscle, pulmonary, and cardiac systems as well as motor function.

The objective of the 6MWT is to walk (not run or jog) as far as possible for 6 minutes. The timed walk test should be performed with walking shoes on a flat surface. Subjects may use an assistive device (eg, cane, walker, rollator) to perform the 6MWT. If they do so at the Screening Visit of Study ATB200-03, they should use the same assistive device at all subsequent visits. If a subject has a change in the use of an assistive device that was used to perform the 6MWT during Study ATB200-03, then the 6MWT must be repeated at the Baseline Visit. Also, any changes in the use of an assistive device must be clearly documented and include description of assistive device and date of change.

The tests should be administered by the same person, as much as possible, at each visit. The identity and qualification of the test administrator will be recorded. Training will be provided for site personnel by a central vendor.

The clinical evaluator will make an assessment of validity (ie, valid or invalid), according to detailed criteria in the study functional assessment manual. The assessment of validity by the clinical evaluator will be used for determining eligibility at screening.

Separate detailed instructions for this test will be provided in the study functional assessment manual.

12.3.19. Muscle Strength Testing

Muscle groups tested include shoulder abductors, shoulder adductors, elbow extensors, elbow flexors, hip flexors, hip abductors, hip adductors (hand-held dynamometer only), knee extensors, and knee flexors.

Manual muscle strength will be assessed by neurological (physical exam) assessment using the Medical Research Council scale (0 to 5 points, with 5 indicating normal function). The same rater and method must be utilized as much as possible throughout the subject's participation in the study.

Quantitative muscle strength will also be measured using a hand-held dynamometer and measured in kg of pressure. If possible, the tests should be administered by the same person at each visit. The identity and qualification of the test administrator will be recorded. Training will be provided for site personnel.

Separate detailed instructions for these tests will be provided in the study functional assessment manual.

13. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

13.1. Definitions

13.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, biologic (at any dose), or medical device, which does not necessarily have a causal relationship with the treatment. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medical product.

According to this protocol, expected or anticipated evolution of the disease under treatment will be evaluated as part of the disease symptom assessment. Changes in Pompe disease symptoms must be reviewed by the investigator or a medically qualified sub-investigator and recorded as "clinically significant" or "not clinically significant" in subjects' source records (see Appendix 3). Expected or anticipated changes in the clinical condition may not qualify as AEs. However, if there is a clinically relevant worsening of a sign or symptom of the disease under treatment and the outcome fulfills the definition of an AE, it must be reported as directed in the protocol.

For subjects who participated in Study ATB200-03, any AE that begins after the first dose of open-label study drug will be considered a treatment-emergent adverse event (TEAE).

Subjects experiencing AEs should be followed up until their health has returned to baseline status or stabilized.

Adverse events include the following:

- the onset of new signs, symptoms, conditions, and illnesses
- exacerbation of pre-existing conditions or illnesses
- abnormal laboratory findings deemed clinically significant by the investigator
- physical examination changes deemed clinically significant by the investigator
- abnormal medical evaluation findings (eg, ECG) that are not documented at the last visit in Study ATB200-03 and/or, in the investigator's opinion, represent a clinically significant change in the subject's health during study participation

13.1.2. Serious Adverse Events

A SAE is any AE that

- results in death
- is life-threatening
  - An AE, in the view of either the investigator or Amicus, that places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more serious form, might have caused death.

- requires inpatient hospitalization or prolongs existing hospitalization
  - Hospitalization signifies that the subject has been admitted, regardless of duration, for observation and/or treatment that would not have been appropriate in a physician's office or outpatient setting.
  - Hospitalizations for elective or preplanned treatment of a pre-existing condition do not have to be reported as SAEs, provided that
    - the condition is documented in the subject's medical history and has not worsened since the informed consent form (ICF) was first signed, and
    - the planned procedure is documented in the subject's eCRF at the Baseline Visit.

      Note: Outpatient procedures performed in a hospital do not qualify as an SAE.
  - Emergency room/department or outpatient treatments that do not result in admission do not have to be reported as an SAE, unless another SAE criterion is met.
    - Events assessed and treated in these circumstances should be captured as AEs.
  - Hospitalizations solely based on logistics (eg, subject is admitted due to limited hospital accessibility for what would otherwise be an outpatient procedure) do not have to be reported as SAEs.
    - These hospitalizations should be clearly defined as such in the subject's source record.
- results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, as decided by the investigator
- is a congenital anomaly/birth defect

An important medical event that may not result in one of the above-mentioned serious outcomes may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the serious outcomes. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

For all subjects, AEs and SAEs will be reported from time of first dose of open-label study drug until 30 days after the last dose of study drug. If the investigator becomes aware of an SAE in a subject or receives an unsolicited report of an SAE from a subject more than 30 days after the last treatment, and considers the event possibly, probably, or definitely related to previous study treatment, he or she should contact the Amicus medical monitor to determine how the SAE should be documented and reported.

13.1.3. Infusion-associated Reactions

An IAR is defined as a disorder characterized by 1 or more adverse reaction(s) to the infusion of pharmacological or biological substances. These reactions are classified into 2 major subtypes, early and late, according to the time interval between the infusion and the onset of an infusion-related AE.

The reactions are divided into 5 severity grades as follows:

1. Mild (requires observation only); for example, transient flushing or rash
2. Moderate (minimal, usually oral, intervention suffices); for example, urticaria/myalgia/drug fever
3. Severe (vital organ involved yet not in a life-threatening manner; usually requires parenteral medication); for example, bronchospasm/angioedema/hypotension
4. Life threatening (multisystem involvement of vital organs, urgent and critical care required); for example, systemic anaphylactic reaction
5. Death

Early IARs is any symptom or sign occurring during or within 24 hours of completion of the infusion and deemed a drug-related AE by the investigator, unless an alternative obvious explanation exists, eg, mechanical fall. Early IARs commonly involve 1 or more of the following systems: skin (urticaria and erythema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (wheezing, bronchospasm), and gastrointestinal tract (diarrhea, vomiting).

Late IAR is any symptom or sign occurring more than 24 hours (usually 1 to 3 days) after completion of the infusion that, in the investigator's opinion, fits the clinical description of a symptom or sign associated with an IAR. The most common symptoms of late IARs are pruritic skin eruptions, fever, malaise, and polyarthralgia.

Note: The list of IAR symptoms provided in Table 9 is not comprehensive. It is meant to serve as a guideline to the investigators to report and manage IAR as AE. Table 9 also provides a guideline for management of IARs and anaphylaxis (see also Appendix 2). The guideline is intended for sites that do not have such procedures in place. It is at the investigator's discretion to follow the guidelines or implement treatment protocol that their center is accustomed to following.

When an IAR occurs, it is important to report and indicate in the eCRF all AEs that are associated with the IAR. All available details of the events observed with an IAR are necessary to assess the evolution of the AEs after premedication for subsequent infusions.

In the event that a subject experiences an IAR, the subject should be premedicated for subsequent infusions with antihistamines, steroids, and/or acetaminophen, infusion rate adjustments, or other steps taken. If these measures are not successful, the investigator/designee should contact the medical monitor for guidance. The premedications should be continued for all remaining infusions.

