Official Title:	A Phase 3 Double-blind Randomized Study to Assess the Efficacy and Safety of Intravenous ATB200 Co-administered With Oral AT2221 in Adult Subjects With Late-Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo
NCT Number:	NCT03729362
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CLINICAL STUDY PROTOCOL

A PHASE 3 DOUBLE-BLIND RANDOMIZED STUDY TO ASSESS THE EFFICACY AND SAFETY OF INTRAVENOUS ATB200 CO-ADMINISTERED WITH ORAL AT2221 IN ADULT SUBJECTS WITH LATE-ONSET POMPE DISEASE COMPARED WITH ALGLUCOSIDASE ALFA/PLACEBO

Protocol Number: ATB200-03

Original Protocol: 19 March 2018

Amendment 1: 21 September 2018

Amendment 2: 25 January 2019

Amendment 3: 14 August 2020

EudraCT Number: 2018-000755-40

US IND Number: 127,387

Compounds: ATB200 and AT2221

Sponsor

Amicus Therapeutics, Inc.

1 Cedar Brook Drive

Cranbury, NJ

08512, USA

Phone: +1-609-662-2000

Table 1: Serious Adverse Event Contact Information

Role	Contact Information
Reporting of serious adverse events	**Safety FAX number**: +1-866-693-2307 **Email address:** blindedsafetyreporting@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, Inc.

The information it contains is consistent with the following:

- the current benefit-risk evaluation of ATB200 (recombinant human acid α-glucosidase) co-administered with AT2221 (*N*-butyl-deoxynojirimycin)
- the safety information of alglucosidase alfa
- 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 ATB200 co-administered with AT2221.

Date: 14 Aug 2020 Signature: Amicus

Amicus Therapeutics, Inc.

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, Inc. (Amicus)

Name of Investigational Products: ATB200 and AT2221

Name of Active Ingredients:
ATB200: Recombinant human acid α-glucosidase (rhGAA)
AT2221: *N*-butyl-deoxynojirimycin
ATB200/AT2221: ATB200 co-administered with AT2221

Title of Study: A Phase 3 Double-blind Randomized Study to Assess the Efficacy and Safety of Intravenous ATB200 Co-administered With Oral AT2221 in Adult Subjects With Late-Onset Pompe Disease Compared With Alglucosidase Alfa/Placebo

Study Sites: Up to approximately 90 sites globally

Phase of Development: 3

Objectives:

Primary

- To assess the efficacy of ATB200/AT2221 co-administration on ambulatory function, as measured by the 6-Minute Walk Test (6MWT), compared with alglucosidase alfa/placebo

Secondary

- To assess the efficacy of ATB200/AT2221 co-administration on pulmonary function, as measured by sitting forced vital capacity (FVC) (% predicted), compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on muscle strength, compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on health-related patient-reported outcomes, compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on motor function, compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on overall clinical impression as assessed by both physician and subject, compared with alglucosidase alfa/placebo
- To assess the safety, tolerability, and immunogenicity of ATB200/AT2221 co-administration compared with alglucosidase alfa/placebo
- To assess the effect of ATB200/AT2221 co-administration on biomarkers of muscle injury and disease substrate compared with alglucosidase alfa/placebo

- To characterize the population pharmacokinetics of ATB200 and alglucosidase alfa in enzyme replacement therapy (ERT)-experienced subjects using plasma total acid α-glucosidase (GAA) protein level by signature peptide assay and plasma AT2221 concentration
- To characterize the pharmacokinetics of ATB200, alglucosidase alfa, and AT2221 in ERT-naïve subjects using noncompartmental analysis
- To explore the exposure-response relationship for ATB200/AT2221 and alglucosidase alfa/placebo co-administration

Methodology:

This is a double-blind, randomized, multicenter, international study of ATB200/AT2221 in adult subjects with late-onset Pompe disease (LOPD) who have received enzyme replacement therapy with alglucosidase alfa (ie, ERT-experienced) or who have never received ERT (ie, ERT-naïve) compared with alglucosidase alfa/placebo. As this study was initially designed to assess the effects of ATB200/AT2221 in ERT-experienced subjects who continued to receive alglucosidase alfa in Study POM-003, subjects from that study who meet the eligibility criteria for this study will make up part of the ERT-experienced study population.

The study will consist of a screening period up to 30 days, a 12-month treatment period, and a 30-day safety follow-up period. Subjects who missed visits due to SARS-CoV-2 (COVID-19) related quarantines, travel restrictions, and risk of infection may be enrolled longer than 12 months in the study. Subjects who complete this study will have the option to participate in an open-label extension study to receive ATB200/AT2221 under a separate protocol.

Enzyme replacement therapy-experienced subjects will continue to take alglucosidase alfa during the screening period; treatment with alglucosidase alfa will then be replaced by study drug (ATB200/AT2221 or alglucosidase alfa/placebo) on the same schedule without interruption (ie, every 2 weeks). The Screening Visit will occur over 2 or more days to allow for repeated 6MWT and pulmonary function test assessments. The repeated tests for 6MWT or for pulmonary function (FVC, slow vital capacity [SVC], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and sniff nasal inspiratory pressure [SNIP]) should not be done on the same day. No other assessments should be performed on the day that the 6MWT and pulmonary function tests are repeated. Eligible subjects will be randomly assigned in a 2:1 ratio to receive ATB200/AT2221 or alglucosidase alfa/placebo and stratified by ERT status (ERT-experienced, ERT-naïve) and baseline 6-minute walk distance (6MWD) (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters).

Infusion visits will be scheduled every 2 weeks throughout the study; assessments (eg, clinical laboratory tests) for initial safety monitoring will be performed at these visits for the first 6 weeks of the study. Study visits that include efficacy, safety, and other assessments will be scheduled approximately every 3 months and may occur over 2 or more days, provided all study assessments and procedures (with the exception of pharmacokinetic [PK] sample collection) are performed before administration of study drug. During the conduct of the study, the 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 wherever possible for subjects who may be eligible. If infusions were missed near the scheduled assessments on Week 26, 38, or 52, 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. If 5 or more consecutive infusions are missed due to any circumstance, including COVID-19, the subject must be discontinued from this protocol. Any subjects discontinued due to COVID-19 may be eligible for ATB200-07 with Amicus approval.

Efficacy assessments (ie, functional assessments) include evaluation of ambulatory function (6MWT), motor function tests (Gait, Stair, Gower, and Chair maneuver [GSGC] test and Timed Up and Go [TUG] test), muscle strength (manual muscle testing and quantitative muscle testing), and pulmonary function tests (FVC, SVC, MIP, MEP, and SNIP). Patient-reported outcomes (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). The Physician's Global Impression of Change will also be performed.

Pharmacodynamic assessments include measurement of biomarkers of muscle injury (creatine kinase [CK]) and disease substrate (urinary hexose tetrasaccharide [Hex4]). Sparse blood samples will be collected for determination of total GAA protein levels and AT2221 concentrations in plasma for a population PK analysis in ERT-experienced subjects. Serial blood sampling for characterization of the PK profile of total GAA protein and AT2221 will be done in ERT-naïve subjects. GAA activity may be evaluated during the terminal phase in all subjects (ie, ERT-experienced and ERT-naïve subjects). Safety assessments include monitoring of adverse events (AEs), including infusion-associated reactions (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 planned sample size is approximately 110 subjects, with a total of 100 subjects (including at least 30 ERT-naïve subjects) expected to complete the study.

Diagnosis and Main Criteria for Inclusion:

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

Inclusion Criteria

1. Subject must provide signed informed consent prior to any study-related procedures being performed.
2. Male and female subjects are ≥ 18 years old and weigh ≥ 40 kg at screening.
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.
4. Subject must have a diagnosis of LOPD based on documentation of one of the following:
   a. deficiency of GAA enzyme
   b. *GAA* genotyping
5. Subject is classified as one of the following with respect to ERT status:
   a. ERT-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa) at the recommended dose and regimen (ie, 20 mg/kg dose every 2 weeks) for ≥ 24 months
      – Specific to Australia, ERT-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa) at the recommended dose and regimen, at a dose of 20 mg/kg based on lean or ideal body weight every 2 weeks
   b. ERT-naïve, defined as never having received investigational or commercially available ERT

6. Subject has a sitting FVC ≥ 30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III) at screening.
7. Subject performs two 6MWTs at screening that are valid, as determined by the clinical evaluator, and that meet all of the following criteria:
    a. both screening values of 6MWD are ≥ 75 meters
    b. both screening values of 6MWD are ≤ 90% of the predicted value for healthy adults
    c. the lower value of 6MWD is within 20% of the higher value of 6MWD

Exclusion Criteria

1. Subject has received any investigational therapy or pharmacological treatment for Pompe disease, other than alglucosidase alfa, within 30 days or 5 half-lives of the therapy or treatment, whichever is longer, before Day 1 or is anticipated to do so during the study.
2. Subject has received gene therapy for Pompe disease.
3. Subject is taking any of the following prohibited medications within 30 days before Day 1:
    - miglitol (eg, Glyset®)
    - miglustat (eg, Zavesca®)
    - acarbose (eg, Precose® or Glucobay®)
    - voglibose (eg, Volix®, Vocarb®, or Volibo®)

    Note: None of these medications have a half-life that, when multiplied by 5, is longer than 30 days.
4. Subject requires the use of invasive or noninvasive ventilation support for > 6 hours per day while awake.
5. Subject has a hypersensitivity to any of the excipients in ATB200, alglucosidase alfa, or AT2221.
6. Subject 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.
7. Subject, if female, is pregnant or breastfeeding at screening.
8. Subject, whether male or female, is planning to conceive a child during the study.
9. Subject refuses to undergo genetic testing.

Investigational Product, Dosage, and Mode of Administration:

ATB200/AT2221 will be administered as a combination treatment regimen, consisting of AT2221 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 ATB200 20 mg/kg (reconstituted lyophilized drug product for intravenous [IV] infusion, 105 mg/vial). The ATB200/AT2221 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 AT2221.

Duration of Treatment:

The duration of treatment is 52 weeks. Subjects who complete this study will have the option to participate in an open-label extension study to receive ATB200/AT2221 under a separate protocol.

Reference Therapy, Dosage, and Mode of Administration:

Alglucosidase alfa/placebo will be administered as a combination treatment regimen, consisting of 4 placebo oral capsules for subjects weighing ≥ 50 kg and 3 placebo oral capsules for subjects weighing ≥ 40 kg to < 50 kg, followed approximately 1 hour later by alglucosidase alfa 20 mg/kg (reconstituted lyophilized drug product for IV infusion, 50 mg/vial). The alglucosidase alfa/placebo 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 placebo.

Criteria for Evaluation:

The primary efficacy endpoint is the change from baseline to Week 52 in 6MWD.

Key secondary efficacy endpoints are as follows:

- change from baseline to Week 52 in sitting FVC (% predicted)
- change from baseline to Week 52 in the manual muscle test score for the lower extremities
- change from baseline to Week 52 in the total score for the PROMIS – physical function
- change from baseline to Week 52 in the total score for the PROMIS – fatigue
- change from baseline to Week 52 in GSGC total score
- change from baseline to Week 26 in 6MWD

Other secondary efficacy endpoints are as follows:

- change from baseline to Week 52 in the following variables related to motor function:
  - 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 Gower's maneuver of the GSGC test
  - time to arise from a chair as part of the GSGC test
  - time to complete the TUG test
- change from baseline to Week 52 in the following variables related to muscle strength:
  - manual muscle test score for the upper extremities
  - manual muscle test total score
  - quantitative muscle test value (kg) for the upper extremities
  - quantitative muscle test value (kg) for the lower extremities
  - quantitative muscle test total value (kg)
- change from baseline to Week 52 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 at Week 52, as measured by the Subject's Global Impression of Change
  - overall physical wellbeing
  - 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) at Week 52, as measured by the Physician's Global Impression of Change
- change from baseline to Week 52 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 to Week 52 in serum CK level
- change from baseline to Week 52 in urinary Hex4 level

Pharmacokinetic endpoints from a population PK analysis of total GAA protein level and AT2221 concentration will be provided in a separate modeling and simulation plan.

The safety profile of ATB200/AT2221 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. The impact of immunogenicity to ATB200 and alglucosidase alfa on safety and efficacy will also be described.

Statistical Methods:

Randomization

The following 2 factors have been identified as design stratification variables:

1. baseline 6MWD (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters)
2. ERT status (ERT-experienced, ERT-naïve)

These 2 factors form 6 factorial combinations (ie, levels, strata).

A centralized block randomization procedure will be used to balance the above risk factors, 1) to reduce bias and increase the precision of statistical inference, and 2) to allow various planned and unplanned subset analyses. The block randomization scheme will be performed for each of the 6 strata. The randomization ratio is 2:1 ATB200/AT2221 to alglucosidase alfa/placebo, fixed.

Sample Size Calculation

A 2-group t-test with a 2-sided significance level of 0.05 and a 2:1 randomization scheme (66 subjects in the ATB200/AT2221 group and 33 subjects in the alglucosidase alfa/placebo group, for a total sample size of 99 subjects) will have approximately 90% power to detect a standardized effect size of 0.7 between the 2 groups in a superiority test. This calculation was performed using Nquery 8©®. Assuming a 10% dropout rate, the sample size will be approximately 110 subjects.

Efficacy Analyses

The primary efficacy endpoint (ie, change from baseline to Week 52 in 6MWD) will be analyzed using a parametric analysis of covariance (ANCOVA) model to compare between the new treatment and the control. This model would typically adjust for baseline 6MWD (as a continuous covariate), and the 2 factors used to stratify randomization: ERT status (ERT-naïve vs. ERT-experienced) and baseline 6MWD (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters). However, the baseline 6MWD cannot be used in the model twice (both as a continuous and a categorical variable) due to the expected high point-biserial correlation between them. Thus, the 6MWD continuous variable will remain in the model but the categorical 6MWD will be removed. The ANCOVA model then has terms for treatment, baseline 6MWD (continuous), and ERT status (categorical).

Additionally, potential treatment-by-covariate interactions (ie, TREATMENT-by-ERT-STATUS and TREATMENT-by-BASELINE 6MWD continuous) will be examined. If an interaction term is statistically significant (eg, $p < 0.10$, 2-sided), and there is logical biological interpretation, then the interaction term can potentially be added in the final ANCOVA model that will be used for the primary endpoint analysis. The data would then be analyzed based on the ANCOVA model, and all the relevant estimates (eg, LS means for each treatment group, LS means difference, 95% confidence intervals [CIs] for the LS mean difference, and p-value for comparing between the 2 treatment groups) would be provided.

To support the interpretation of clinical benefit, a composite subject-level response will be defined based on the totality of the treatment outcome data. Subjects will be classified by an ordinal response variable consisting of significant improvement, moderate improvement, or minor/no improvement based on treatment outcomes.

Key secondary endpoints will be analyzed according the hierarchical order as specified in the protocol, using stepwise closed testing procedure to control the type I error rate. Key secondary and other secondary endpoints will be analyzed separately with a similar method used for the primary endpoint analysis.

Safety Analyses

Safety data will be summarized using counts and percentages for categorical data and descriptive statistics (mean, standard deviation, median, minimum, maximum) for continuous data.

4. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

LIST OF FIGURES

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
Ab(s)	antibody(ies)
AE	adverse event
ATB200	recombinant human acid α-glucosidase (rhGAA)
AT2221	*N*-butyl-deoxynojirimycin
ATB200/AT2221	ATB200 co-administered with AT2221
AUC	area under the plasma concentration-time curve
AUC_{0-t}	area under the plasma drug concentration-time curve from 0 time (predose) to the time of last quantifiable concentration (t), calculated with the linear up/log-down trapezoidal method
$AUC_{0-\infty}$	the area under the plasma drug concentration-time curve from 0 time (predose) extrapolated to infinite time will be calculated as follows: $AUC_{0-\infty} = AUC_{0-t} + C_t/+\lambda_z$ where C_t is the last observed quantifiable concentration
$AUC_{tmax-24h}$	partial area under the plasma drug concentration-time curve from the time of maximum concentration (t_{max}) to 24 hours post initiation of ATB200 infusion
BLQ	below the limit of quantification
CL_T	total plasma clearance of drug after intravenous administration, calculated as dose/$AUC_{0-\infty}$
CL_T/F	total plasma clearance from an oral administration, calculated as dose/$AUC_{0-\infty}$
CK	creatine kinase
C_{max}	maximum observed concentration obtained directly from the concentration profile
COVID-19	SARS-CoV-2
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5 Dimensions-5 Levels Instrument
ERT	enzyme replacement therapy

Abbreviation or Specialist Term	Definition of Term
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
GSGC	Gait, Stair, Gower, and Chair maneuver
Hex4	hexose tetrasaccharide
IAR	infusion-associated reaction
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IND	Investigational New Drug
IOPD	infantile-onset Pompe disease
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
K_{el} or λ_z	the apparent terminal phase elimination rate constant will be estimated by linear regression of logarithmically transformed concentration versus time data; only those data points which are judged to describe the terminal log-linear decline will be used in the regression
Ki	dissociation constant
LOPD	late-onset Pompe disease
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
mITT	modified intent-to-treat
PD	pharmacodynamic
PK	pharmacokinetic
PROMIS®	Patient-Reported Outcomes Measurement Information System
R-PAct	Rasch-built Pompe-specific Activity
rhGAA	recombinant human acid α-glucosidase

Abbreviation or Specialist Term	Definition of Term
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SNIP	sniff nasal inspiratory pressure
SUSAR	suspected unexpected serious adverse reaction
SVC	slow vital capacity
$t_{½}$	terminal elimination half-life
$t_{½\alpha}$	the alpha-phase terminal half-life, calculated as $\ln(2)/\lambda_z$ from the first 3 or more quantifiable concentrations after C_{max}; estimated for plasma total GAA protein concentration only
$t_{½\beta}$	the beta-phase terminal elimination half-life, calculated as $\ln(2)/\lambda_z$ from the last 3 or more quantifiable concentrations from the beta phase of elimination
t_{max}	observed time to reach C_{max}; time of the first occurrence of the maximum observed concentration obtained directly from the concentration profile
TUG	Timed Up and Go
US(A)	United States (of America)
V_z/F	volume of distribution based on the terminal elimination phase from an oral administration, calculated as dose/($AUC_{0-\infty} \bullet \lambda_z$)

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 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 et al 2002). Lower enzyme activity is generally associated with a more severe clinical course of the disease (Kishnani et al 2006).

Pompe disease may be categorized into 2 classes: infantile-onset Pompe disease (IOPD; 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 IOPD, 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 wheel chair 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 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 United States (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 et al 2010; Schoser 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 et al 2012).

In 2012, a systematic review of all studies performed in subjects with LOPD was performed by Toscano and Schoser 2013. This review included data on 368 subjects with LOPD from

published studies, including 27 juvenile subjects (age range: 2 to17 years old) and 251 adult subjects who received alglucosidase alfa for at least 2 preceding years. Results indicated that > 30% of subjects do not show an initial improvement during treatment with alglucosidase alfa and continue to experience deterioration of muscular and respiratory functions despite treatment.

In the group of subjects who initially respond to alglucosidase alfa treatment, several additional longer-term studies show that improvements usually last for only approximately 2 years. Thereafter, subjects generally plateau before beginning to progressively decline.

In 2012, the United Kingdom Health Technology Assessment program, as part of the National Institute for Health Research (Wyatt et al 2012), issued recommendations drawn from review of longitudinal data for 81 patients with Pompe disease (including infantile- and late-onset forms [children and adults]) who received the current approved ERT standard of care, alglucosidase alfa. Key markers of Pompe disease progression (forced vital capacity [FVC], ventilation dependency, mobility, 6-Minute Walk Test [6MWT], muscle strength, and body mass index) were assessed and modeled with time of treatment on alglucosidase alfa therapy. Results of this assessment indicated that improvements in FVC, 6-minute walk distance (6MWD), and muscle strength by patients with LOPD occur for the first 2 years after commencing ERT with alglucosidase alfa, and decline occurs with continuing treatment beyond this timeframe. Additionally, a 3-year study in 38 subjects with LOPD receiving alglucosidase alfa showed that the subjects demonstrated an improvement in motor function in the first year of treatment, which remained generally stable in the second year and began to decline in the third year (Regnery et al 2012).

Furthermore, a recent report providing a 10-year follow-up on the Phase 3 Lumizyme® (Genzyme Corporation) (LOTS) study showed that after experiencing some improvement in motor and pulmonary function during the first couple of years of treatment, subjects began to slowly decline with ongoing treatment (van der Ploeg et al 2017). In this study, from years 3 to 6 on therapy, there was an average decline of approximately 10% in percent predicted 6MWD, with approximately 80% of subjects experiencing a decline.

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 (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.

In 2017, a systematic review of the literature was undertaken by the European Pompe Consortium, a network of experts from 11 European countries in the field of Pompe disease (van der Ploeg et al 2017). Based on the data obtained from 1 clinical study and 43 observational studies, covering a total of 586 individual adult subjects, evidence of an effect of ERT at group level was assessed by the consortium. The current European Pompe Consortium consensus is to discontinue ERT therapy upon the occurrence of severe IARs or the progressive clinical worsening of disease symptoms, as well as occurrence of high-neutralizing antibody (Ab) titers, which effectively inactivate the existing ERT treatment. The European Pompe Consortium

consensus recommendation also included consideration for re-initiation of ERT treatment if disease progression and clinical worsening recur after ERT has been stopped.

Co-administration of ATB200 (rhGAA) with AT2221 (miglustat; *N*-butyl deoxynojirimycin) (ATB200/AT2221) is designed to address these limitations of alglucosidase alfa and meet this unmet medical need.

6.2. ATB200/AT2221

ATB200/AT2221 is a novel first-in-class combination product approach for the treatment of adult and pediatric patients with LOPD. ATB200/AT2221 is being developed as a combination product for which (1) ATB200 is the main active substance (enzyme) that is engineered for optimal targeting to lysosomes, the site of glycogen catabolism in affected tissues and (2) AT2221 is a co-administered small molecule enzyme stabilizer that stabilizes ATB200 from denaturation in systemic circulation, which enhances the delivery of the active component ATB200 to lysosomes.

ATB200: ATB200 is a next-generation rhGAA enzyme. ATB200 differs structurally from currently approved rhGAA (alglucosidase alfa) enzyme. Based on the published literature, ATB200 matches the sequence for human alpha glucosidase but has important differences on its posttranslational glycan structures that enable more rapid cellular uptake and lysosomal targeting of the enzyme. ATB200 is a new biological entity and is currently being evaluated in clinical trials.

AT2221: AT2221 is an iminosugar that functions as a small molecule enzyme stabilizer of ATB200. Because ATB200 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). AT2221 binds to ATB200 and protects ATB200 from denaturation in blood. This interaction of AT2221 with ATB200 results in stabilization of the ATB200 enzyme in the blood and enhancement of the pharmacokinetics of the ATB200 leading to a more efficient percentage of active enzyme being delivered to key disease-relevant tissue (ie, muscles).

6.2.1. Pharmacokinetics of AT2221

AT2221 capsules contain the same active ingredient, *N*-butyl deoxynojirimycin, as in Zavesca® (Actelion Pharmaceuticals US Inc.) and Yargesa® (Edenbridge Pharmaceuticals, LLC) which is approved for the treatment of adults with type I Gaucher disease (in the US and European Union) and for treatment of adults and pediatrics with Niemann Pick-C disease (in European Union). As of 2017, Yargesa is approved as a generic miglustat product for the treatment of adults with type I Gaucher disease. The pharmacokinetics of miglustat have been well characterized in subjects with Gaucher disease. In this study, AT2221 acts as a small molecule enzyme stabilizer that stabilizes ATB200 and enhances its activity. AT2221 is administered at a lesser frequency (1 dose every 2 weeks) in contrast to dosing with miglustat for Gaucher disease (3 times daily) (see Section 11.5 for dosing for this study).

Absorption: After a 100-mg oral dose of miglustat, the observed time to reach maximum plasma concentration (t_{max}) of miglustat ranged from 2.0 to 2.5 hours in subjects with Gaucher disease. Plasma concentrations show a bi-exponential decline, characterized by a short distribution phase

and a longer elimination phase. The effective terminal elimination half-life ($t_{½}$) of miglustat is approximately 6.0 to 7.0 hours, which predicts that steady-state will be achieved by 1.5 to 2.0 days following the start of 3 times daily dosing.

Miglustat, dosed at 50 and 100 mg 3 times daily in subjects with Gaucher disease, exhibits dose-proportional pharmacokinetics. The pharmacokinetics of miglustat was not altered after repeated dosing 3 times daily for up to 12 months. In healthy subjects, co-administration of Zavesca® with food results in a decrease in the rate of absorption of miglustat (maximum observed concentration [C_{max}] in plasma was decreased by 36% and t_{max} was delayed for 2 hours) but had no statistically significant effect on the extent of absorption of miglustat (area under the plasma concentration-time curve [AUC] was decreased by 14%). The mean oral bioavailability of a 100-mg miglustat capsule is about 97% relative to an oral solution administered under fasting conditions. The pharmacokinetics of miglustat was similar between adult subjects with type I Gaucher disease and healthy subjects after a single dose administration of miglustat 100 mg (Zavesca Labeling-Package Insert 2014). The absolute bioavailability of miglustat was approximately 80% (Wraith and Imrie 2009).

Distribution: Miglustat does not bind to plasma proteins. Mean apparent volume of distribution of miglustat is 83 to 105 L in Gaucher patients. At steady state, the concentration of miglustat in cerebrospinal fluid of 6 subjects without Gaucher disease was 31.4% to 67.2% of that in plasma, indicating that miglustat crosses the blood-brain barrier (Zavesca Labeling-Package Insert 2014).

Metabolism and Excretion: The major route of excretion of miglustat is via kidney. Following administration of a single dose of 100 mg ^{14}C-miglustat to healthy subjects, 83% of the radioactivity was recovered in urine and 12% in feces. In healthy subjects, 67% of the administered dose was excreted unchanged in urine over 72 hours. The most abundant metabolite in urine was miglustat glucuronide accounting for 5% of the dose. The $t_{½}$ of radioactivity in plasma was 150 hours, suggesting the presence of 1 or more metabolites with a prolonged half-life. The metabolite accounting for this observation has not been identified but may accumulate and reach concentrations exceeding those of miglustat at steady state. Miglustat did not inhibit or induce substrates of cytochrome P450 enzymes (Zavesca Labeling-Package Insert 2014).

6.2.2. Use of AT2221 as a Small Molecule Enzyme Stabilizer

N-butyl deoxynojirimycin, the active ingredient in AT2221, is a small molecule acting as a small molecule enzyme stabilizer and has been shown to bind and stabilize GAA to improve its pharmacological properties. Two clinical studies (see Section 6.2.2.1 and Section 6.2.2.2) evaluating the co-administration of miglustat with the current approved ERT (alglucosidase alfa) in Pompe disease have been reported in the literature (Parenti et al 2015; Doerfler et al 2014).

6.2.2.1. Effect of Miglustat on Plasma α-Glucosidase Activity of Alglucosidase Alfa

In a clinical study conducted in 13 subjects with Pompe disease (3 subjects with IOPD and 10 subjects with LOPD) at 4 treatment sites in Italy, 20 to 40 mg/kg alglucosidase alfa was administered alone and then co-administered with 4 doses of 80 mg/m^2 miglustat every 2 weeks. Compared with alglucosidase alfa alone, the results of the study showed a mean of 6.8-fold increase in GAA activity exposure (measured in terms of AUC) following co-administration (Parenti et al 2015).

6.2.2.2. Characterization of Plasma Miglustat With Alglucosidase Alfa in Subjects With Pompe Disease

A study conducted at the University of Florida evaluated the pharmacokinetics of plasma miglustat when co-administered with IV infusion of alglucosidase alfa to subjects with Pompe disease. Preliminary plasma miglustat pharmacokinetic (PK) data following oral administrations of 100 mg and 200 mg miglustat on the day of alglucosidase alfa infusion are available. Plasma miglustat exposures were approximately dose proportional. Maximum observed concentration values following administration of 100 and 200 mg miglustat were 1120 and 2450 ng/mL, respectively, and area under the plasma drug concentration-time curve from time 0 (predose) to the time of last quantifiable concentration (t) (AUC_{0-t}) values were 8587 and 16092 ng•h/mL, respectively. Miglustat reached peak concentrations at approximately 3 hours after single-dose administration, and the $t_{½}$ ranged from 4.5 to 6.0 hours. Volume of distribution ranged from 78 to 94 L (Doerfler et al 2014).