Table 9: Guidelines for Management of Early Infusion-associated Reactions

Severity	Symptoms (such as, but not restricted to)	Management Guidelines
Mild reaction	Flushing Nausea Mild headache Tachycardia (pulse < 100 bpm) Abdominal pain	REDUCE INFUSION RATE BY 50% Contact investigator. Give oral antihistamine/acetaminophen and/or IV antihistamine. Prepare emergency equipment for any subsequent study drug escalation. Subject must be observed at site or medical facility for 2 to 4 hours after resolution of the symptoms. Record all details of times, concomitant medications and nondrug therapies, and infusion rates. Record all details. Report AE, if applicable. IF SYMPTOMS PERSIST: STOP THE INFUSION After 30 minutes, if subject has improved, increase to previous infusion rate on direction of investigator/designee. If subject has not improved after 60 minutes, consult with investigator as to whether additional medications should be administered. If subject reacts for second time after return to the prior infusion rate, reduce rate by 50% and contact investigator/designee. IF IN DOUBT, STOP INFUSION
Moderate reaction	Localized itchiness, and/or raised Urticarial rash (hives) Severe headache Fever or shivering Tachycardia (pulse > 100 bpm) Tachypnea Flushing Nausea Irritability Headache Vomiting Diarrhea Abdominal cramps Myalgia	** STOP INFUSION ** Immediately contact investigator. Administer high-flow oxygen if respiratory symptoms/distress. Give IM or IV antihistamines (eg, promethazine 25 to 50 mg). Give IV fluid bolus, if warranted. Give IV steroids (hydrocortisone 100 mg) on direction of investigator/designee. Continue management as directed by the investigator/designee. If deemed appropriate by investigator/designee, resume study drug infusion at reduced rate and prepare emergency equipment. If deemed appropriate by investigator/designee, infusion can be suspended and reinitiated 48 hours later with premedications and at the infusion rate that was last tolerated. Observe subject for a minimum of 6 hours after resolution of the event. Record all details. Report AE, if applicable.

Table 9: Guidelines for Management of Early Infusion-associated Reactions (Continued)

Severity	Symptoms (such as, but not restricted to)	Management Guidelines
Severe reaction, anaphylaxis, or anaphylactoid reactions	Chest pain Generalized urticarial/ angioedema Symptomatic hypotension (subject feeling faint, paleness) Hoarseness of voice/laryngeal edema Bronchospasm	** STOP INFUSION ** Activate emergency response and immediately contact investigator. For chest pain and symptomatic hypotension, initiate emergency procedures. Administer high-flow oxygen or intubate and mechanically ventilate as appropriate. Give IM adrenaline 300 mcg EpiPen into thigh (avoid buttock). If no response, repeat dose in 5 minutes. Prepare infusion of adrenaline 3 mg/50 mL NS (60 µg/mL), if needed. Give IV fluids 10- to 20-mL/kg fluid bolus on direction of investigator/designee. Give IV antihistamines (promethazine 25 to 50 mg in 10 mL WFI over 2 to 3 minutes). Give IV steroids (hydrocortisone 100- to 500-mg bolus IV injection; dilute in 10 mL NS for doses between 100 and 500 mg) and infuse over 2 minutes. Give nebulized beta-2 agonists with high-flow oxygen on direction of investigator/designee. Administer other treatments and/or transfer patient to hospital/ICU as recommended by investigator/designee. Observe subject for a minimum of 24 hours after resolution of the event. If deemed appropriate by investigator/designee, study drug infusion can be re-initiated 7 to 14 days with premedications and at the 4-hour duration. Record all details. Report AE, if applicable.

Abbreviations: AE = adverse event; GAA = human acid α-glucosidase; ICU = intensive care unit; IgE = immunoglobulin E; IM = intramuscular; IV = intravenous; NS = normal saline; WFI = water for injection
Source: Vogel 2010; Sampson, Muñoz-Furlong et al. 2006

13.1.4. Relationship to Study Drug

The investigator or a qualified sub-investigator will review each event and assess its relationship to ERT based on available information according to the following guidelines:

- Definite: A reaction that follows a distinct temporal relationship from administration of the study drug, that follows a known reaction to the agent or chemical group of the study drug, and that cannot be explained by the subject's clinical state or other factors. By definition, IARs (immediate or late type) are considered definite (see Section 13.1.3).

- Probable: A reaction that follows a reasonable temporal sequence from administration of the study drug, that follows a known or expected response pattern to the suspected study drug, and that could not be reasonably explained by the known characteristics of that subject/subject's clinical state.
- Possible: A reaction that follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.
- Unlikely: A reaction that does not follow a reasonable temporal sequence from administration of the study drug. However, causality from the study drug cannot be ruled out.
- Unrelated: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

For the purpose of reporting SAEs to regulatory authorities and IRBs/IECs/REBs, any AE assessed by the investigator as definitely, probably, or possibly related to study drug will be considered "related" to study drug (ie, associated with the use of the study drug). Any AE assessed as unlikely or unrelated will be considered "not related" to study drug (ie, not associated with the use of study drug).

13.1.5. Assessment of Severity

The following definitions for rating severity will be used:

- Mild: Awareness of sign, symptom, or event, but the AE is easily tolerated and does not interfere with daily activity.
- Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention, but the subject is still able to function.
- Severe: Incapacitating with inability to do usual activities or significantly affects clinical status and requires medical intervention.

When the determination of AE severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of the investigator or a qualified sub-investigator.

13.2. Reporting of Adverse Events

Information regarding AEs is to be obtained by questioning or examining the subject.

For subjects who participated in Study ATB200-03, AEs will be recorded in the eCRF and subject's source record beginning after the first dose of open-label study drug until 30 days after the last treatment visit.

A single diagnosis should be entered when known. If a clear diagnosis cannot be determined at the time of the eCRF and subject's source record entries, each sign and symptom must be recorded individually, until a final diagnosis is established. Pompe-related conditions, signs,

symptoms, etc, that are present in the subject's medical history should only be reported as AEs if they worsen (ie, increase in severity) during the subject's participation in the study.

For each AE reported, the date and time the event started and ended, action taken, outcome (resolved, resolved with sequelae, ongoing, or fatal), and severity must be noted.

All subjects who have AEs, whether or not considered associated with the use of study drug, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied, if possible. For all AEs that require or result in subject discontinuation from the study, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

If the investigator considers it necessary to report a nonserious AE in a study subject more than 30 days after the last visit, he or she should contact Amicus to determine how the AE should be documented and reported.

13.3. Reporting Requirements for Serious Adverse Events

If an AE is serious (as defined in Section 13.1.2), the investigator must submit an SAE report form at the time the SAE is identified. All SAEs must be immediately reported by the investigator to Amicus or Amicus' designee, but no later than 24 hours after any study site personnel is aware of the event. Serious adverse event report forms must be faxed to the designated safety fax number (+1 866-422-1278) or sent via email to safetyreporting@amicusrx.com. All supporting documentation available at the time of reporting, with all subject identifiers redacted in accordance with local requirements, must be included in the fax along with the SAE report form.

The initial report must be completed as soon as possible. All known details of the SAE and an assessment of the causal relationship between the event and study drug, or study procedure should be included in the initial report. All information not available at the time of the initial report (eg, event end date, discharge summary, or results of diagnostic procedures/evaluations related to the event) must be provided in a follow-up report. Follow-up information must be reported using the designated fax number within 24 hours of receipt at study sites.

Every attempt should be made to describe events in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms should not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Study endpoints that meet SAE criteria (as per Section 13.1.2) must also be immediately reported by the investigator to Amicus or Amicus' representative but no later than 24 hours after any study site personnel is aware of the event.

If a nonserious event becomes serious, the event must be reported as described above.

If the investigator becomes aware of an SAE in a subject or receives an unsolicited report of an SAE from a subject more than 30 days after the last treatment, and considers the event possibly, probably, or definitely related to previous study treatment, he or she should contact the Amicus medical monitor to determine how the SAE should be documented and reported.

The Amicus Safety Physician will determine the expectedness of AEs according to current safety reference document (eg, current Investigator's Brochure or other safety-related information as available).

13.3.1. Additional Reporting Requirements for Suspected Unexpected Serious Adverse Reaction

Any AE that is serious, unexpected, and associated with the use of the study drug (suspected unexpected serious adverse reaction [SUSAR], also referred to as Expedited Safety Report and Investigational New Drug Safety Report) has additional reporting requirements. All investigators conducting clinical studies with the study drug will be notified of such events and must inform their IRBs/IECs/REBs as required in accordance with local law. Amicus will ensure that SUSARs are reported to regulatory agencies in accordance with local law in each country where study sites are located.

- If the SUSAR is fatal or life-threatening, associated with the use of the study drug, and unexpected, regulatory authorities and IRBs/IECs/REBs will be notified within 7 calendar days after Amicus learns of the event.
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study drug, and unexpected, regulatory authorities and IRBs/IECs/REBs will be notified within 15 calendar days after Amicus learns of the event.

Safety updates will be provided periodically to the regulatory authorities and IRBs/IECs/REBs responsible for the study according to the rules in effect in each country where study sites are located. These updates will include information on SUSARs and other relevant safety findings.

13.3.2. Overdose/Underdose

A product overdose/underdose (whether accidental or intentional) is considered by Amicus to be an AE and must be recorded as such in EDC. If a subject experiences an overdose or an underdose during the course of the study (as defined below for each product, whether symptomatic or not), the Amicus medical monitor must be notified within 5 working days of the investigator or study personnel first becoming aware of the overdose/underdose.

- Overdose
  - cipaglucosidase alfa: ≥ 20% higher than the assigned dose of study drug for a single administration (20 mg/kg x patient weight)
  - miglustat: ≥ 1 capsule more than the assigned dose of study drug for a single administration

- Underdose
  - cipaglucosidase alfa: ≥ 20% lower than the assigned dose of study drug for a single administration (20 mg/kg x patient weight)
  - miglustat: ≥ 1 capsule less than the assigned dose of study drug for a single administration (eg, if a subject is supposed to receive 4 capsules, but only receives 1, 2, or 3 capsules; or if a subject is supposed to receive 3 capsules but only receives 1 or 2 capsules)

Follow-up information must be forwarded on the outcome of the overdose/underdose as applicable. If an SAE occurs in conjunction with the overdose/underdose, the same SAE reporting requirements described in Section 13.3 apply.

13.3.3. Missed Dose

If a subject is unable to schedule a treatment (infusion) up to 7 days after the scheduled date, this is considered as a missed dose. The subject will receive his or her next dose per his or her schedule, ie, approximately 4 weeks following the previous dose, since the subject missed a dose at 2 weeks following the last dose. This is recorded as a protocol deviation. Any AE that occurs as a result of missed dose should be recorded as such. The Amicus medical monitor should be notified as soon as feasible after the investigator or study personnel first become aware of the missed dose. Follow-up information on the outcome must be forwarded as applicable. If an SAE occurs in conjunction with the missed dose, the same SAE reporting requirements described in Section 13.3 apply.

Study subjects who missed infusions close to their scheduled assessments at Week 12, Week 26, or at any of the study visits scheduled every 26 weeks after Week 26 should postpone the assessments and receive a sufficient number of catch-up infusions prior to undergoing the study assessments. Each instance of missed infusion should be discussed with, and course of action approved by, the medical monitor. A reason for the missed visit should be entered into the EDC. The relevant IRBs, IECs, and REBs should be notified of any deviations from the protocol.

13.4. Reporting of Pregnancy

Pregnancy information for female subjects and female partners of male subjects participating in the study is collected by Amicus. Pregnancy, in and of itself, is not regarded as an AE (unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication).

If a female subject becomes pregnant during the course of this study, or if the female partner of a male subject becomes pregnant during the subject's participation in the study, the event must be reported within 5 working days of the investigator or study personnel becoming aware of the pregnancy. Study drug will be discontinued, and the subject will be monitored for the duration of pregnancy and the baby for 6 months following birth. If an SAE occurs in conjunction with the pregnancy, the SAE must be reported as described in Section 13.3. Amicus will provide pregnancy report forms and instructions to study personnel regarding collection of pregnancy and outcome information (subject to receipt of data privacy release approvals where required under local privacy laws).

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was withdrawn from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

14. DATA MANAGEMENT

For this study, subject data will be entered into an electronic data capture system managed by Amicus (or designee). The data will be transmitted via a secure electronic method to Amicus (or designee) as defined in the Data Management Plan.

Management of clinical data will be performed in accordance with applicable Amicus standards, ICH, GCP, CFR Part 11, and data cleaning procedures to ensure the integrity of the data (eg, determining errors and inconsistencies in the data and ensuring data are corrected by site personnel or designees).

After database lock, each study site will receive an electronic file containing all of their site-specific eCRF data as entered into the electronic data capture system for the study, including full discrepancy and audit history. Additionally, an electronic copy of all of the study site's data from the study will be retained by Amicus and designee for storage. In the event that the subject revokes authorization to collect or use protected health information, the investigator retains the ability to use all information collected prior to the revocation of subject authorization.

15. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The final analysis of the whole data set detailed in this section will be performed for the final CSR based on a data cutoff date of 31 December 2024. Any data collected after this date will be provided as an addendum to the final CSR when all subjects have completed the study or have been withdrawn from the study.

For subjects continuing in the study after approval of this amendment, please refer to Appendix 1 for details on the data analysis and statistical considerations.

15.1. Endpoints

15.1.1. Safety Endpoints

The long-term safety profile of cipaglucosidase alfa/miglustat will be characterized using incidence of TEAEs, SAEs, and AEs leading to discontinuation of study drug, frequency and severity of immediate and late IARs, and any abnormalities noted in other safety assessments (eg, clinical laboratory tests, ECGs, vital signs). Immunogenicity to cipaglucosidase alfa will also be described.