6.3. Interim Data From Ongoing Study ATB200-02

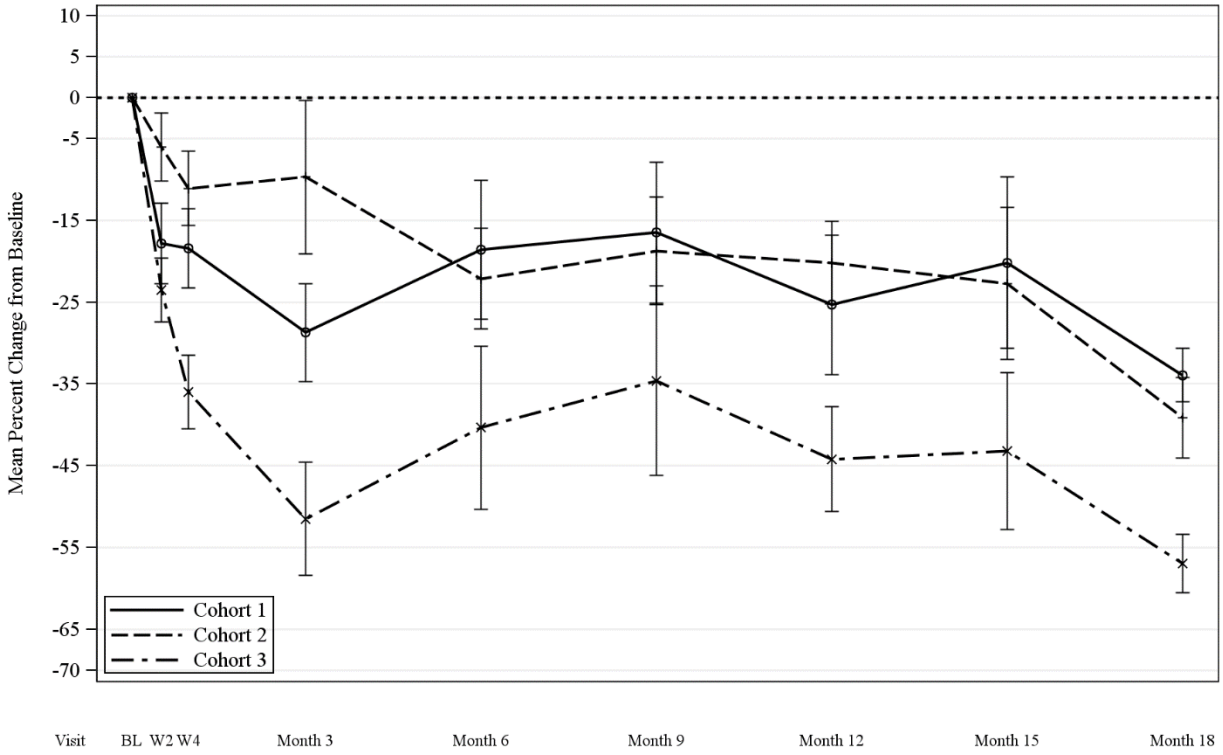
A clinical development program is being conducted by Amicus Therapeutics, Inc. (Amicus) that evaluates ATB200/AT2221 co-administration for treatment of LOPD. A Phase 1/2 (ATB200-02, NCT-02675465) open-label, fixed-sequence, ascending-dose clinical study is ongoing to assess safety, tolerability, pharmacokinetics, pharmacodynamics, and interim efficacy of IV infusion of ATB200 with AT2221 in adult subjects with Pompe disease (subjects with LOPD). The ATB200-02 study is ongoing in the US, Germany, United Kingdom, the Netherlands, New Zealand, and Australia. As of August 2018, results from an interim analysis (n = 21) of data from subjects in Cohorts 1 through 3 are available through Month 18.

Subjects treated with ATB200/AT2221 for up to 18 months showed improvements in 6MWD and other measures of motor function, stability or increases in FVC, and durable reductions in biomarkers of muscle damage and disease substrate.

6.3.1. Pharmacodynamics

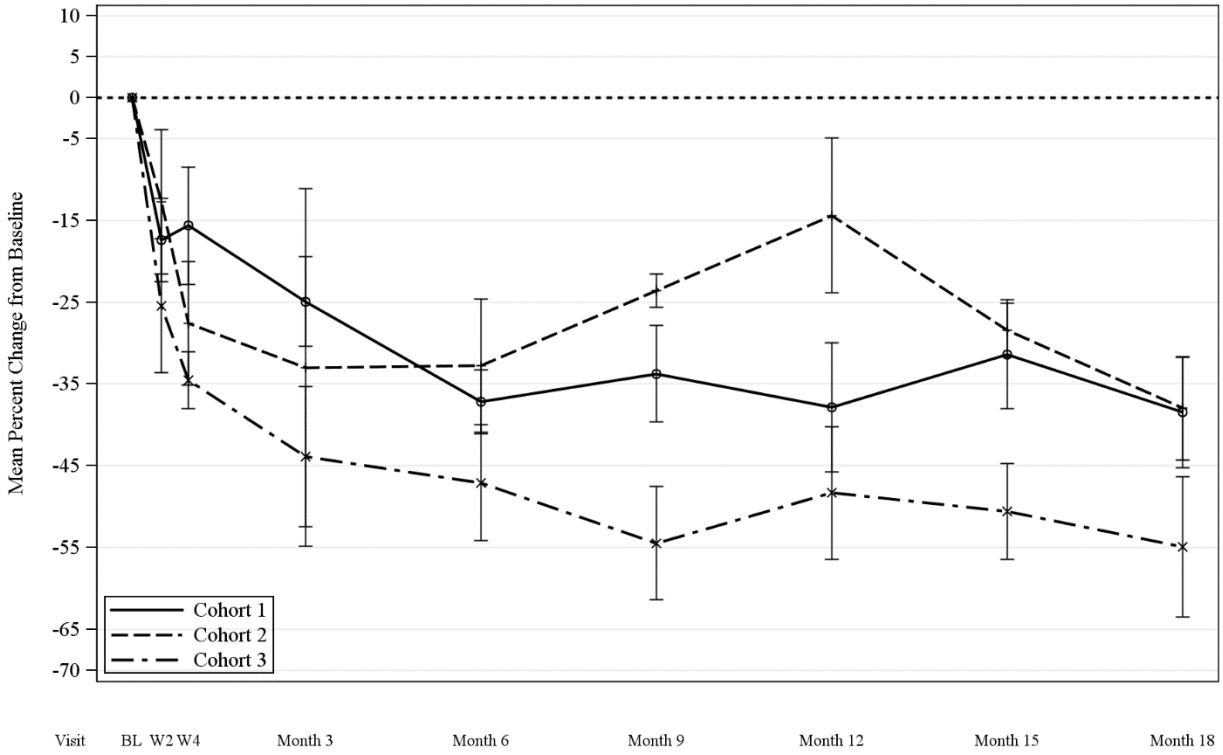
All cohorts demonstrated persistent improvement in biomarkers of muscle damage (CK) (Figure 1) and disease substrate (urinary Hex4) (Figure 2) for up to 18 months.

Figure 1: Mean Percentage Change from Baseline in Creatine Kinase Through Month 18: All Cohorts



Notes: Cohort 1 includes ERT-experienced (2 to 6 years) subjects; Cohort 2 includes ERT-experienced (≥ 2 years) subjects; Cohort 3 includes ERT-naïve subjects. Reported through interim data analysis (maximum 18 months); missing values either unable to be analyzed or not yet analyzed.
Source: Interim Analysis 6 (data cutoff of August 2018), Figure 14.2.1.4

Figure 2: Mean Percentage Change from Baseline in Urinary Hexose Tetrasaccharide Through Month 18: All Cohorts



Notes: Cohort 1 includes ERT-experienced (2 to 6 years) subjects; Cohort 2 includes ERT-experienced (≥ 2 years) subjects; Cohort 3 includes ERT-naïve subjects. Reported through interim data analysis (maximum 18 months); missing values either unable to be analyzed or not yet analyzed.
Source: Interim Analysis 6 (data cutoff of August 2018), Figure 14.2.1.5

6.3.2. Functional Outcomes

A primary measure of motor function in Pompe disease subjects, 6MWD, improved in both ERT-naïve and ERT-experienced subjects with continued benefit observed through Month 18 (Table 2).

- For ERT-naïve subjects from Cohort 3 (n=5), mean increases in 6MWD were observed at all time points through Month 18 (42 m at Month 6, 64 m at Month 9, 63 m at Month 12, and 49 m at Month 18).
- For ERT-experienced subjects in Cohort 1, mean increases in 6MWD were observed at all time points through Month 18 (24 m at Month 6 [n = 10], 25 m at Month 9 [n = 10], 42 m at Month 12 [n = 10], and 52 m at Month 18 [n = 9]).

Table 2: Change in 6-minute Walk Test Distance in Meters in Cohorts 1 and 3 Through Month 18

Cohort	Mean (SD)	Mean (SD) Change from Baseline			
	Baseline	Month 6	Month 9	Month 12	Month 18
1[a] ERT-experienced (2 to 6 years)	(n = 10) **397.2** (96.8)	(n = 10) **+23.9** (52.2)	(n = 10) **+24.5** (40.8)	(n = 10) **+42.2** (46.5)	(n = 9) **+51.7** (45.9)
3 ERT-naïve	(n = 5) **399.5** (83.5)	(n = 5) **+41.8** (29.4)	(n = 5) **+63.5** (23.1)	(n = 5) **+63.1** (29.1)	(n = 5) **+49.0** (28.3)

Abbreviations: ERT = enzyme replacement therapy; n = number of patients; SD = standard deviation
[a] For the purposes of assigning nominal time points to data from Cohort 1, the 6-week duration of Stage 1 (single ascending doses of ATB200) and the 12-week duration of Stage 2 (multiple ascending doses of miglustat [130 mg for 6 weeks, followed by 260 mg for 6 weeks]) were included. Therefore, the Month 6, 9, 12, and 18 time points reflect cumulative data to Stage 3 Month 3, Stage 3 Month 6, Stage 3 Month 9, and Stage 3 Month 15, respectively.
Source: Interim Analysis 6 (data cutoff date of August 2018), Table 14.2.1.3

There was a trend toward improvement in Gait, Stair, Gower, and Chair maneuver (GSGC) total score across the first 18 months with Cohort 1 showing improvement at Months 12 and 18 and Cohort 3 showing improvement at Months 6, 9, 12, and 18.

6.3.3. Pulmonary Function

Forced vital capacity was improved in ERT-naïve subjects and was generally stable in ERT-experienced subjects (Table 3).

Table 3: Change in Percentage Predicted Sitting FVC (%) in Cohorts 1 and 3 Subjects Through Month 18

Cohort	Mean (SD)	Mean (SD) Change from Baseline			
	Baseline	Month 6	Month 9	Month 12	Month 18
1[a] ERT-experienced (2 to 6 years)	(n = 9) **52.6** (14.7)	(n = 9) **–1.3** (4.1)	(n = 9) **–1.7** (3.9)	(n = 9) **–3.3** (6.1)	(n = 8) **–4.0** (7.0)
3 ERT-naïve	(n = 5) **53.4** (20.3)	(n = 5) **+4.2** (5.6)	(n = 5) **+6.2** (5.3)	(n = 5) **+4.4** (8.7)	(n = 5) **+6.8** (2.5)

Abbreviations: FVC = forced vital capacity; ERT = enzyme replacement therapy; n = number of patients; SD = standard deviation
[a] For the purposes of assigning nominal time points to data from Cohort 1, the 6-week duration of Stage 1 (single ascending doses of ATB200) and the 12-week duration of Stage 2 (multiple ascending doses of miglustat [130 mg for 6 weeks, followed by 260 mg for 6 weeks]) were included. Therefore, the Month 6, 9, 12, and 18 time points reflect cumulative data to Stage 3 Month 3, Stage 3 Month 6, Stage 3 Month 9, and Stage 3 Month 15, respectively.
Source: Interim Analysis 6 (data cutoff date of 03 August 2018), Table 14.2.1.1

6.3.4. Pharmacokinetics

The clinical PK profile of ATB200/AT2221 combination therapy has been consistent with previously reported nonclinical data; see Section 6.4.2 for a summary of pharmacokinetics and the Investigator's Brochure for additional details.

6.3.5. Safety

Safety and tolerability data in all 21 subjects reflect 18 months of treatment (data cutoff date of August 2018), with 1 subject having received ATB200/AT2221 for over 28 months. Adverse events (AEs) have been generally mild to moderate and transient. ATB200/AT2221 has resulted in a low rate of IARs following more than 900 infusions (8 events of IARs in 6 subjects).

6.4. Human Dosing Rationale

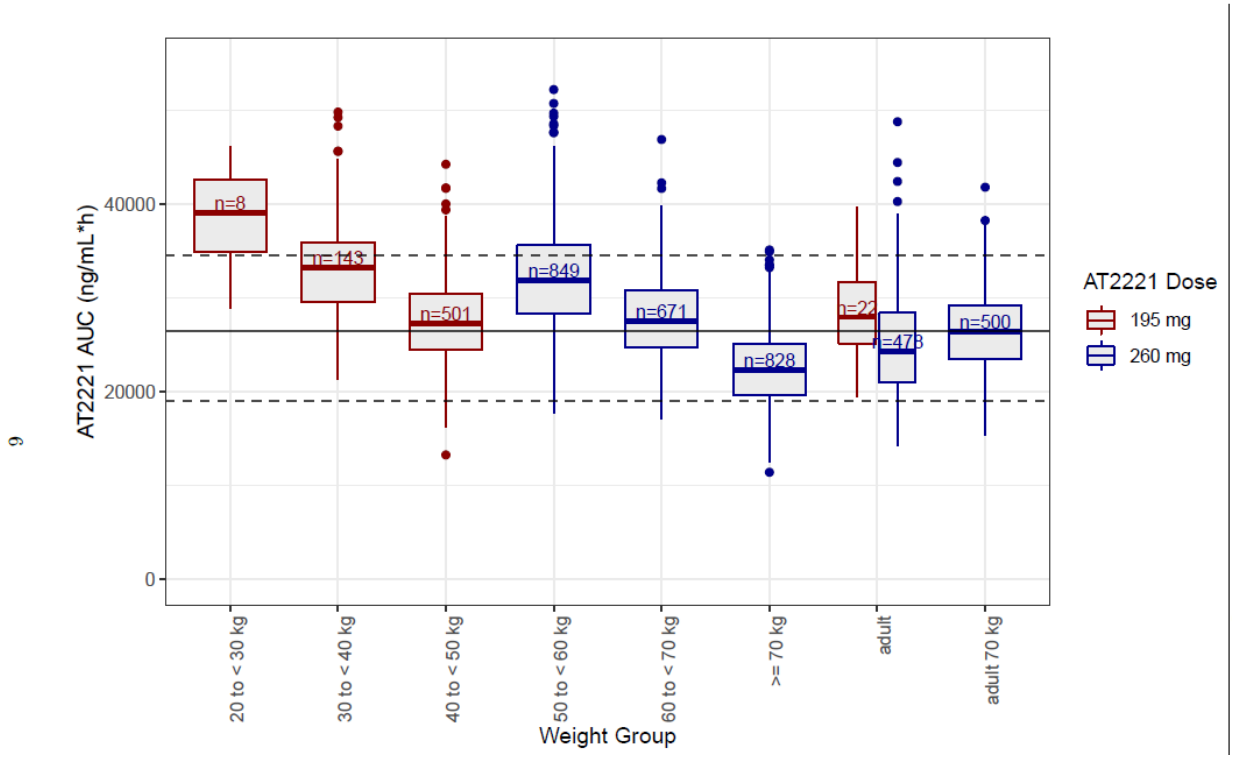
In clinical study ATB200-02, ATB200/AT2221, at a co-administered dose of 20 mg/kg ATB200 + 260 mg AT2221 every 2 weeks, was safe and efficacious in subjects with LOPD. Furthermore, the PK disposition of ATB200 alone in plasma confirmed the human exposure predicted by translational modeling. Addition of AT2221, at doses of 130 mg and 260 mg, prolonged distribution phase plasma $t_{½}$ of total GAA protein by 20% and 40%, respectively, and increased partial $AUC_{tmax\text{-}24h}$ by 25% to 46%, respectively, thus confirming the mechanism of action of AT2221 as a small molecule enzyme stabilizer that stabilizes exogenously administered ATB200 (data on file).