15.1.2. Efficacy Endpoints

Efficacy endpoints are as follows:

- change from baseline in 6MWD
- change from baseline in 6MWD (% predicted)
- change from baseline in sitting FVC (% predicted)
- change from baseline in the manual muscle test score for the lower extremities
- change from baseline in the total score for the PROMIS – physical function
- change from baseline in the total score for the PROMIS – fatigue
- change from baseline in the following variables related to motor function:
  - GSGC total score
  - time to complete the 10-meter walk (ie, assessment of gait) of the GSGC test
  - time to complete the 4-stair climb of the GSGC test
  - time to complete the Gowers' maneuver of the GSGC test
  - time to arise from a chair as part of the GSGC test
  - change from baseline in the time to complete the TUG test
- change from baseline in the following variables related to muscle strength:
  - manual muscle test score for the upper extremities
  - manual muscle test total score (upper and lower extremities combined)
  - quantitative muscle test value (kg) for the upper extremities

  - quantitative muscle test value (kg) for the lower extremities
  - quantitative muscle test total value (kg) (upper and lower extremities combined)
- change from baseline in the following variables from patient-reported outcome measures:
  - total score for the PROMIS – dyspnea
  - total score for the PROMIS – upper extremity
  - R-PAct Scale total score
  - EQ-5D-5L health status
- actual value of the subject's functional status (improving, stable, or declining) pertaining to the effects of study drug in the following areas of life, as measured by the SGIC:
  - overall physical well-being
  - effort of breathing
  - muscle strength
  - muscle function
  - ability to move around
  - activities of daily living
  - energy level
  - level of muscular pain
- actual value of the subject's functional status (improving, stable, or declining), as measured by the PGIC
- change from baseline in the following measures of pulmonary function, as follows:
  - sitting SVC (% predicted)
  - MIP (cmH_2O)
  - MIP (% predicted)
  - MEP (cmH_2O)
  - MEP (% predicted)
  - SNIP (cmH_2O)

15.1.3. Pharmacodynamic Endpoints

Pharmacodynamic endpoints are as follows:

- change from baseline in serum CK level
- change from baseline in urinary Hex4 level

15.1.4. Pharmacokinetic Endpoints (in Subjects at Sites in Japan Only)

Pharmacokinetic endpoints (applicable for subjects at sites in Japan only):

- sparse blood sampling for determination of total GAA protein levels and miglustat concentrations in plasma for a population PK analysis

Pharmacokinetic endpoints derived from a population PK analysis of total GAA protein and miglustat concentrations will be provided in a separate modeling and simulation plan.

15.2. Sample Size Considerations

No formal sample size calculation was performed for this open-label extension study. The maximum sample size for this study is based on the number of subjects who complete Study ATB200-03, which has a target enrollment of 110 subjects.

15.3. Data Analysis Considerations

The Statistical Analysis System (SAS®) version 9.4 (or latest version at the time of the analysis) and R© software will be used for all statistical procedures and analyses.

Full details of the data and analysis methods will be provided in the statistical analysis plan.

15.3.1. Analysis Populations

The open-label extension enrolled subjects (OLE-ES) is a subset of the ATB200-03 intent-to-treat (ITT) population, and it includes all subjects who satisfied the eligibility requirements (based on the inclusion and exclusion criteria) and entered Study ATB200-07. This population will be used for the analyses of all efficacy and pharmacodynamic endpoints involving Studies ATB200-03 and ATB200-07 integrated data.

The open-label extension full analysis set (OLE-FAS) includes all subjects who entered the OLE Study ATB200-07 who had both a valid baseline and at least one post-baseline assessment, for at least 1 of these efficacy endpoints (6MWD, sitting % predicted FVC, MMT-lower extremities, PROMIS – physical function, PROMIS – fatigue, and GSGC). This analysis set will be used for the analyses of the main efficacy and pharmacodynamic endpoints involving Study ATB200-07 stand-alone data.

The open-label extension safety population includes all subjects who took at least 1 dose of cipaglucosidase alfa/miglustat co-administration in Study ATB200-07. This population will be used for the summaries of medical history, drug exposure, and any other specific safety-related summaries for Study ATB200-07 stand-alone data.

The safety population consists of all subjects who took at least 1 dose of study drug in either Study ATB200-03 or Study ATB200-07. This population will be analyzed per the actual treatment received and will be used for all integrated safety summaries.

The treatment switched population is defined as subjects who were randomized to and received alglucosidase alfa/placebo in Study ATB200-03 and subsequently received cipaglucosidase alfa/miglustat in Study ATB200-07. This population will be used for specific analyses involving these treatment-switched subjects.

15.3.2. Treatment Groups

Appropriate reporting treatment groups will be defined in the statistical analysis plan for all analyses involving ATB200-07 stand-alone data as well as ATB200-03 and ATB200-07 integrated data.

15.3.3. Statistical Methods

15.3.3.1. Interim Analyses

Interim analysis or analyses may be performed for purposes of writing an interim clinical study report.

15.3.3.2. Adjustment for Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed. All analyses will be descriptive.

15.3.3.3. Missing Data Handling

For all efficacy endpoints based on patient-reported outcome/clinical outcome assessment instruments, the scoring algorithms (including the standard or published data imputation or pro-rating methods contained in the scoring algorithms) will be implemented.

No data imputation are planned for missing efficacy data. If any imputations are decided upon later, the details will be provided in the statistical analysis plan.

In general, missing safety data will not be imputed. However, attributes such as missing dates for AEs and concomitant medications will be imputed using similar methods as described for ATB200-03 in order to ensure consistency. Details will be provided in the statistical analysis plan.

15.3.3.4. Windowing Conventions

By-visit assessments for safety and efficacy will be summarized based on visit windows.

15.3.3.5. Statistical Tests

No formal hypotheses are planned to be tested. Unless otherwise specified, only descriptive statistics will be presented. Any inferential analyses will be presented for summary purposes. Where appropriate, 2-sided 95% confidence intervals will also be provided for summary purposes.

15.3.3.6. Common Calculations

In general, continuous variables will be summarized using descriptive statistics (the number of subjects with available data, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized using counts and percentages.

15.3.4. Analyses

15.3.4.1. Efficacy Analyses

In general, continuous data will be summarized using descriptive statistics, and categorical data will be summarized using counts and percentages, as described above in Section 15.3.3.6. Specific analysis details and display format will be described in the statistical analysis plan.

15.3.4.1.1. Analyses of Ambulatory Function, Motor Function, Pulmonary Function, and Muscle Strength

The OLE-FAS and OLE-ES populations will be used for the analysis of 6MWD, FVC % predicted, GSGC total score, other manual muscle tests, quantitative muscle tests, and other pulmonary function tests. The % predicted 6MWD will also be summarized, where the predicted value will be calculated using the reference equations from Enright and Sherill (Enright and Sherill 1998). These continuous endpoints will be summarized as described in Section 15.3.3.6, by treatment group and visit. The change from baseline will be similarly summarized by treatment group and visit, and the 95% confidence intervals for the mean change will be provided for each treatment group. In addition, these analyses will be conducted on the treatment switched population (where applicable) for 6MWD and FVC % predicted.

15.3.4.1.2. Patient-reported Outcomes and Physician's Global Impression of Change

The OLE-FAS and OLE-ES populations will be used for patient-reported outcome analyses. Summary of each item as well as total score (raw total score and change from baseline in total score) for R-PAct Scale, EQ-5D-5L (domain scores are to be analyzed as both categorical and continuous variables), and PROMIS instruments will be summarized by treatment group and visit. The change from baseline in the total scores will be analyzed as described in Section 15.3.3.6, by treatment group and visit, and the 95% confidence intervals for the mean change will be provided for each treatment group.

Each item/domain of the SGIC will be summarized by treatment group and visit. The scores will be analyzed as both categorical and continuous variables. Additionally, the response scale for each item will be divided into 3 categories (improving, stable, or declining) which reflect the functional status, and these will be summarized by treatment group.

Summary of response score for actual values for PGIC will be summarized by treatment group and visit.

15.3.4.2. Biomarker Analyses

The OLE-ES population will be used for biomarker analyses involving serum CK and urinary Hex4. These continuous endpoints will be summarized as described in Section 15.3.3.6, by treatment group and visit. Changes from baseline will be similarly summarized by treatment group and visit, and the 95% confidence intervals for the mean and/or median change will be provided for each treatment group.

15.3.4.3. Pharmacokinetic Analyses (Data from Sites in Japan Only)

After sparse sampling in Japanese subjects, PK endpoints derived from a population PK analysis of total GAA protein and miglustat concentrations will be provided in a separate modeling and

simulation plan. These data will be incorporated into previously developed population PK models and will be used to update the analyses.

The effects of demographic factors on variability of cipaglucosidase alfa and miglustat PK in Japanese subjects will be investigated throughout the modeling process.

15.3.4.4. Safety Analyses

Safety analyses will be based on the safety population (for ATB200-03 and ATB200-07 integrated data) as well as the open-label extension safety population (for ATB200-07 stand-alone data).

Safety data will be summarized using descriptive statistics for continuous data and using counts and percentages for categorical data, as described in Section 15.3.3.6.

Exposure to study medication will be calculated in weeks and analyzed as continuous variables using descriptive statistics. In addition, the duration of exposure will be categorized and a frequency distribution of the categories (each summarized by count and percentage) will be presented.

An overall summary of incidence of AEs (which includes the total number of TEAEs, total number of serious TEAEs as well as the total number of subjects) will be presented. The number and percentage of subjects who experienced nonserious TEAEs as well as serious TEAEs will be summarized by preferred term within system organ class. The summary of nonserious and serious TEAEs will also be presented by intensity (mild, moderate, severe), as well as by relationship to study medication. In addition, the number of AEs (as opposed to the number and percentage of subjects) will be presented.

Serious adverse events, including deaths, will be summarized and listed. Separate listings of death, SAEs (treatment-emergent and nontreatment-emergent), and discontinuations due to AEs will be provided.

Summaries and listings will also be provided for deaths, SAEs, and AEs leading to discontinuation and infusion-associated reactions. Adverse events will be coded using Medical Dictionary for Regulatory Activities version 18 or higher.

Clinical laboratory results, ECG parameters, and vital signs will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) by treatment group and visit for actual values and changes from baseline. The proportion of subjects with abnormalities will be provided for clinical laboratory results, ECGs, and vital signs. Shift tables will also be provided for clinical laboratory results.

Prior and concomitant medications and nondrug therapies will be summarized by treatment group. Concomitant medications terms will be coded using the World Health Organization Drug Dictionary (September 2013 DDE).

15.3.4.5. Immunogenicity Analyses

The effect of immunogenicity results on efficacy and safety will be explored. Analysis of immunogenicity data will be described separately.

16. STUDY CONDUCT CONSIDERATIONS

This global study will include both US sites operating under the Investigational New Drug (IND) application (ie, IND sites) and foreign sites (ie, non-IND sites). All investigators will be required to certify their compliance with both International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) and their respective country's applicable laws and regulations. Both IND and non-IND sites will be operating under a single protocol (ie, there will not be a separate protocol for non-IND sites). The sponsor will ensure the conduct, monitoring, auditing, recording, analysis, and reporting of clinical trial results are in accordance with ICH GCP, providing assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

The study will be conducted in compliance with the protocol, with the Regulation (EU) No 536/2014, and with the principles of GCP.

16.1. Posting of Information on Publicly Available Clinical Trial Registers

Amicus will be responsible for registering this clinical study in global public registries that meet the requirements specified by the International Council of Medical Journal Editors, such as ClinicalTrials.gov, and for publication of study results. Investigators will provide contact information to Amicus for the study listing.

16.2. Regulatory and Ethical Considerations

16.2.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the current version of the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and Amicus' policy on bioethics.

16.2.2. Independent Ethics Committees/Institutional Review Boards Approval and Study Compliance

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC/REB, as appropriate. The investigator must submit written approval to Amicus (or designee) before he or she can recruit any subject into the study.

The principal investigator is responsible for informing the IRB/IEC/REB of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC/REB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/IEC/REB upon receipt of amendments and annually, if applicable, as local regulations require.

16.2.3. Ongoing Information for Independent Ethics Committees/Institutional Review Boards

The information listed below must be submitted to the IECs/IRBs/REBs according to timelines specified by individual IEC/IRB/REB-documented submission policies and procedures, or by local law:

- adverse event information

- expedited safety reports
- periodic reports on the progress of the study

Submissions may be made by Amicus (or designee) or by the investigator.

16.2.4. Subject Information and Informed Consent

Signed written informed consent is to be obtained from each subject prior to any study-related procedures being performed. Consent must be in a language understandable to the subject and must specify who informed the subject. Informed consent process must follow local regulations. Where required by local law, the person who informs the subject must be a physician.

The subject must be given the opportunity to read the ICF and have all their questions and concerns addressed before giving consent in writing. If the subject is unable to read, oral presentation and explanation of the written ICF and information to be supplied to the subject must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject (eg, subject's thumbprint or mark). Details about why oral presentation was used, how the information was presented, and how the subject provided consent must be described in the medical records. In addition, subjects are not allowed to share, discuss, or comment on social media about their participation in this study.

A copy of the signed ICF will be given to the subject, and the original will be retained by the site. An entry must be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a copy of the signed ICF.

The witness and the person conducting the informed consent discussions must also sign and personally date the ICF. Until a signed written consent has been obtained, the investigator will not undertake any measures specifically required for this study.

If informed consent is obtained by telephone (as allowed by individual IRBs/IECs/REBs), the subject must be provided a copy of the informed consent document in advance of a telephone discussion with the investigator. The investigator must explain the research and assess subject comprehension of the study according to site consent procedures. If the subject agrees to participate, the subject signs the consent form and returns it to the investigator (eg, via fax) for signature before any study assessments begin. When the subject is seen at the site, an updated in-person consent form will be obtained before any additional study procedures are performed.

16.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Amicus procedures, Amicus monitors or designee will contact the site prior to the start of the study to review with the site personnel the protocol; study requirements; and their responsibilities to satisfy regulatory, ethical, and Amicus' or its designee's requirements. When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items for which the eCRF will serve as the source document.