6.4.1. Dose Selection for Co-administered ATB200/AT2221

Dose selection of 20 mg/kg ATB200 + 260 mg AT2221 for Study ATB200-03 to assess the safety and efficacy of ATB200/AT2221 co-administration in LOPD subjects, has been based on a body of evidence that includes clinical pharmacokinetics/ pharmacodynamics, efficacy, and safety data from Phase 1/2 Study ATB200-02, nonclinical PK/pharmacodynamics (PD) data from studies conducted in the murine gene encoding acid α-glucosidase (mouse protein) (ie, *Gaa*) knockout model, and in vitro data demonstrating the stabilizing effects of AT2221 on the ATB200 enzyme. Based on the mouse model, AT2221 at a dose of 260 mg 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 ATB200 and AT2221 for a First-In-Human Study in Patients with Late-Onset Pompe Disease, AMIC-PCS-102. Sep 2015].

For patients who weigh ≥ 40 kg to < 50 kg, AT2221 dose modification is necessary. Patients in this body weight category will receive 195 mg AT2221 (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 (Figure 3).

Figure 3: Distributions of AUC by Weight for 260 mg AT2221 versus 195 mg AT2221



Notes: N represents number of simulated subjects. Black solid and dashed lines are the median and 95% prediction interval for a typical 70-kg subject.
Source: Data on file

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 AT2221 increased to 260 mg (4 × 65-mg capsules). If their body weight subsequently decreases and returns to a level below 50 kg, then the AT2221 dose would be reduced to 195 mg (3 × 65-mg capsules).

6.4.1.1. Dose Selection for ATB200

Dose selection for ATB200 (20 mg/kg) is based on providing a comparable total protein dose for ATB200 as labelled for alglucosidase alfa. The labelled total protein dose is determined by the spectrophotometric analysis (ultraviolet absorbance 280 nm, A_{280}). The specific activity (GAA enzyme activity/mg protein/hour) as determined by Amicus for alglucosidase alfa (129,171 nmol/mg/hr), compared to the specific activity for ATB200 (127,712 to 133,523 nmol/mg/hr) are essentially the same. Although similarity in total protein and specific activity is demonstrated, a lower administered dose of ATB200 (approximately 7% to 8%) is expected simply based on methodological differences (A280 extinction coefficient) used for the 2 products. Overall lower exposures of ATB200 in humans as compared to alglucosidase alfa are also expected based on the advantages of the improved ATB200 targeting effects of the ATB200.

A similar ATB200 clinical dose (20 mg/kg) as compared to alglucosidase alfa is selected so as to maintain exposures at/or below established exposures as demonstrated alglucosidase alfa, yet to demonstrate superior clinical benefits of ATB200/AT2221 co-administration, including benefits

associated with improved lysosomal targeting due to optimal glycan structure and phosphorylation (ATB200) and enzyme stabilization in blood (AT2221). ATB200 is the primary active agent with an enzymatic mechanism of action specifically to reduce intramuscular glycogen, the primary lysosomal storage material in LOPD. ATB200 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 distinguishing features of ATB200 from alglucosidase alfa is substantially more (~95%) of the initial ATB200 dose can bind CI-MPR whereas only ~27% of alglucosidase alfa binds receptor at equivalent enzyme concentrations. The substantially higher binding of ATB200 to the CI-MPR receptor is due to the greater bis-M6P content of ATB200 compared to alglucosidase alfa, which has 10X higher affinity to bind to the receptor compared to M6P. As a result, ATB200 is internalized into the disease-relevant muscles at a much greater magnitude than alglucosidase alfa and therefore is more potent. In vitro studies have demonstrated this by improved uptake of ATB200 into muscle cells as well as by substantially greater glycogen reduction with 20 mg/kg ATB200 compared to 20 mg/kg alglucosidase alfa. In addition, in vivo studies have indicated that the co-administration of AT2221 with ATB200 shows even greater trends in glycogen reduction compared to ATB200 alone as well as alglucosidase alfa. Therefore, a 20 mg/kg dose of ATB200 with AT2221 is expected to provide improved uptake into muscle tissue than even higher doses at 40 mg/kg of alglucosidase alfa.

Pharmacokinetics of ATB200 and ATB200 co-administered with AT2221 is well-characterized, as part of Stages 1 and 2 of Cohort 1 of the ATB200-02 clinical study. Safety and tolerability data in 20 subjects reflect greater than 20 months of treatment and greater than 550 infusions. As of the most recent data-cut, AEs have been generally mild and transient. No clinically significant risks have been identified that would preclude the use of ATB200 co-administered with AT2221 in the LOPD subjects. Based on confirmatory evidence of the pharmacokinetics for ATB200/AT2221 in the ATB200-02 study, as well as evidence of safety and functional benefit on 6MWD to LOPD subjects in this study, an ATB200 clinical dose of 20 mg/kg is planned for evaluation in the current study.

6.4.1.2. Dose Selection for AT2221

Dose selection for AT2221 is based on nonclinical (in vitro and in vivo), clinical (ATB200-02) data, and population PK modeling. These data confirm that the selected doses (260 mg for subjects ≥ 50 kg and 195 mg for subjects ≥ 40 kg to < 50 kg) acts as a small molecule enzyme stabilizer when co-administered with ATB200.

As a small molecule enzyme stabilizer, AT2221 demonstrates specific and reversible interaction with the ATB200 enzyme. Due to the specific binding characteristics of AT2221 with the ATB200 enzyme at neutral (pH 7, blood) and acidic pH (pH 4 to 5, lysosome), an administered dose of 260 mg in humans result in exposures producing effective interaction (and stabilizing effects) with ATB200 in blood and dissociation from ATB200 in the lysosome.

The dissociation constant (Ki value) represents the binding affinity of AT2221 towards the ATB200 enzyme. Nonclinical in vitro studies have confirmed Ki values of 0.18 μM at pH 5.2 and 0.21 μM at pH 7.4 for AT2221 with ATB200. Based on the Ki values for the AT2221, blood exposures of AT2221 at concentrations > 0.21 μM (pH 7.4, blood) result in

effective interaction with ATB200 and AT2221 concentrations < 0.18 μM (pH 5.2) result in effective dissociation of AT2221 from the ATB200 enzyme.

AT2221 exposures in blood and muscle tissue were subsequently confirmed in nonclinical in vivo studies. These studies confirmed that an orally administered AT2221 dose (10 mg/kg) in mice produced concentrations required for effective interaction with ATB200 in the blood (plasma > 30 μM). Nonclinical in vivo studies also confirmed that a 10 mg/kg-dose of AT2221 (at 24 hours post-administration) produced concentrations in targeted muscle tissue (muscle ~ 0.013 μM) greater than 10-fold lower than required for effective dissociation from ATB200 in the lysosomal microenvironment. Higher doses of AT2221 (> 10 mg/kg) resulted in improvements in exposures of ATB200 (limited additional increase of ATB200 exposure). Nonclinical in vitro studies (thermostabilization of ATB200 enzyme and stabilization of ATB200 in blood) also confirm the stabilizing properties of AT2221 as a small molecule enzyme stabilizer of ATB200 at these determined clinically relevant concentrations.

The efficacy and safety of the ATB200 20 mg/kg AT2221 260 mg co-administration regimen in adults has also been subsequently confirmed in the clinical study ATB200-02.

6.4.2. Pharmacokinetics of Co-administered ATB200/AT2221

The PK portion of first-in-human clinical study ATB200-02 is complete. A summary of the PK data from 11 ERT-experienced (Cohort 1) adult subjects with LOPD is presented in Table 4 and Table 5.

Table 4: Pharmacokinetic Summary of Single Ascending Doses of ATB200 in Cohort 1 Subjects with Late-onset Pompe Disease

Total GAA Protein Signature Peptide T09 PK Summary									
Treatment Group	**N**	**C_{max}[a] (µg/mL)**	**t_{max}[b] (h)**	**AUC_{0-t}[a] (µg•h/mL)**	**$AUC_{tmax-24h}$[a] (µg•h/mL)**	**$AUC_{0-\infty}$[a] (µg•h/mL)**	**F[a,c] Ratio**	**ALPHA $t_{½}$[d] (h)**	**CL_T[d] (L/h)**
5 mg/kg	10	58.4 (19.1)	4.0 (3.0-4.0)	208 (17.4)	108 (25.1)	211 (17.2)	-	1.1 (10.2)	2.15 (16.9)
10 mg/kg	11	135 (18.3)	4.0 (3.5-4.0)	534 (24.4)	287 (25.6)	538 (24.4)	2.63 (9.4)	1.3 (10.6)	1.65 (22.4)
20 mg/kg	11	325 (13.5)	4.0 (3.5-4.0)	1414 (17.1)	844 (20.8)	1418 (16.9)	6.89 (7.4)	1.5 (8.5)	1.26 (18.4)

AUC = area under the plasma concentration-time curve; AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last quantifiable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; $AUC_{tmax-24h}$ = area under the plasma concentration-time curve from observed time to reach C_{max} to 24 hours; CL_T = total plasma clearance of drug after intravenous administration; C_{max} = maximum observed concentration; CV% = coefficient of variation; F = fraction bioavailable expressed as an AUC ratio; GAA = human acid α-glucosidase; max = maximum; min = minimum; PK = pharmacokinetic; $t_{½}$ = terminal elimination half-life; t_{max} = observed time to reach C_{max}.

[a] Geometric mean (CV%).

[b] Median (min-max).

[c] Area under the plasma concentration-time curve ratios for 20 mg/kg and 10 mg/kg are relative to 5 mg/kg.

[d] Arithmetic mean (CV%).

Table 5: Summary of PK Parameters for ATB200/AT2221 Co-administration vs ATB200 Alone in Cohort 1 Subjects

Total GAA Protein Signature Peptide T09 PK Summary									
Treatment Group	**N**	**C_{max}[a] (µg/mL**	**t_{max}[b] (h)**	**AUC_{0-t}[a] (µg•h/mL)**	**$AUC_{tmax-24h}$[a] (µg•h/mL)**	**$AUC_{0-\infty}$[a] (µg•h/mL)**	**F[a,c] Ratio**	**ALPHA $t_{½}$[d] (h)**	**CL_T[d] (L/h)**
20 mg/kg	11	325 (13.5)	4.0 (3.5-4.0)	1414 (17.1)	844 (20.8)	1418 (16.9)	-	1.5 (8.5)	1.26 (18.4)
20 mg/kg ATB200 + 130 mg AT2221 single dose	11	329 (14.3)	4.0 (3.5-4.0)	1634 (17.2)	1057 (19.6)	1643 (16.9)	1.16 (6.7)	1.8 (9.7)	1.09 (18.8)
20 mg/kg ATB200 + 130 mg AT2221 multiple doses	11	335 (15.4)	4.0 (3.5-5.0)	1654 (20.8)	1062 (23.8)	1662 (20.5)	1.17 (7.7)	1.8 (21.8)	1.08 (20.5)
20 mg/kg ATB200 + 260 mg AT2221 single dose	10	339 (12.9)	4.0 (3.5-4.0)	1780 (17.7)	1198 (18.2)	1789 (17.6)	1.29 (7.0)	2.1 (19.5)	0.99 (21.8)
20 mg/kg ATB200 + 260 mg AT2221 multiple doses	11	345 (18.5)	4.0 (3.5-4.0)	1815 (21.4)	1203 (24.2)	1821 (21.5)	1.28 (9.4)	2.1 (16.1)	0.99 (22.7)

AUC = area under the plasma concentration-time curve; AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last quantifiable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; $AUC_{tmax-24h}$ = area under the plasma concentration-time curve from observed time to reach C_{max} to 24 hours; CL_T = total plasma clearance of drug after intravenous administration; C_{max} = maximum observed concentration; CV% = coefficient of variation; F = fraction bioavailable expressed as an AUC ratio; GAA = human acid α-glucosidase; max = maximum; min = minimum; PK = pharmacokinetic; $t_{½}$ = terminal elimination half-life; t_{max} = observed time to reach C_{max}.

[a] Geometric mean (CV%).

[b] Median (min-max).

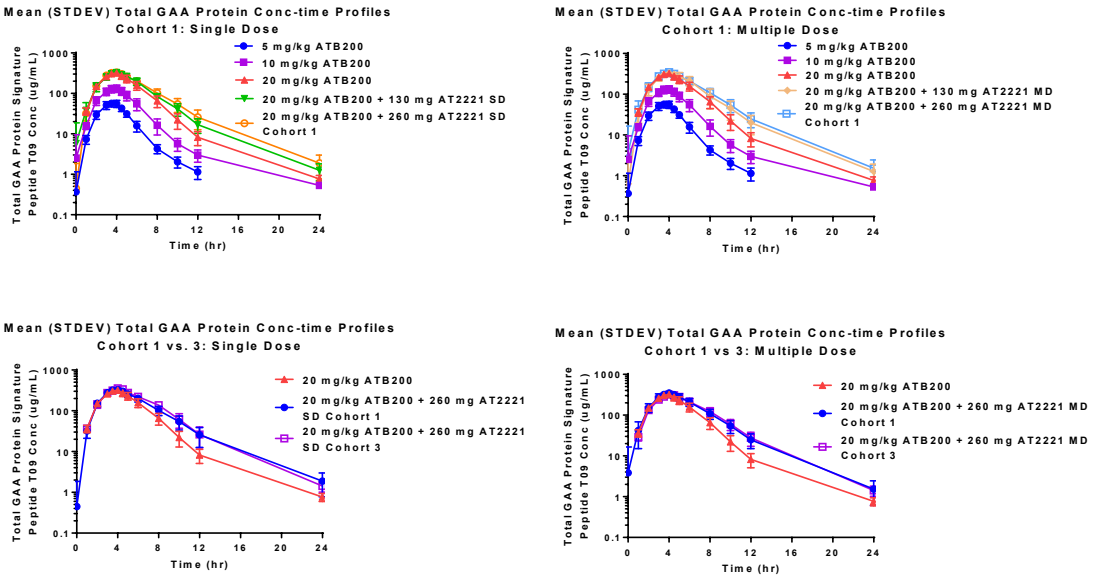
[c] Area under the plasma concentration-time curve ratios for 20 mg/kg + AT221 are relative to 20 mg/kg alone.

[d] Arithmetic mean (CV%).

6.4.3. Total GAA Protein Using Signature Peptide(s) T09/T50

Total GAA protein in plasma was measured by signature peptides T09 (primary) and T50. Generally, the pharmacokinetics of signature peptide T50 was similar to T09, and therefore confirmed the results of the assay. Mean (standard deviation) plasma total GAA activity by signature peptide T09 concentration-time profiles for Cohorts 1 and 3 are presented in Figure 4. As shown for Cohort 1 in Figure 5, dose-related increases in plasma total GAA protein are observed during Stage 1 for ATB200 alone. Further increases, particularly during the distribution elimination phase, are observed during Stage 2 with co-administration of low-dose and high-dose AT2221 following both single and multiple dose administrations. Cohort 3 demonstrates a similar total GAA protein profile to Cohort 1.