Risk-based monitoring will be performed on the primary characteristics of the study, as detailed in the Monitoring Plan. Amicus or its designee will monitor the study as indicated to ensure the following:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

16.3.1. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Amicus may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit, or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their personnel to discuss the conduct of the study and any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

16.3.2. Confidentiality

Subject names will not be supplied to Amicus. A unique subject number will be recorded in the eCRF, and if the subject's name appears on any other document (eg, a laboratory report), it must be obliterated on the copy of the document to be supplied to Amicus. Study findings stored on a computer will be stored in accordance with local data protection laws (eg, EU Directive 95/46/EC, EU Directive 94/45/EC, and EU GDPR 2016/679). The subject will be informed that representatives of Amicus, the IEC/IRB/REB, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

16.3.3. Data Protection

The conduct of this study and the processing of any personal data collected from each subject (or from a subject's healthcare professional or other relevant third-party sources) by the sponsor or its designee, the site and the investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the GDPR EU 2016/679. The sponsor or its designee shall ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law. Site-based organizational and technical arrangements to avoid unauthorized access vary by site but all include access-controlled/access-limited document control and technical solutions

including passwords and security control measures to protect study-specific data, both in paper and electronic format.

The investigator shall report any data breaches that might occur to the sponsor or its designee, without undue delay. The sponsor has implemented a Business Practice to address Data Breaches that complies with the requirements of applicable laws and regulations including the GDPR. The Data Breach procedures in the Business Practice provide specific responses to actual or potential threats and involve investigation, containment, and mitigation. If applicable, the authorities and the data subjects shall be notified of a data breach within the required timeframes of the applicable laws and regulations, including those of the GDPR.

16.3.4. Protocol Amendments and Deviations

If a clarification on a procedure or an error is found in the protocol, a protocol clarification memo will be sent to all sites and the IRB/IEC/REB before an amendment is issued.

Changes to the administrative aspects of the study (eg, changes in contact information or study personnel) will not require formal protocol amendments or IRB/IEC/REB approval but can be treated as administrative amendments. However, the IRB/IEC/REB should be kept informed of such changes.

Nonadministrative changes to the protocol, initiated either by Amicus or the investigator, will require a formal amendment procedure. Approval of all amendments must be obtained from Amicus, relevant IRB/IEC/REB, and regulatory authorities (in accordance with local requirements) prior to implementation.

Protocol deviations that may significantly impact subject safety or scientific integrity (eg, changes to eligibility criteria, addition or deletion of tests, dosing, duration of treatment, and/or other aspects of study design) are not permitted under GCP or by Amicus, unless necessary to eliminate an immediate hazard to the subject(s). Where Amicus and/or the investigator must take urgent safety measures to protect subjects from an immediate hazard, a protocol deviation may be allowed prior to obtaining approval from the relevant IRB/IEC/REB (and/or regulatory authorities) according to 21 Code of Federal Regulations 312.30(b) (2). In such cases, Amicus and the IRB/IEC/REB must be notified within 1 business day.

Amicus and the relevant IRB/IEC/REB, where required by local law, must be informed of all protocol deviations and violations, and the investigators shall document such protocol deviations and violations in subject source documents and eCRFs.

16.3.5. Delegation of Investigator Duties

The investigator should ensure that all persons assisting with this study are adequately qualified and informed about their study-related duties and functions, the protocol, any amendments to the protocol, and the study treatment.

Amicus will select a coordinating investigator as a representative of all investigators for this study. Each investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom they delegate significant study-related duties.

Should the investigator delegate the supervision of the administration of the study drugs, the designee should have the appropriate medical qualifications to effectively conduct or supervise

any potential resuscitation procedures. Even if the investigator delegates any trial-related duties to other qualified members of his or her study staff, the investigator retains ultimate responsibility for obtaining informed consent from study subjects; for ensuring that the investigation is conducted according to the protocol, the signed investigator statement (Form FDA 1572 or Statement of Foreign Investigator), and applicable regulations; for protecting the rights, safety, and welfare of study subjects; and for the control of investigational products under evaluation.

16.3.6. Study and Site Closure

Upon completion or termination of the study, the Amicus monitor or its designee will conduct site closure activities with the investigator or site personnel (as appropriate), in accordance with applicable regulations, GCP, and standard operating procedures of Amicus or its designee.

Amicus reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If Amicus determines that such action is required, Amicus will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Amicus will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, Amicus will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Amicus or its designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC/REB promptly and provide the reason(s) for the suspension/termination.

16.4. Legal and Financial Aspects

16.4.1. Liability and Insurance

Liability and insurance provisions for this study are provided in separate agreements.

16.4.2. Financial Disclosure

Before the start of the study, the investigator will disclose to Amicus any proprietary or financial interests he or she might hold in the investigational products, miglustat (as in Zavesca), Myozyme, Lumizyme, or Amicus, as outlined in the financial disclosure form provided by Amicus. The investigator agrees to update this information in case of significant changes during the study or within 1 year of its completion. The investigator also agrees that, where required by law or regulation, Amicus may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Where required by regulation:

- The investigator will disclose his/her financial interests to the subjects in the informed consent information.
- The investigator or Amicus, on behalf of the investigator, will submit the financial arrangements for the study to the regulatory authorities or to the IRB/IEC/REB.

Each sub-investigator to whom the investigator delegates significant study-related responsibilities will provide financial disclosures.

16.5. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (eg, for a sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site personnel.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (eg, microfiche, scanned, and electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Amicus (or designee) will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Amicus' standard operating procedures, and/or institutional requirements.

The investigator must notify Amicus of any changes in the archival arrangements, including, but not limited to, archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

16.6. Use of Study Findings

All information concerning the operation of Amicus that has been provided by Amicus and is unpublished is confidential and must remain the sole property of Amicus. The investigator agrees to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Amicus is obtained.

Amicus has full ownership of the data collected as part of the study.

By signing the clinical study protocol and the confidentiality agreement, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

Amicus will ensure that a final report on the study is prepared and will ensure that the study findings are reported in a manner that complies with applicable requirements for reporting clinical study results. The final analysis will be performed for the final CSR based on a data cutoff date of 31 December 2024. Any data collected after this date will be provided as an addendum to the final CSR when all subjects have completed the study or have been withdrawn from the study.

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APPENDIX 1. NEW UPDATED STUDY DESIGN FOR AMENDMENT 3

7. OBJECTIVE

The objective of this amendment is to continue collecting long-term safety and efficacy data on LOPD subjects treated with cipaglucosidase alfa/miglustat while decreasing some of the burden on those subjects taking part, and continuing to provide treatment where regulatory approval has not yet been granted or the product is not yet commercially available.

8. INVESTIGATIONAL PLAN

8.1. Study Design

This is a multicenter, international, open-label extension study of cipaglucosidase alfa/miglustat in adult subjects with LOPD who completed Study ATB200-03. No additional subjects will be enrolled after data cutoff date of 31 December 2024.

Upon approval of this amendment, any subjects continuing in the study will follow the updated Schedule of Assessments in Table 10.