Figure 4: Mean (STDEV) Total GAA Protein Concentration-time Profiles for Cohort 1 (Stages 1 and 2) and Cohort 3 (Stage 3)

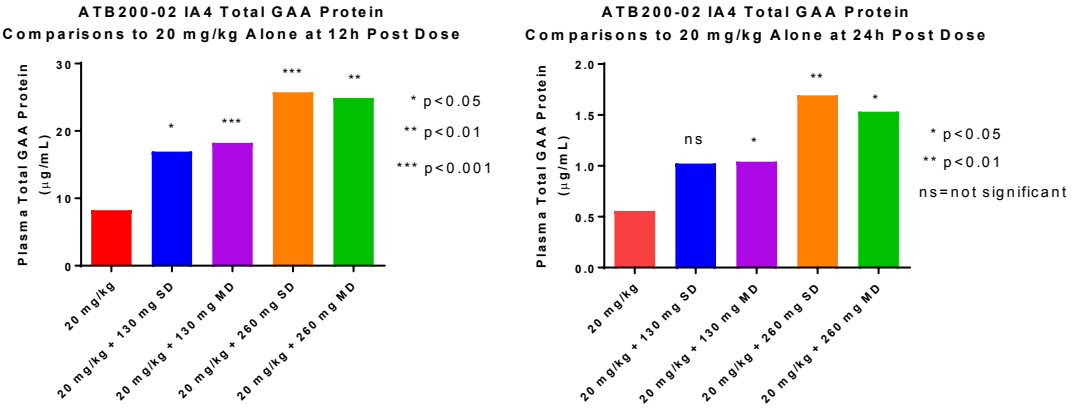


Abbreviations: ATB200 = recombinant human acid α-glucosidase; AT2221 = *N*-butyl deoxynojirimycin; GAA = human acid α-glucosidase; hr = hour; MD = multiple dose; SD = single dose; STDEV = standard deviation
Source: Amicus data on file

In Cohort 1 (ERT-experienced LOPD subjects), total GAA protein by signature peptide T09 exposures (C_{max} and AUC) demonstrated greater than dose-proportional increases during Stage 1 (single ascending doses of 5, 10, and 20 mg/kg ATB200), as shown in column "F" in the table. Co-administration with 130 mg AT2221 resulted in a 16% to 17% increase in total GAA protein mean AUC. Co-administration with 260 mg AT2221 increased total GAA protein AUCs by 28% to 29%. These increases were mainly observed during the early, distribution terminal phase, as shown by observed increases in the alpha half-life. The increased distribution phase area can be more clearly observed in the partial AUCs from t_{max} to 24-hours post-dose. These increases suggest stabilization of ATB200 by the small molecule enzyme stabilizer, AT2221, while in blood. Clearance of plasma total GAA protein decreased with dose escalation with further decreases observed when co administered with AT2221, again suggesting better stabilization of ATB200 while in circulation. Further evidence of stabilization can be observed in Figure 4 and

Figure 5. During terminal phase time points, 12 hours and 24 hours, statistically significant increases in total GAA protein are observed following co-administration with low-dose and high-dose AT2221 relative to 20 mg/kg ATB200 alone. At 12 hours post dose, the differences were highly significant ($p < 0.01$ or $p < 0.001$) for high-dose AT2221 co-administration.

Figure 5: Plasma Total GAA Protein Concentration Comparisons Between Co-administration Treatments vs ATB200 Alone at 12 and 24 Hours Post-dose (1-sided t-tests) for Cohort 1



Abbreviations: ATB200 = recombinant human acid α-glucosidase; h = hour; IA = interim analysis; GAA = human acid α-glucosidase; MD = multiple dose; SD = single dose
Source: Amicus data on file

Generally, the pharmacokinetics of 20 mg/kg ATB200 based on plasma total GAA protein was similar between single and multiple doses when co-administered with 130 mg AT2221, and between single and multiple doses when co-administered with 260 mg AT2221.

The plasma total GAA protein PK profile of Cohort 3 (ERT-naïve subjects with LOPD) was generally similar to Cohort 1 and not statistically different as shown in Table 6, where all comparisons are contained with the 90% to 125% confidence intervals.

Table 6: Statistical Comparisons by ANOVA Between Cohort 1 Single Dose vs Multiple Dose and Between Cohort 1 and Cohort 3

ANOVA for Total GAA Protein by Signature Peptide T09 AUC (µg·h/mL)				
		AUC Ratio	90% Lower-bound CI	90% Upper-bound CI
Reference	Test	% Ref		
Cohort 1 Single Dose	Cohort 1 Multiple Dose	98.0	94.9	101.2
Cohort 1 Single Dose	Cohort 3 Single Dose	100.1	82.3	121.8

Table 6: Statistical Comparisons by ANOVA Between Cohort 1 Single Dose vs Multiple Dose and Between Cohort 1 and Cohort 3 (Continued)

ANOVA for Total GAA Protein by Signature Peptide T09 AUC (µg·h/mL)				
		AUC Ratio	90% Lower-bound CI	90% Upper-bound CI
Reference	Test	% Ref		
Cohort 1 Multiple Dose	Cohort 3 Multiple Dose	97.5	80.2	118.6

Abbreviations: ANOVA = analysis of variance; AUC = area under the plasma concentration-time curve; GAA = human acid α-glucosidase; CI = confidence interval
Source: Data on file

A PK summary of plasma AT2221 is presented in Table 7. Plasma AT2221 exposures (C_{max} and AUC) are approximately dose proportional. The rate of absorption (t_{max}) values support dosing with AT2221 1 hour before the start of ATB200 infusion, so that peak AT2221 concentrations are attained midway into infusion. Termination elimination half-life was consistent at approximately 5 to 6 hours, as was plasma clearance (approximately 10 L/h) and terminal volume of distribution (77 to 106 L). Generally, the PK profile of dose-normalized AT2221 is similar to marketed formulations of miglustat.

Overall, the preliminary exposures of ATB200 and AT2221 subjects with LOPD are well within the limits of the established safety margins.

Table 7: ATB200-02 PK Summary from Preliminary Plasma AT2221 Concentrations Sampled From Cohort 1 and Cohort 3 Subjects with Late-onset Pompe Disease

AT2221 PK Summary									
Treatment Group (N)	Cohort	C_{max}[a] (ng/mL)	t_{max}[b] (h)	AUC_{0-t}[a] (ng•h/mL)	$AUC_{0-\infty}$[a] (ng•h/mL)	F_{rel} Ratio	$t_{½}$[c] (h)	CL/F[c] (L/h)	V_z/F[c] (L)
20 mg/kg ATB200 + 130 mg AT2221 SD (11)	1	1527 (26.0)	3.5 (1.5 – 5.0)	11870 (24.2)	12721 (24.7)	-	6.1 (18.9)	10.5 (22.1)	92.1 (32.0)
20 mg/kg ATB200 + 130 mg AT2221 MD (11)	1	1505 (23.9)	3.0 (1.5 – 4.0)	11968 (24.5)	12913 (25.6)	-	6.5 (29.3)	10.3 (21.3)	97.3 (39.3)
20 mg/kg ATB200 + 260 mg AT2221 SD (10)	1	2665 (31.8)	4.0 (2.0 – 5.0)	22928 (33.0)	24803 (33.3)	1.98 (24.8)	6.7 (17.1)	10.9 (26.6)	106 (33.1)
20 mg/kg ATB200 + 260 mg AT2221 MD (11)	1	3089 (28.8)	3.0 (1.0 – 4.0)	23565 (29.8)	25029 (30.4)	1.94 (14.9)	6.0 (18.4)	10.7 (25.5)	94.4 (35.8)
20 mg/kg ATB200 + 260 mg AT2221 SD (5)	3	3559 (25.8)	2.0 (1.5 – 3.0)	25747 (13.2)	26936 (12.3)	NA	5.5 (19.2)	9.71 (12.7)	77.3 (25.4)
20 mg/kg ATB200 + 260 mg AT2221 MD (5)	3	3083 (34.0)	2.5 (2.0 – 3.0)	25306 (17.8)	26591 (15.5)	NA	5.7 (19.4)	9.87 (14.6)	81.8 (29.5)

Abbreviations: ATB200 = recombinant human acid α-glucosidase; AT2221 = *N*-butyl deoxynojirimycin; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last quantifiable concentration; CL/F = apparent total plasma clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; F_{rel} = relative bioavailability; $t_{½}$ = terminal elimination half-life; Max = maximum; Min = minimum; N = number of subjects; NA = not applicable; t_{max} = observed time to reach C_{max}; V_z/F = apparent volume of distribution.

[a] Geometric mean (CV%)

[b] Median (Min – Max)

[c] Arithmetic mean (CV%)

Source: Data on file

6.5. Primary Endpoint Rationale

The primary efficacy variable in this study is the 6MWD as measured by the 6MWT. This measure has been used in registration studies in Pompe, and it is part of the Clinical Outcome Assessment Compendium (December 2015). The 6MWD was also used in the approval of alglucosidase alfa.

In LOPD, the disease course varies substantially among patients with respect to age at onset and rate of decline of muscular and respiratory function. Furthermore, there is no clear pattern in the sequence of clinical deterioration of respiratory and skeletal muscles (Hagemans et al 2005). The 6MWT evaluates the global and integrated responses of all the systems involved during ambulatory function, including the pulmonary and cardiovascular systems, systemic circulation, neuromuscular units, and muscle metabolism (ATS 2002). Thus, the 6MWT is a more holistic assessment than other measures, such as the Timed Up and Go (TUG) or FVC.

The improvement in the endurance test (6MWT) is a reflection of overall improvement in the subject's muscular and pulmonary functions. Based on predicted values for 6MWD in healthy adults (Enright, Sherrill 1998) and adults with pathology (Bohannon, Crouch 2017), a minimum of 20 meters is considered a clinically important difference. Therefore, Study ATB200-03 will use 6MWD as measured by the 6MWT for its primary endpoint.

6.6. Summary of Known Potential Risks and Benefits

A summary of the known and potential risks and benefits are provided in a separate document, Benefit Risk Profile Document.

7. STUDY OBJECTIVES

7.1. Primary Objective

- To assess the efficacy of ATB200/AT2221 co-administration on ambulatory function, as measured by the 6MWT, compared with alglucosidase alfa/placebo

7.2. Secondary Objectives

- To assess the efficacy of ATB200/AT2221 co-administration on pulmonary function, as measured by sitting FVC (% predicted) compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on muscle strength, compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on health-related patient-reported outcomes, compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on motor function, compared with alglucosidase alfa/placebo
- To assess the efficacy of ATB200/AT2221 co-administration on overall clinical impression as assessed by both physician and subject, compared with alglucosidase alfa/placebo
- To assess the safety, tolerability, and immunogenicity of ATB200/AT2221 co-administration compared with alglucosidase alfa/placebo
- To assess the effect of ATB200/AT2221 co-administration on biomarkers of muscle injury and disease substrate compared with alglucosidase alfa/placebo
- To characterize the population pharmacokinetics of ATB200 and alglucosidase alfa in ERT-experienced subjects using plasma total GAA protein level by signature peptide assay and plasma AT2221 concentration
- To characterize the pharmacokinetics of ATB200, alglucosidase alfa, and AT2221 in ERT-naïve subjects using noncompartmental analysis
- To explore the exposure-response relationship for ATB200/AT2221 and alglucosidase alfa/placebo co-administration

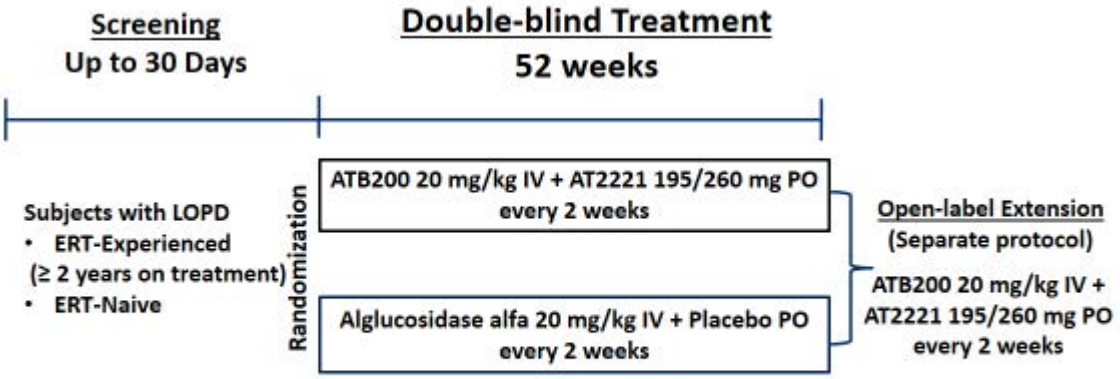
8. INVESTIGATIONAL PLAN

8.1. Study Design

This is a double-blind, randomized, multicenter, international study of ATB200/AT2221 in adult subjects with LOPD who have received ERT with alglucosidase alfa (ie, ERT-experienced) or who have never received ERT (ie, ERT-naïve) compared with alglucosidase alfa/placebo. As this study was initially designed to assess the effects of ATB200/AT2221 in ERT-experienced subjects who continued to receive alglucosidase alfa in Study POM-003, subjects from that study who meet the eligibility criteria for this study will make up part of the ERT-experienced study population.

Enzyme replacement therapy-experienced subjects will continue to take alglucosidase alfa during the screening period; treatment with alglucosidase alfa will then be replaced by study drug (ATB200/AT2221 or alglucosidase alfa/placebo) on the same schedule without interruption (ie, every 2 weeks). The Screening Visits will occur over 2 or more days to allow for repeated 6MWT and pulmonary function test assessments. The repeated tests for 6MWT or for pulmonary function (FVC, slow vital capacity [SVC], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and sniff nasal inspiratory pressure [SNIP]) should not be done on the same day. No other assessments should be performed on the day that the 6MWT and pulmonary function tests are repeated. Eligible subjects will be randomly assigned in a 2:1 ratio to receive ATB200/AT2221 or alglucosidase alfa/placebo and stratified by ERT status (ERT-experienced, ERT-naïve) and baseline 6MWD (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters) (Figure 6).

Figure 6: Study Design Schematic



Abbreviations: ERT = enzyme replacement therapy; IV = intravenous; PO = oral

Infusion visits will be scheduled every 2 weeks throughout the study; assessments (eg, clinical laboratory tests) for monitoring of initial safety will be performed at these visits for the first 6 weeks of the study. Subjects may be eligible for administration of study drug at their home after participating in the study for 6 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 wherever possible for subjects who may be eligible (see Section 12.2.3). Study visits that include efficacy, safety, and other assessments will be scheduled approximately every 3 months and may occur over 2 or more days, provided all study assessments and procedures (with the exception of pharmacokinetic [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 Voice/Web Response 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 research ethics boards (REBs) should be notified of any deviations from the protocol. If infusions were missed near the scheduled assessments on Week 26, 38 or 52, 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. If 5 or more consecutive infusions are missed due to any circumstance, including COVID-19, the subject must be discontinued from this protocol. Any subjects discontinued due to COVID-19 may be eligible for ATB200-07 with Amicus approval.

Efficacy assessments (ie, functional assessments) include evaluation of ambulatory function (6MWT), motor function tests (GSGC test and TUG test), muscle strength (manual muscle testing and quantitative muscle testing), and pulmonary function tests (FVC, SVC, MIP, MEP, and SNIP). Patient-reported outcomes (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). The Physician's Global Impression of Change will also be performed.

Pharmacodynamic assessments include measurement of biomarkers of muscle injury (CK) and disease substrate (urinary Hex4). Blood samples will be collected for determination of total GAA protein levels and AT2221 concentrations in plasma for a population PK analysis. Safety assessments include monitoring of 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.