Upon approval of this amendment, study visits that include minimal efficacy, safety, and other assessments will be scheduled approximately every 52 weeks. These visits may occur over 2 days, provided all study assessments and procedures are performed before administration of study drug. The relevant IRBs, ECs, and REBs should be notified of any deviations from the protocol.

Efficacy assessments (ie, functional assessments) include evaluation of ambulatory function (6MWT) and pulmonary function tests (FVC). Safety assessments include monitoring of AEs, including IARs, vital signs, physical examinations including weight. Concomitant medications and nondrug therapies will also be recorded.

The study will continue until one of the conditions outlined in Section 8.2 in the main body of the protocol is met.

9. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Please refer to Section 9 in the main body of the protocol.

10. TREATMENT OF SUBJECTS

Please refer to Section 10 in the main body of the protocol.

11. STUDY DRUG MATERIALS AND MANAGEMENT

Please refer to Section 11 in the main body of the protocol.

12. STUDY PARAMETERS AND PROCEDURES

12.1. Schedule of Assessments

A Schedule of Assessments showing each study assessment and procedure along with the scheduled time of occurrence is provided for subjects who continue in the study upon approval of this protocol amendment (Table 10).

All study assessments should be conducted by the investigator and/or a suitably qualified designee. Information will be recorded in the source documents and, where appropriate, in the eCRF.

Visits may occur over 2 days; if assessments are not able to be completed in 2 days, an additional day may be scheduled. Once established, every effort should be made to maintain the order of procedures, approximately at the same time of day, at each study visit throughout the study, regardless of the number of days that are used for the visit.

If an infusion (or infusions) were missed close to the scheduled assessments at any of the study visits, it should be communicated with the Amicus Medical Monitor to determine on a case by case basis whether catch-up infusions are needed and how many catch-up infusions are needed prior to the study assessments. The rationale for the missed infusion should be captured.

For additional details on study visits and description of study assessments, please refer to Section 12.2 and Section 12.3.

Table 10: Schedule of Assessments for Subjects Who Continue Under Protocol Amendment 3

Study Visit	Treatment			Follow-up
	Infusion Visits (Every 2 Weeks Through EOS/ET)	Every 52 Weeks[a]	EOS/ET	≥ 30 Days After Last Dose
Visit Window (Days)	**±3**	**±3**	**±3**	**±3**
Schedule next visit	X	X	X	
Clinical Assessment				
Concomitant medications and nondrug therapies (12.3.3)	X	X	X	X
Complete PE[b] (12.3.4)		X	X	
Vital signs (12.3.6)	X	X	X	
Weight[c] (12.3.5)		X	X	
AEs/SAEs, including IARs (13)	X	X	X	X
12-lead ECG[d] (12.3.10)		X	X	
Serum chemistry, hematology[d] (12.3.11.1)		X	X	
Urine pregnancy test[e] (12.3.11.2)	X	X	X	
Pulmonary Function Tests				
FVC (sitting, supine) (12.3.16)		X	X	
Motor Function Assessments				
6MWT (12.3.18)		X	X	

Table 10: Schedule of Assessments for Subjects Who Continue Under Protocol Amendment 3 (Continued)

Study Visit	Treatment			Follow-up
	Infusion Visits (Every 2 Weeks Through EOS/ET)	**Every 52 Weeks[a]**	**EOS/ET**	**≥ 30 Days After Last Dose**
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**
Study Drug Administration				
Miglustat (10)	Every 2 weeks 1 hour before infusion of cipaglucosidase alfa			
Cipaglucosidase alfa (10)	Every 2 weeks			

Abbreviations: 6MWT = 6-minute walk test; AE = adverse event; ECG = electrocardiogram; EOS = end of study; ET = early termination; FVC = forced vital capacity; IRT = interactive response technology; PE = physical examination; SAE = serious adverse event

[a] Study visits will be scheduled every 52 weeks until study termination by the sponsor.

[b] Complete physical examinations will include assessment of head, ears, eyes, nose, throat (HEENT), respiratory, cardiovascular, lymphatic, gastrointestinal, and neurologic systems.

[c] Weight will be entered into the IRT system every 52 weeks for calculation of cipaglucosidase alfa dose.

[d] Test to be performed locally.

[e] Urine pregnancy tests are performed locally only for female subjects of childbearing potential. If the urine pregnancy test has a positive result, study drug will not be administered and a confirmatory serum pregnancy test will be performed.

13. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Please refer to Section 13 in the main body of the protocol.

14. DATA MANAGEMENT

Please refer to Section 14 in the main body of the protocol.

15. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

15.1. Endpoints

15.1.1. Safety Endpoints

The long-term safety profile of cipaglucosidase alfa/miglustat will be characterized using incidence of TEAEs, SAEs, and AEs leading to discontinuation of study drug, frequency and severity of immediate and late IARs, and any abnormalities noted in other safety assessments (eg, clinical laboratory tests, ECGs, vital signs). Immunogenicity to cipaglucosidase alfa will also be described.

15.1.2. Efficacy Endpoints

Efficacy measures are as follows:

- 6MWD
- 6MWD (% predicted)
- sitting FVC (% predicted)

15.2. Sample Size Considerations

No formal sample size calculation was performed for this open-label extension study. The maximum sample size for this study is based on the number of subjects who complete Study ATB200-03, which has a target enrollment of 110 subjects.

15.3. Data Analysis Considerations

The Statistical Analysis System (SAS®) version 9.4 (or latest version at the time of the analysis) and R© software will be used for all statistical procedures and analyses.

Full details of the data and analysis methods will be provided in the statistical analysis plan.

15.3.1. Analysis Populations

The open-label extension remaining safety (OLE-RS) population includes all subjects who remained in the open-label extension study ATB200-07 and continued to receive treatment under this amendment. The OLE-RS population will be used for all analyses (including safety and efficacy).

15.3.2. Treatment Groups

There will be a single treatment group to be analyzed following this amendment, and that is the subjects who remained in the OLE study under Protocol Amendment 3.

15.3.3. Statistical Methods

15.3.3.1. Interim Analyses

Not applicable.

15.3.3.2. Adjustment for Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed. All analyses will be descriptive.

15.3.3.3. Missing Data Handling

For all efficacy endpoints based on patient-reported outcome/clinical outcome assessment instruments, the scoring algorithms (including the standard or published data imputation or pro-rating methods contained in the scoring algorithms) will be implemented.

No data imputation are planned for missing efficacy data. If any imputations are decided upon later, the details will be provided in the statistical analysis plan.

In general, missing safety data will not be imputed. However, attributes such as missing dates for AEs and concomitant medications will be imputed using similar methods as described for ATB200-03 in order to ensure consistency. Details will be provided in the statistical analysis plan.

15.3.3.4. Windowing Conventions

By-visit assessments for safety and efficacy will be summarized based on visit windows.

15.3.3.5. Statistical Tests

No formal hypotheses are planned to be tested. Unless otherwise specified, only descriptive statistics will be presented. Any inferential analyses will be presented for summary purposes. Where appropriate, 2-sided 95% confidence intervals will also be provided for summary purposes.

15.3.3.6. Common Calculations

In general, continuous variables will be summarized using descriptive statistics (the number of subjects with available data, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized using counts and percentages.