8.2. Duration of Study

The study will consist of a screening period up to 30 days, a 12-month treatment period, and a 30-day safety follow-up period. Subjects who missed visits due to COVID-19 related quarantines, travel restrictions, and risk of infection may be enrolled longer than 12 months in the study. In addition, subjects who discontinue study drug for any reason will be followed for up to 12 months for monitoring of immunogenicity; these results will be reported separately.

Subjects who complete this study will have the option to participate in an open-label extension study to receive ATB200/AT2221 under a separate protocol.

8.3. Criteria for Termination of the Study

The study may be terminated by the sponsor for any of the following reasons:

- evidence suggesting that safety risks associated with ATB200/AT2221 treatment outweigh the potential benefits or at the recommendation of the Data Monitoring Committee (DMC) (Section 13.5)
- lack of efficacy
- inability to enroll the targeted number of subjects

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 when all subjects have completed the study or have been withdrawn from the study.

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

This is a double-blind, active/placebo-controlled, randomized study.

The study design includes randomization to a control, alglucosidase alfa/placebo, in order to provide adequate blinding of the study population and to address potential bias. This is a standard design for a registration study.

9. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

9.1. Number of Subjects

The planned sample size is approximately 110 subjects at up to approximately 90 sites globally. A total of 100 subjects (including at least 30 ERT-naïve subjects) are expected to complete the study.

9.2. Eligibility Criteria

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

9.2.1. Inclusion Criteria

1. Subject must provide signed informed consent prior to any study-related procedures being performed.
2. Male and female subjects are ≥ 18 years old and weigh ≥ 40 kg at screening.
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.
4. Subject must have a diagnosis of LOPD based on documentation of one of the following:
   a. deficiency of GAA enzyme
   b. *GAA* genotyping
5. Subject is classified as one of the following with respect to ERT status:
   a. ERT-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa) at the recommended dose and regimen (ie, 20 mg/kg dose every 2 weeks) for ≥ 24 months
      – Specific to Australia, ERT-experienced, defined as currently receiving standard of care ERT (alglucosidase alfa) at the recommended dose and regimen, at a dose of 20 mg/kg based on lean or ideal body weight every 2 weeks
   b. ERT-naïve, defined as never having received investigational or commercially available ERT
6. Subject has a sitting FVC ≥ 30% of the predicted value for healthy adults (National Health and Nutrition Examination Survey III) at screening.
7. Subject performs two 6MWTs at screening that are valid, as determined by the clinical evaluator, and that meet all of the following criteria:
   a. both screening values of 6MWD are ≥ 75 meters
   b. both screening values of 6MWD are ≤ 90% of the predicted value for healthy adults
   c. the lower value of 6MWD is within 20% of the higher value of 6MWD

9.2.2. Exclusion Criteria

1. Subject has received any investigational therapy or pharmacological treatment for Pompe disease, other than alglucosidase alfa, within 30 days or 5 half-lives of the therapy or treatment, whichever is longer, before Day 1 or is anticipated to do so during the study.
2. Subject has received gene therapy for Pompe disease.
3. Subject is taking any of the following prohibited medications within 30 days before Day 1:

   - miglitol (eg, Glyset®)
   - miglustat (eg, Zavesca®)
   - acarbose (eg, Precose® or Glucobay®)
   - voglibose (eg, Volix®, Vocarb®, or Volibo®)

   Note: None of these medications have a half-life that, when multiplied by 5, is longer than 30 days.
4. Subject requires the use of invasive or noninvasive ventilation support for > 6 hours per day while awake.
5. Subject has a hypersensitivity to any of the excipients in ATB200, alglucosidase alfa, or AT2221.
6. Subject 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.
7. Subject, if female, is pregnant or breastfeeding at screening.
8. Subject, whether male or female, is planning to conceive a child during the study.
9. Subject refuses to undergo genetic testing.

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
- 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
- missed 5 consecutive infusions at any time during the study

- 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 (Abs) will complete follow-up immunological testing for up to 12 months (see Section 12.2.7).

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. 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.

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

- total abstinence, when this is in line with the preferred and usual lifestyle of the subject
- 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

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 be randomized with a randomization ratio of at least 2:1 to receive either ATB200/AT2221 or alglucosidase alfa/placebo according to the treatment assignment in Table 8.

Table 8: Treatment Assignment

Treatment Assignment	Treatment	Regimen
ATB200/AT2221	AT2221[a]	Subjects ≥ 50 kg: 260 mg (4 × 65-mg oral capsules) 1 hour prior to ATB200 infusion every 2 weeks Subjects ≥ 40 kg to < 50 kg: 195 mg (3 × 65-mg oral capsules) 1 hour prior to ATB200 infusion every 2 weeks
	ATB200	20 mg/kg IV infusion over a 4-hour duration every 2 weeks
Alglucosidase alfa/placebo	Placebo	Subjects ≥ 50 kg: Placebo (4 oral capsules) 1 hour prior to alglucosidase alfa infusion every 2 weeks Subjects ≥ 40 kg to < 50 kg: Placebo (3 oral capsules) 1 hour prior to alglucosidase alfa infusion every 2 weeks
	Alglucosidase alfa	20 mg/kg IV infusion over a 4-hour duration every 2 weeks

Abbreviations: IV = intravenous

[a] Note: Subjects are required to fast at least 2 hours before and 2 hours after administration of AT2221 or placebo.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

Study drug is defined in this protocol as ATB200, AT2221, alglucosidase alfa, placebo, or a combination of these. Investigational product refers only to ATB200, AT2221, or a combination of these.

The study drug will be administered every 2 weeks at the study site in a blinded fashion. After 6 months in the study without any IARs, subjects may be eligible for administration of study drug at their home (see Section 12.2.3). 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.

ATB200 (rhGAA) functions as ERT. AT2221 (*N*-butyl-deoxynojirimycin) is an iminosugar that functions as a selective small molecule enzyme stabilizer of rhGAA.

Table 9 provides details on the investigational products.

Table 9: Investigational Products

Product name	**ATB200**	**AT2221**
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
Excipients	sodium citrate dihydrate, citric acid monohydrate, mannitol, polysorbate-80	Microcrystalline cellulose, pregelatinized starch, Emprove® sucralose powder, 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

Alglucosidase alfa (Myozyme/Lumizyme) functions as ERT. Its dosage form is lyophilized powder for IV infusion, and its unit dose is 5 mg/mL. It is a sterile, nonpyrogenic, white to off-white lyophilized cake or powder supplied in single-use, clear 20-mL (cc) glass vials. Excipients include mannitol, polysorbate-80, sodium phosphate dibasic heptahydrate, and sodium phosphate monobasic monohydrate. Alglucosidase alfa is manufactured by Genzyme Corporation (Cambridge, MA). Placebo oral capsules match AT2221 in appearance, contain the same excipients as AT2221, and are manufactured by Alcami (Wilmington, NC).

11.2. Study Drug Packaging and Labeling

AT2221 (65 mg capsule) and associated placebo will be supplied by Amicus as hard gelatin capsules in high density polyethylene bottles and will be administered orally.

ATB200 (105 mg/vial) will be supplied by Amicus 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.

Alglucosidase alfa (50 mg/vial) will be supplied by Amicus 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.

Each container will be labeled in conformance to 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 will be instructed to store AT2221 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 to (40°C or 104°F) in a secure area, free from environmental extremes, and with restricted access.

Sites will be instructed to store ATB200 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 short excursions permitted 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 the ATB200 and alglucosidase alfa products are stored and the temperature of the storage room (or cabinet) where the AT2221 and placebo 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 institutions 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, have met all entry criteria, and are randomized using the interactive response technology (IRT).

Alglucosidase alfa will be stored in the same manner as described for ATB200. Placebo will be stored in the same manner as described for AT2221.

Because the vial sizes and appearance of ATB200 and alglucosidase alfa differ, vials should be kept inside of cartons (which appear identical between both product types) if possible while

being stored to avoid the potential of partial unblinding and should only be removed by an unblinded pharmacist at the time of reconstitution in an area with restricted access for unblinded staff. If it is not possible to keep the vials in the carton due to space limitations at a particular site, vials must be stored in a secure location in which only the unblinded pharmacist has access. Cartons containing ATB200/alglucosidase alfa should only be handled by unblinded staff because they may have slight differences in weight. Details of the storage conditions can be found in the pharmacy manual.

11.4. Study Drug Preparation

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

Only unblinded qualified personnel will handle and/or prepare the study drugs to maintain the integrity of the double-blind design of the study.

11.5. Administration

11.5.1. ATB200/Alglucosidase Alfa

The dose of ATB200/alglucosidase alfa is 20 mg/kg body weight. Dose will be calculated based on actual body weight, even if a subject's previous dose was based on lean body weight. The value for body weight will be obtained at the previous protocol-specified visit for obtaining weight.

ATB200/alglucosidase alfa does not contain any preservatives. Vials are single-use only. Reconstituted vials should be retained at the site until the monitor checks accountability.

ATB200/alglucosidase alfa is to be administered every 2 weeks as an approximate 4-hour IV infusion. Changes in the duration of ATB200/alglucosidase alfa 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 ATB200/alglucosidase alfa should be performed by unblinded qualified study personnel (eg, pharmacist or pharmacy technician or nurse under physician supervision). Intravenous administration of ATB200/alglucosidase alfa should be performed by qualified study personnel. Subjects should be carefully monitored during and after the first 3 infusions (Section 12.2.3). Any delegation of this responsibility must follow Section 16.3.4. Rate and duration of infusion must be constant for each infusion. Changes in the rate and/or duration of infusion due to safety or tolerability issues will be documented.

The protocol-specified administration of alglucosidase alfa is consistent with the Lumizyme Prescribing Information (August 2014) and the Myozyme Summary of Product Characteristics (December 2018).

11.5.2. AT2221/Placebo

The dose of AT2221 is 260 mg (4 capsules at the 65-mg strength) for subjects weighing ≥ 50 kg and 195 mg (3 capsules at the 65-mg strength) for subjects weighing ≥ 40 kg to < 50 kg.

The dose of placebo is 3 or 4 placebo capsules of the same size as AT2221, that is, size 2.

AT2221/placebo is administered orally, approximately 1 hour before ATB200/alglucosidase alfa infusion according to their treatment arm. Subjects will take 3 or 4 capsules of AT2221/placebo, depending on their body weight. Subjects should fast for at least 2 hours before and 2 hours after administration of AT2221/placebo. Fasting is defined as nothing by mouth except for water; this includes prescription or over-the-counter medications, vitamins, or herbal supplements other than premedications for administration of ATB200. Subjects should arrive at the clinic at least 1 hour prior to the start of the ATB200/alglucosidase alfa infusion to receive AT2221/placebo.

11.6. Randomization and Blinding

11.6.1. Randomization

The randomization code used in this study was generated and will be maintained by an external resource not involved with the conduct of the study.

11.6.2. Blinding

The following methods are used to maintain the blind of the investigator and site personnel, sponsor, and/or subject:

- use of IRT to randomly assign subjects to study drug and to calculate dose of study drug
- an unblinded pharmacist to handle and prepare the study drug
- an unblinded monitor to perform study drug accountability at the site
- an unblinded medical monitor to review select laboratory results that could potentially unblind a subject's treatment assignment
- black or dark covering over ATB200 and alglucosidase alfa reconstituted solution to be used during infusion
- a matching placebo for AT2221 to be used with alglucosidase alfa

11.6.3. Unblinding of Treatment Assignment

The medical care of subjects includes medical decisions, such as whether to start or stop treatment or institute alternative treatment, if required. In emergency situations, the investigator may need to unblind a subject's treatment assignment immediately using IRT (see the IRT manual) or as quickly as possible if he/she finds it is in the best interest of the subject. If IRT is unavailable or inaccessible at the time of an emergency unblinding, investigators are to contact IRT Technical Support, as described in the pharmacy manual. A subject's treatment assignment should be unblinded only if knowledge of the study drug administered will affect the treatment options available to that subject. It is the responsibility of the investigator to promptly document and explain any premature unblinding of treatment assignment to the Sponsor.

11.7. Study Drug Accountability

In accordance with local regulatory requirements, the investigator, designated site personnel, or head of the medical institution (where applicable) 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

Because vials of ATB200 and alglucosidase alfa are distinguishable, the unblinded pharmacist or appropriately assigned unblinded designee will inventory and acknowledge receipt of all shipments of the study drugs. The investigator must keep an accurate record/log of the quantities of study drug dispensed and administered to each subject. The unblinded monitor will periodically check the supplies of study drugs held at the site 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 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 this study:

- miglitol (eg, Glyset®)
- non-study miglustat (eg, Zavesca®)
- Myozyme or Lumizyme after treatment with ATB200/AT2221 has begun
- acarbose (eg, Precose® or Glucobay®)
- voglibose (eg, Volix®, Vocarb®, or Volibo®)
- any investigational/experimental drug

Subjects who are taking β_2-receptor agonists or non-selective β-blockers (eg, propranolol, nadalol, carvedilol) before Day 1 must maintain a stable dose for the duration of the study.

12. STUDY PARAMETERS AND PROCEDURES

12.1. Schedule of Assessments

The Schedule of Assessments displays each study assessment and procedure along with the scheduled time of occurrence (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, the eCRF.