15.3.4. Analyses

All analyses under this amendment will be based only on the stand-alone additional data collected following the database lock (DBL) for the final CSR, and there will be no integration with any data that existed prior to the DBL.

In general, continuous data will be summarized using descriptive statistics, and categorical data will be summarized using counts and percentages. Specific analysis details and display format will be described in the statistical analysis plan.

15.3.4.1. Efficacy Analyses

In general, continuous data will be summarized using descriptive statistics, and categorical data will be summarized using counts and percentages, as described above in Section 15.3.3.6. Specific analysis details and display format will be described in the statistical analysis plan.

15.3.4.1.1. Analyses of Ambulatory Function and Pulmonary Function

Efficacy variables (6MWD [m]), percent predicted 6MWD, and percent predicted sitting FVC) will be summarized over time for the assessment visits that occurred post-DBL of the final CSR, based on the OLE-RS population. Where a change from baseline summary is required, the baseline result will be based on the last assessment prior to the DBL of the final CSR. A 95% confidence interval for the mean change from baseline will be provided where applicable. For the analysis of percent predicted 6MWD, the predicted value will be calculated using the reference equations from Enright and Sherill (Enright and Sherill 1998).

15.3.4.2. Safety Analyses

Safety data will be summarized on the OLE-RS population. Visit-based safety variables will be summarized over time for the assessment visits that occurred post-DBL of the final CSR. Where change from baseline or percent change from baseline summaries are required, the baseline results will be based on the last assessment made prior to the DBL of the final CSR.

Safety data will be summarized using descriptive statistics for continuous data and using counts and percentages for categorical data, as described in Section 15.3.3.6.

Exposure to study medication will be calculated in weeks and analyzed as continuous variables using descriptive statistics. In addition, the duration of exposure will be categorized and a frequency distribution of the categories (each summarized by count and percentage) will be presented.

An overall summary of incidence of AEs (which includes the total number of TEAEs, total number of serious TEAEs as well as the total number of subjects) will be presented. The number and percentage of subjects who experienced nonserious TEAEs as well as serious TEAEs will be summarized by preferred term within system organ class. The summary of nonserious and serious TEAEs will also be presented by intensity (mild, moderate, severe), as well as by relationship to study medication. In addition, the number of AEs (as opposed to the number and percentage of subjects) will be presented.

Serious adverse events, including deaths, will be summarized and listed. Separate listings of death, SAEs (treatment-emergent and nontreatment-emergent), and discontinuations due to AEs will be provided.

Summaries and listings will also be provided for deaths, SAEs, and AEs leading to discontinuation and infusion-associated reactions. Adverse events will be coded using Medical Dictionary for Regulatory Activities version 18 or higher.

Clinical laboratory results, ECG parameters, and vital signs will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) by treatment group and visit for actual values and changes from baseline. The proportion of subjects with abnormalities will be provided for clinical laboratory results, ECGs, and vital signs. Shift tables will also be provided for clinical laboratory results.

Concomitant medications and nondrug therapies will be summarized by treatment group. Concomitant medications terms will be coded using the World Health Organization Drug Dictionary (September 2013 DDE).

16. STUDY CONDUCT CONSIDERATIONS

Please refer to Section 16 in the main body of the protocol.

APPENDIX 2. SAMPSON CRITERIA FOR ANAPHYLAXIS

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson, Muñoz-Furlong et al. 2006

APPENDIX 3. POTENTIALLY CLINICALLY SIGNIFICANT GUIDELINES

Criteria for identifying abnormalities as potentially clinically significant are based on the Guidelines for the Division of Neuropharmacological Drug Products, US Food and Drug Administration (revised on 2 April 1987). The laboratory values identified below are not inclusive of all the safety laboratory analytes that will be assessed during this clinical trial. Safety laboratory analytes that are known to be elevated in some adults with Pompe disease (eg, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase) and safety laboratory analytes which are not listed below will be reviewed to determine if they are to be noted as potentially clinically significant based on the magnitude of the out of range value as compared with the normal range and the subject's baseline value, and whether the out of range value is coded as clinically significant by the principal investigator.

Laboratory Values			
Variable		**Criterion Values**	
		Standard Units	**SI Units**
Chemistry			
SGOT (AST)		≥ 3 x Upper Limit Normal	
SGPT (ALT)		≥ 3 x Upper Limit Normal	
Alkaline Phosphatase		≥ 3 x Upper Limit Normal	
LDH		≥ 3 x Upper Limit Normal	
BUN		≥ 30 mg/dL	≥ 10.7 µM
Creatinine		≥ 2.0 mg/dL	≥ 176.8 µM
Uric Acid	Male	≥ 10.5 mg/dL	≥ 624.6 µM
	Female	≥ 8.5 mg/dL	≥ 505.6 µM
Bilirubin (Total)		≥ 2.0 mg/dL	≥ 34.2 µM
Hematology			
Hematocrit	Male	≤ 37%	
	Female	≤ 32%	
Hemoglobin	Male	≤ 11.5 g/dL	
	Female	≤ 9.5 g/dL	
Platelets		≤ 75,000/mm^3 or ≥ 700,000/mm^3	≤ 75 x 10^9/L or ≥ 700 x 10^9/L
Leukocytes		≤ 2,800/mm^3 or ≥ 16,000/mm^3	≤ 2.8 x 10^9/L or ≥ 16 x 10^9/L
Eosinophils		≥ 10%	
Neutrophils		≤ 15%	
Urinalysis			
Protein		Increase of ≥ 2 units	
Glucose		Increase of ≥ 2 units	
Casts		Increase of ≥ 2 units	

Abbreviations: BUN = blood urea nitrogen; LDH = lactate dehydrogenase; SGOT (AST) = serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT (ALT) = serum glutamic pyruvic transaminase (alanine aminotransferase)

Vital Sign Values			
Variable	**Criteria**		**Change Relative to Baseline**
Heart Rate	≥ 120 bpm	and an	increase of ≥ 15 bpm
	≤ 50 bpm	and a	decrease of ≥ 15 bpm
Systolic Blood Pressure	≥ 180 mmHg	and an	increase of ≥ 20 mmHg
	≤ 90 mmHg	and a	decrease of ≥ 20 mmHg
Diastolic Blood Pressure	≥ 105 mmHg	and an	increase of ≥ 15 mmHg
	≤ 50 mmHg	and a	decrease of ≥ 15 mmHg
Weight			change of ≥ 7% body weight

ECG Values		
ECG Parameter	**Low**	**High**
PR interval (ms)	< 120 ms	≥ 210 ms
QRS duration (ms)	≤ 50 ms	> 120 ms
QTcB interval (ms)	Not applicable	> 450 ms for males and > 470 ms for females and QTcB increases from baseline > 60 ms (males and females)
Ventricular rate (bpm)	A decrease from reference[a] ≥ 15 bpm, and an absolute value < 50 bpm	An increase from reference[a] ≥ 15 bpm, and an absolute value > 120 bpm

Abbreviations: ECG = electrocardiogram; QTcB = QT interval for corrected heart rate
[a] Reference value: baseline or initial visit value, as appropriate