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 10: Schedule of Assessments

Study visit	Screening/Baseline (Day –30 to Day –1)[a]		Treatment						Follow-up
	Screening 1[b]	Screening 2	Day 1	Infusion visits (every 2 weeks through Week 52)[c]	Weeks 2, 4, 6	Week 12	Week 26, 38	Week 52/ ET[d]	≥ 30 days after last dose
Visit window (days)	—	—	—	± 3	± 3	± 3	± 3	± 3	± 3
Administrative									
Informed consent	X								
Randomization		**>Day –10**							
Assign subject number	X								
Demographics	X								
Eligibility criteria	X		X						
Schedule next visit	X		X	X	X	X	X	X	
Clinical assessment									
Medical history	X								
Retrospective data collection	See Section 12.3.4.								
Prior/concomitant medications and nondrug therapies	X		X	X	X	X	X	X	X
Complete PE	X							X	
Brief physical examination			X		X	X	X		
Vital signs	X		X	X	X	X	X	X	
Weight[e]	X		X			X	X	X	
Height	X								
AEs/SAEs, including IARs	X	X	X	X	X	X	X	X	X

Table 10: Schedule of Assessments (Continued)

Study visit	Screening/Baseline (Day –30 to Day –1)[a]		Treatment						Follow-up
	Screening 1[b]	Screening 2	Day 1	Infusion visits (every 2 weeks through Week 52)[c]	Weeks 2, 4, 6	Week 12	Week 26, 38	Week 52/ ET[d]	≥ 30 days after last dose
Visit window (days)	—	—	—	± 3	± 3	± 3	± 3	± 3	± 3
Subject/physician-reported outcomes[f]									
R-PAct Scale	X					X	X	X	
PROMIS instruments for physical function, fatigue, dyspnea, upper extremity	X					X	X	X	
EQ-5D-5L	X					X	X	X	
Physician's Global Impression of Change						X	X	X	
Subject's Global Impression of Change						X	X	X	
Laboratory assessments									
12-Lead ECG	X		X			X	X	X	
Serum chemistry, hematology	X		X		X	X	X	X	
Anti-rhGAA Abs (total, cross-reactive, and neutralizing)			X	X[g]	X	X	X	X[h]	X
IgE			X	See Section 12.3.13.					
Urine pregnancy test (FOCBPs only)[i]	X		X	X	X	X	X	X	
Urinary Hex4			X		X	X	X	X	
Urinalysis	X		X		X	X	X	X	

Table 10: Schedule of Assessments (Continued)

Study visit	Screening/Baseline (Day –30 to Day –1)[a]		Treatment						Follow-up
	Screening 1[b]	Screening 2	Day 1	Infusion visits (every 2 weeks through Week 52)[c]	Weeks 2, 4, 6	Week 12	Week 26, 38	Week 52/ ET[d]	≥ 30 days after last dose
Visit window (days)	—	—	—	± 3	± 3	± 3	± 3	± 3	± 3
PK blood sampling in ERT-experienced subjects (total GAA protein, AT2221)			X[j]					X[j]	
PK blood sampling in ERT-naive subjects (total GAA protein, AT2221)			X[k]					X[k]	
GAA genotyping	X								
Pulmonary function tests									
MIP, MEP, SNIP	X	X				X	X	X	
FVC, SVC (sitting, supine)	X	X				X	X	X	
Motor function assessments[l]									
TUG	X					X	X	X	
GSGC (10 m walk, 4-Stair climb, Gowers' maneuver, chair)	X					X	X	X	
6MWT	X[m]	X[m]				X	X	X	

Table 10: Schedule of Assessments (Continued)

Study visit	Screening/Baseline (Day –30 to Day –1)[a]		Treatment						Follow-up
	Screening 1[b]	Screening 2	Day 1	Infusion visits (every 2 weeks through Week 52)[c]	Weeks 2, 4, 6	Week 12	Week 26, 38	Week 52/ ET[d]	≥ 30 days after last dose
Visit window (days)	—	—	—	± 3	± 3	± 3	± 3	± 3	± 3
Muscle strength									
Manual muscle strength (MRC)	X					X	X	X	
Quantitative muscle strength (hand-held dynamometer)	X					X	X	X	
Study drug administration									
AT2221/placebo			Every 2 weeks 1 hour before infusion of ATB200/alglucosidase alfa						
ATB200/alglucosidase alfa			Every 2 weeks						

Abbreviations: 6MWT = 6-Minute Walk Test; Abs = antibodies; AE = adverse event; COVID-19 = SARS-CoV-2; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5 Levels-5 Dimensions Instrument; ERT = enzyme replacement therapy; FOCBPs = females of childbearing potential; FVC = forced vital capacity; GAA = human acid α-glucosidase; *GAA* = gene encoding human acid α-glucosidase; GSGC = Gait, climbing stairs, Gower's maneuver, arising from a Chair; Hex4 = hexose tetrasaccharide; IAR = infusion-associated reaction; IgE = immunoglobulin E; IRT = interactive response technology; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; MRC = Medical Research Council; PE = physical examination; 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; SNIP = sniff nasal inspiratory pressure; SVC = slow vital capacity; TUG = Timed Up and Go

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

[b] For ERT-experienced subjects, Screening Visits will be scheduled on approximately Day -30 and/or Day -15, to be 1 to 4 days before the subject's next alglucosidase alfa infusion. For ERT-naïve subjects, the Screening Visit may be scheduled any time before Day -10.

[c] During the conduct of the study, the 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 wherever possible for subjects who may be eligible.

[d] The 6MWT will be performed twice at the Week 52/Early Termination Visit, once on each day of the 2-day visit. Due to COVID-19, the Week 52 visit may be limited to a 1-day visit.

[e] Weight will be entered into IRT at quarterly visits for calculation of dose.

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

[g] Blood samples to test for presence of rhGAA Abs will be collected at the first 3 infusion visits after Day 1 (ie, approximately Days 14, 28, and 42).

[h] Subjects who are confirmed to have a positive result for anti-rhGAA Abs at 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 or until they begin treatment with another ERT or investigational therapy (ie, at 6 months and 12 months) after the last dose of study drug.

[i] If the urine pregnancy test has a positive result, study drug will not be administered and a confirmatory serum pregnancy test will be performed.

[j] On Day 1 and Week 52, sparse blood samples will be collected for PK analysis in ERT-experienced subjects at the time points specified in Section 12.3.15.1.

[k] Serial PK blood sampling in ERT-naïve subjects may be performed on Day 1 in coordination with the first infusion of study drug, or at the infusion visits for the second or third infusions of study drug. Sparse PK blood sampling in ERT-naïve subjects will be performed at Week 52 at the time points specified in Section 12.3.15.1.

[l] Consenting subjects at sites where videotaping is feasible will have motor function tests videotaped at the Screening Visit and the Week 52/Early Termination Visit, and the 6MWT may be videotaped at every visit.

[m] If a subject fails inclusion criterion #7 (see Section 9.2.1), then the 2 screening 6MWTs may be repeated within approximately 2 weeks if, in the opinion of the investigator, the subject is considered likely to meet this criterion on a second attempt. If either screening 6MWD is ≥ 90% of the predicted value for healthy adults, that subject will not be permitted to repeat the 6MWTs or rescreen at a later date and will be considered a screen failure.

12.2. Additional Details on Study Visits

12.2.1. Screening/Baseline

For ERT-experienced subjects, the Screening Visits will be scheduled on approximately Day -30 and/or Day -15, 1 to 4 days before the subject's next alglucosidase alfa infusion. For ERT-naïve subjects, the Screening Visit may be scheduled any time before Day -10. The Screening Visit will occur over 2 or more days to allow for repeated 6MWT and pulmonary function test assessments. The repeated tests for 6MWT or for pulmonary function (FVC, SVC, MIP, and MEP, and SNIP) should not be done on the same day. No other assessments should be performed on the day that the 6MWT and pulmonary function tests are repeated.

The informed consent form (ICF) must be signed before any study procedures are performed. Subjects will then be registered using IRT.

Subjects who meet eligibility criteria at screening will be randomly assigned to study drug using IRT at least 10 days prior to the first scheduled infusion on Day 1 to allow sufficient lead time for the first drug shipment. All subsequent shipments will be sent automatically through IRT. Refer and comply with detailed guidelines in the IRT manual. The subject does not have to be present for randomization.

Baseline efficacy assessments will be performed during screening. The average of the 2 screening 6MWDs will be the baseline 6MWD value. For FVC, the higher of the 2 screening values will be the baseline value, and baseline values for all other pulmonary function tests (SVC, MIP, MEP, and SNIP) will be those obtained at the same visit during which the higher value for FVC was obtained.

Subjects who fail to qualify for the study may be rescreened up to 2 times in consultation with the Amicus medical monitor, with the following exception regarding inclusion criterion #7 (see Section 9.2.1).

If a subject fails inclusion criterion #7, then the 2 screening 6MWTs may be repeated within approximately 2 weeks from the initial screening visit if, in the opinion of the investigator, the subject is considered likely to meet this criterion on a second attempt. If either screening 6MWD is ≥ 90% of the predicted value for healthy adults (calculated automatically using IRT [Enright, Sherill 1998]), that subject will not be permitted to repeat the 6MWTs or rescreen at a later date.

Subjects who sign an ICF but fail to qualify for the study will be considered screen failures. The reason for not being started on study drug will be entered into the electronic data capture system. The demographic information, informed consent, and Inclusion/Exclusion pages must be completed for subjects who are considered screen failures. Subjects who are rescreened after 1 month must re-sign the ICF and re-perform all screening assessments. For those subjects who had already undergone the confirmatory *GAA* genotyping as part of the previous screening procedures, no repeat *GAA* genotyping is required. Instead, the results of GAA genotyping can be used to determine subject's eligibility during the rescreening process.

12.2.2. Day 1

Day 1 is the first day of study drug administration. All study assessments will be performed predose and results from this visit will serve as baseline for safety assessments.

12.2.3. Infusion Visits and Home Infusion Visits

Infusion visits will be scheduled every 2 weeks for administration of study drug. 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 10, each site should follow their facility guidelines for performing infusions to monitor vital signs or other safety procedures that may be in place.

At visits 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 ATB200/AT2221 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 IRBs/IECs/REBs and regulatory authorities. Home infusions of ATB200 will be performed by a trained home infusion nurse provided by an Amicus designated home infusion service provider. 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:

- Resides in a country where it is permissible to administer alglucosidase alfa outside of a hospital setting
- Meets the following requirements regarding feasibility of the home site for ERT infusion:
  - Availability of sufficient space to prepare and administer ATB200 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 home infusion nurse for preparation/administration
  - Preparation of ATB200 lyophilized drug product for reconstitution or alglucosidase alfa by an unblinded, qualified individual while maintaining the blind of the subject
  - Infusion of large volume parenteral product
  - Disposal of waste and discarding of 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/home infusion nurse with respect to providing advice and support as needed by the home infusion nurse

Exclusion Criteria:

- 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.

During the conduct of the study, the 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 wherever possible for subjects who may be eligible. For subjects who may be eligible for home infusions, the approval to receive home infusions is contingent upon all the following conditions being satisfied:

- Approval by the Amicus clinical and safety group upon review of the subject's medical history and overall AEs reported during the study
- Investigator agreeing to provide additional oversight and support to home care nurses either in person or via telemedicine (eg. video chat) and to closely monitor safety for the first few infusions

These contingency measures are planned to be followed until resolution of COVID-19 related issues specific to the individual subject.

12.2.4. Post-baseline Assessment Visits

Assessments may occur over 2 or more days for each post-baseline visit, provided all assessments (with the exception of PK sampling) are performed before administration of study drug.

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.

During the conduct of the study, the COVID-19 pandemic emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. If infusions were missed close to the scheduled assessments on Week 26 or 38, 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.

12.2.5. Unscheduled Visits

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

12.2.6. Week 52/Early Termination (End of Study)

Subjects who complete 52 weeks of study drug administration, who discontinue study drug, or who are withdrawn from the study will be asked to return for the Week 52/Early Termination Visit.

The 6MWT will be performed twice at the Week 52/Early Termination Visit, once on each day of the 2-day visit. Due to COVID-19, the Week 52 visit may be limited to a 1-day visit. The average of these 2 values for 6MWD will be the Week 52 value for analysis purposes. If either of the two 6MWTs is invalid, as determined by the clinical evaluator, then that test will be repeated. The subject will not complete the study until the subject has 2 valid 6MWD values or has exceeded 4 attempts. During the conduct of the study, the COVID-19 pandemic emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. If infusions were missed close to the scheduled assessments on Week 52, 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.

12.2.7. Follow-up Period

A 30-day safety follow-up visit for monitoring of any AEs that were ongoing at end of study and collection of a blood sample for anti-rhGAA Abs will be scheduled only for subjects who do not continue treatment with ATB200/AT2221 in Study ATB200-07.

Subjects who are confirmed to have a positive result for anti-rhGAA Abs at 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 (ie, at 6 months and 12 months) after the last dose of study drug.

12.3. Description of Study Assessments

All assessments will occur according to the Schedule of Assessments displayed in Table 10.

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

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

Demographic data to be collected include date of birth/age, sex, and race.

12.3.2. Medical History

Comprehensive medical history, including a history of falls will be collected. Details are to be recorded for any past IARs (including intensity, start date, stop date, and outcome), medication use to manage symptoms (including dosage, frequency of administration, start date, and stop date), and any laboratory tests that were obtained as part of the assessment of IARs. An IAR is defined in Section 13.1.3.

Pompe disease history will include onset of symptoms, date of diagnosis, and start of ERT, if applicable.

12.3.3. Prior/Current Medications

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 and have taken for approximately the past 2 years. 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. Retrospective Data Collection

Historical results for 6MWT, MMT, and FVC, as available, obtained in the past 5 years will be recorded.

12.3.5. 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.

12.3.6. Body Weight and Height

Body weight will be entered into IRT each time it is measured at protocol-specified visits for measuring body weight. Calibration or standardization of the scale should be performed on a monthly basis or according to scale specifications.

Height (at screening only) will also be measured.

12.3.7. 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.

12.3.8. Adverse Events

Reporting of AEs begins after written informed consent is provided, including study-related events that occur as a direct result of a study procedure (eg, if a subject falls during a functional assessment) and IARs. 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 prior to enrollment in this study, it should be captured as medical history.

12.3.9. Patient-reported Outcomes

Patient-reported outcomes include R-PAct scale, the EQ-5D-5L, and PROMIS instruments for physical function, fatigue, dyspnea, and upper extremity, 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 labelled '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 Subject's Global Impression of Change is designed to record the subjects' impression of their functional status since starting study drug using a 7-point scale ranging from "very much worse" to "very much improved". The administrator of the Subject's Global Impression of Change 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.

12.3.10. Physician's Global Impression of Change

The Physician's Global Impression of Change 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 screening.

12.3.11. 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.

12.3.12. Clinical Laboratory Tests

12.3.12.1. Chemistry, Hematology, and Urinalysis

Clinical laboratory tests for safety monitoring include serum chemistry (Table 11), hematology (Table 12), and urinalysis (Table 13). 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 2). 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, ALT, and AST will be blinded to investigators and reviewed by an unblinded medical monitor.

Table 11: 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 12: 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 13: Urinalysis Parameters

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

12.3.12.2. 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).

12.3.13. Immunogenicity Assessments

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

Neutralizing Ab assays may include the following:

- inhibition of rhGAA-mediated hydrolysis of 4-MU-α-glucoside
- inhibition of rhGAA-mediated hydrolysis of glycogen
- inhibition of rhGAA binding to CI-MPR

In addition to the time points noted in Table 10, blood samples to test for the presence of rhGAA Abs will be collected at the first 3 infusion visits after Day 1 (ie, approximately Weeks 2, 4, and 6). Subjects who are confirmed to have a positive result for anti-rhGAA Abs at 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 or until they begin treatment with another ERT or investigational therapy (to be confirmed) (ie, at 6 months and 12 months) after the last dose of study drug.

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 for measurement, and the third immediately before the next administration of study drug. Because IgE results could potentially reveal a subject's treatment assignment, 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 Abs 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.

12.3.14. 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 European Union General Data Protection Regulation (GDPR) and any other local applicable regulations.

12.3.15. Blood Samples for Pharmacokinetic Analysis

12.3.15.1. Population Pharmacokinetic Analysis

At the visits outlined in Table 10, ERT-experienced subjects will have sparse blood samples collected just prior to initiation of ATB200/alglucosidase alfa infusion (time 0) and at 1, 4, 6, 12, and 24 hours after the start of ATB200 infusion for plasma total GAA protein signature peptide T09 and plasma AT2221 determinations. Collection of the 12-hour sample will be optional.

For sparse blood sampling, the predose (Time 0) PK blood sample should be collected within 30 minutes before the start of ATB200 infusion. The 1-, 4-, 6-, 12-, and 24-hour PK blood samples should be collected within a ± 30-minute window.

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.

12.3.15.2. Pharmacokinetic Subanalysis (ERT-naïve Subjects Only)

A PK subanalysis will be conducted in ERT-naïve subjects. Serial blood samples will be collected just prior to initiation of ATB200/alglucosidase alfa infusion (time 0) and at 1, 2, 3, 3.5, 4, 4.5, 6, 8, 10, and 24 hours after the start of ATB200 infusion for plasma total GAA protein signature peptide T09 and plasma AT2221 determinations. Collection of a 12-hour sample will be optional.

For serial blood sampling on Day 1, the predose (Time 0) PK blood sample should be collected within 30 minutes before the start of ATB200 infusion. The 1-, 2-, 6-, 8-, 10-, and 12-hour PK blood samples should be collected within a ± 15-minute window. The 3-, 3.5-, 4-, and 4.5-hour

PK blood samples should be collected within a ± 5-minute window. The Day 2, 24-hour PK blood sample should be collected within a ± 30-minute window.

At Week 52, ERT-naïve subjects will also have sparse blood samples taken at same the time points listed for ERT-experienced subjects (Section 12.3.15.1).

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.

12.3.16. 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.

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.

12.3.17. Gene for Encoding Acid α-Glucosidase Genotyping

Regardless of whether previous documentation is provided for a subject's diagnosis of Pompe disease for eligibility purposes (see Section 9.2.1), a blood sample will be collected at the Screening Visit to determine or confirm the subject's *GAA* genotype that may be associated with Pompe disease. Subjects who do not have historic documentation of diagnosis (either deficiency of GAA enzyme or *GAA* genotyping) at the time of screening will need to wait for the results of screening genotyping to be randomized. Subjects who have historic documentation can be randomized prior to receiving the results of screening genotyping. If confirmation of diagnosis is not obtained, then the subject must be withdrawn from the study. No DNA or gene sequencing not related to Pompe disease will be performed.

12.3.18. 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.

12.3.19. Motor Function Tests

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

The GSGC consists of a 10-meter walk for evaluation of gait, a 4-stair climb, Gower's 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 Gower's 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 during screening or 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.

Videotaping of motor function tests may be conducted at the Screening Visit and the Week 52/Early Termination Visit for consenting subjects at sites where this is feasible.

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

12.3.20. 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, they must use the same assistive device at all subsequent visits.

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. Videotaping of the 6MWT may be conducted at all visits for consenting subjects at sites where this is feasible. The assessment of validity by 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.

12.3.21. 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 subinvestigator and recorded as "clinically significant" or "not clinically significant" in subjects' source records (see Appendix 2). 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.

Any AE that begins after the first dose of study drug will be considered a treatment-emergent AE.

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

AEs 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 Screening Visit and/or, in the investigator's opinion, represent a clinically significant change in the subject's health during study participation
  - Screening medical evaluation findings (eg, ECG) that were not previously provided as medical history and that can be determined as starting prior to the Screening Visit are not considered AEs and will be recorded as medical history.

13.1.2. Serious Adverse Events

A serious adverse event (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 ICF was first signed, and
    - the planned procedure is documented in the subject's eCRF at the Screening 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 abovementioned 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 informed consent signing, until 30 days after the last dose of study drug.

13.1.3. Infusion-associated Reactions

An IAR is 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, immediate 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

Immediate-type 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-type reactions first manifest more than 24 hours postinfusion, usually 1 to 3 days postinfusion. The most common symptoms of late-type infusion reactions are pruritic skin eruptions, fever, malaise, and polyarthralgia.

Any symptom or sign occurring during or within 2 hours of completion of the infusion should be reported as an immediate-IAR and deemed drug-related AE, unless an alternative obvious explanation exists, eg, mechanical fall. Any symptom or sign occurring between 2 and 24 hours will be recorded as an IAR if it fits within the description of an IAR in the investigator's opinion. It would be reported as immediate-type IAR and deemed a drug-related AE.

Any symptom or sign occurring between 24 and 96 hours after completion of the infusion that, in the investigator's opinion, fits the clinical description of a symptom or sign associated with an IAR should be reported as a late-type IAR and deemed a drug-related AE.

A symptom or sign that occurs 24 hours or later and in the investigator's opinion is possibly, probably, or likely an IAR should be reported as such and deemed drug-related AE.

Note: The list of IAR symptoms provided in Table 14 is not comprehensive. It is meant to serve as a guideline to the investigators to report and manage IAR as AE. Table 14 also provides a guideline for management of IARs and anaphylaxis (see also Appendix 1). It is at the investigator's discretion to follow the guidelines or implement treatment protocol that their center is accustomed to following.

In the event that a subject experiences an IAR, the subject should be premedicated for subsequent infusions with antihistamines, steroids, and/or acetaminophen. The premedications should be continued for all remaining infusions.

Table 14: Guidelines for Management of Immediate 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/paracetamol and/or IV antihistamine. Prepare emergency equipment for any subsequent study drug escalation. Subject must be observed at site or medical facility for 2-4 hours after resolution of the symptoms. Record all details of times, concomitant medications and nondrug therapies, and infusion rates. Draw IgE and total GAA sample 6 to 8 and 24 hours after the start of the infusion reaction (2 samples). 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

Table 14: Guidelines for Management of Immediate Infusion-associated Reactions (Continued)

Severity	Symptoms (such as, but not restricted to)	Management Guidelines
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 PI/designee. Continue management as directed by the PI/designee. If deemed appropriate by PI/investigator, resume study drug infusion at reduced rate and prepare emergency equipment. If deemed appropriate by PI/investigator, 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. Draw IgE and total GAA sample 6 to 8 and 24 hours after the start of the infusion reaction and immediately before the next administration of study drug (3 samples).

Table 14: Guidelines for Management of Immediate 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 PI/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 PI/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 PI/investigator, study drug infusion can be re-initiated 7 to 14 days with premedications and at the 4-hour duration. Draw IgE and total GAA sample 6 to 8 and 24 hours after the start of the infusion reaction and immediately before the next administration of study drug (3 samples). Record all details. Report AE, if applicable.

Abbreviations: GAA = human acid α-glucosidase; IgE = immunoglobulin E; IM = intramuscular; IV = intravenous; NS = normal saline; PI = Principal Investigator; SAE = serious adverse event; WFI = water for injection
Sources: Vogel 2010; Sampson 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:

- Grade 1/Mild: Awareness of sign, symptom or event, but the AE is easily tolerated and does not interfere with daily activity, intervention not indicated.
- Grade 2/Moderate: Enough discomfort to cause interference with usual activities and may warrant intervention, but the subject is still able to function.
- Grade 3/Severe: Medically significant but not immediately life-threatening, unable to do usual activities or significantly affects clinical status and requires medical intervention.
- Grade 4/Life-threatening: Life-threatening consequences; urgent intervention indicated
- Grade 5/Fatal: Death related to AE

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.

Adverse events will be recorded in the eCRF and subject's source record beginning from the time written consent is provided 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 at the Screening Visit should only be reported as AEs if they worsen (ie, increase in severity) from the Screening Visit.

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' representative, 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 (+1-866-693-2307) or sent to the designated email address (blindedsafetyreporting@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 medical monitor 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/Under Dose

Any event associated with, or observed in conjunction with, a product overdose/under dose (whether accidental or intentional) is considered by Amicus to be an AE and must be reported as such. If a subject experiences an overdose (defined as ≥ 20% higher than the assigned dose of study drug for that period in the protocol) or an under dose (defined as ≥ 20% lower than the

assigned dose of the study drug for that period in the protocol) during the course of the study (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/under dose. Follow-up information must be forwarded on the outcome as applicable. If an SAE occurs in conjunction with the overdose/under dose, 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 must be notified within 5 working days of the investigator or study personnel first becoming 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.

During the conduct of the study, the COVID-19 pandemic emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. Study subjects who missed infusions close to their scheduled assessments on Weeks 26, 38, or 52 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. If a subject misses 5 consecutive infusions at any time during the study, the subject must withdraw from the study. Depending on the circumstances of the missed infusions, the subject may still be eligible to participate in the ATB200-07 study. 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 Voice/Web Response System and EDC. A reason for the missed visit should be entered into the EDC as COVID-19 related. The relevant IRBs, IECs, and REBs should be notified of any deviations from the protocol. If 5 or more consecutive infusions are missed due to any circumstance, including COVID-19, the subject must be discontinued from this protocol. Any subjects discontinued due to COVID-19 may be eligible for ATB200-07 with Amicus approval.

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's treatment assignment will be unblinded. 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.

13.5. Data Monitoring Committee

A DMC will be constituted prior to first subject first visit (date of consent). The DMC will be responsible for reviewing safety data and will provide input on trial stopping or modifications. A meeting will be held with the DMC prior to first subject first visit to describe the board's roles and responsibilities, discuss potential data format and process, and agree upon a charter. A description of the DMC membership and meeting frequency will be outlined in the DMC charter. Additional safety analyses may be performed at the discretion of the DMC.

The DMC may make any of the following recommendations:

- no safety issues, ethical to continue the study as planned
- serious safety concerns precluding further study treatment for individual subjects
- recommendation to continue the study with amendment to the protocol
- recommendation for trial stopping or modification based on safety

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 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

15.1. Endpoints

15.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 52 in 6MWD.

15.1.2. Secondary Efficacy Endpoints

Key secondary efficacy endpoints are as follows:

- change from baseline to Week 52 in sitting FVC (% predicted)
- change from baseline to Week 52 in the manual muscle test score for the lower extremities
- change from baseline to Week 52 in the total score for the PROMIS – physical function
- change from baseline to Week 52 in the total score for the PROMIS – fatigue
- change from baseline to Week 52 in GSGC total score
- change from baseline to Week 26 in 6MWD

Other secondary efficacy endpoints are as follows:

- change from baseline to Week 52 in the following variables related to motor function:
  - 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 Gower's maneuver of the GSGC test
  - time to arise from a chair as part of the GSGC test
  - time to complete the TUG test
- change from baseline to Week 52 in the following variables related to muscle strength:
  - manual muscle test score for the upper extremities
  - manual muscle test total score
  - quantitative muscle test value (kg) for the upper extremities
  - quantitative muscle test value (kg) for the lower extremities
  - quantitative muscle test total value (kg)
- change from baseline to Week 52 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 at Week 52, as measured by the Subject's Global Impression of Change:
  - overall physical wellbeing
  - 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) at Week 52, as measured by the Physician's Global Impression of Change
- change from baseline to Week 52 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 to Week 52 in serum CK level
- change from baseline to Week 52 in urinary Hex4 level

15.1.4. Pharmacokinetic Endpoints

15.1.4.1. Population Pharmacokinetic Analysis (ERT-Experienced Subjects)

After sparse sampling in ERT-experienced subjects (Day 1 and Week 52) and ERT-naïve subjects (Week 52 only), PK endpoints from a population PK analysis of total GAA protein and AT2221 concentrations will be provided in a separate modeling and simulation plan. Plasma GAA activity levels may be evaluated during the terminal phase only.

15.1.4.2. Pharmacokinetic Subanalysis (ERT-naïve Subjects)

After serial blood sampling in ERT-naïve subjects, PK parameters for plasma total GAA protein concentration will be calculated as follows:

- C_{max}: maximum observed concentration obtained directly from the concentration profile
- t_{max}: time of the first occurrence of the maximum observed concentration obtained directly from the concentration profile
- K_{el} or λ_z: the apparent terminal phase elimination rate constant will be estimated by linear regression of logarithmically transformed concentration versus time data; only those data points which are judged to describe the terminal log-linear decline will be used in the regression
- AUC_{0-t}: area under the plasma drug concentration-time curve from 0 time (predose) to the time of last quantifiable concentration (t), calculated with the linear up/log-down trapezoidal method
- $AUC_{0-\infty}$: the area under the plasma drug concentration-time curve from 0 time (predose) extrapolated to infinite time will be calculated as follows:

  $$AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$$

  where C_t is the last observed quantifiable concentration
- $AUC_{tmax-24h}$: partial area under the plasma drug concentration-time curve from the time of maximum concentration (t_{max}) to 24 hours post initiation of ATB200 infusion
- $t_{½\alpha}$: the alpha-phase terminal half-life, calculated as $\ln(2)/\lambda_z$ from the first 3 or more quantifiable concentrations after C_{max}; estimated for plasma total GAA protein concentration only
- CL_T: total plasma clearance after IV administration, calculated as dose/$AUC_{0-\infty}$

Plasma GAA activity levels may be evaluated during the terminal phase only.

Plasma AT2221 PK parameters will be calculated as follows:

- C_{max}: maximum observed concentration obtained directly from the concentration profile
- t_{max}: time of the first occurrence of the maximum observed concentration obtained directly from the concentration profile
- K_{el} or λ_z: the apparent terminal phase elimination rate constant will be estimated by linear regression of logarithmically transformed concentration versus time data; only those data points which are judged to describe the terminal log-linear decline will be used in the regression
- AUC_{0-t}: area under the plasma drug concentration-time curve from 0 time (predose) to the time of last quantifiable concentration (t), calculated with the linear up/log-down trapezoidal method

- $AUC_{0-\infty}$: the area under the plasma drug concentration-time curve from 0 time (predose) extrapolated to infinite time will be calculated as follows:

  $$AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$$

  where C_t is the last observed quantifiable concentration
- $t_{½\beta}$: the beta-phase terminal elimination half-life, calculated as natural log $\ln(2)/\lambda_z$ from the last 3 or more quantifiable concentrations from the beta phase of elimination
- CL_T/F: total plasma clearance from an oral administration, calculated as dose/$AUC_{0-\infty}$
- V_z/F: volume of distribution based on the terminal elimination phase from an oral administration, calculated as dose/($AUC_{0-\infty} \bullet \lambda_z$)

15.1.5. Safety Endpoints

The safety profile of ATB200/AT2221 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. The impact of immunogenicity to ATB200 and alglucosidase alfa on safety and efficacy will also be described.

15.2. Sample Size Considerations

A 2-group t-test with a 2-sided significance level of 0.05 and a 2:1 randomization scheme (66 subjects in the ATB200/AT2221 group and 33 subjects in the alglucosidase alfa/placebo group, for a total sample size of 99 subjects) will have approximately 90% power to detect a standardized effect size of 0.7 between the 2 groups in a superiority test. This calculation was performed using NQuery 8©®. Assuming a 10% dropout rate, the sample size will be approximately 110 subjects.

Further details of the sample size calculation will be provided in a separate statistical analysis plan (SAP).

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 analysis plan will be provided in the SAP.

15.3.1. Analysis Populations

Safety Population: The safety population is defined as all subjects who receive at least 1 dose of study drug (ATB200/AT2221 or alglucosidase alfa/placebo). This population will be used in the assessment and reporting of safety data, and subjects will be analyzed according to the actual treatment received.

Intent-to-Treat Population: The intent-to-treat (ITT) population consists of all randomized subjects (regardless of whether they took a dose of study drug). This population will be analyzed according to the planned treatment groups. The ITT population is the primary population for efficacy analyses.

Modified Intent-to-Treat Population: The modified intent-to-treat (mITT) population consists of all randomized subjects who took at least 1 dose of study drug and have both a 6MWD baseline (ie, average of 2 screening 6MWD values) and at least one post-baseline 6MWD. This population will be analyzed according to the planned treatment groups. The mITT population will be used for supportive/sensitivity analyses of the primary and key secondary efficacy endpoints, as well as for baseline and demographic summaries.

Per-Protocol Population: The per-protocol population is a subset of the ITT population that consists of subjects who have no major protocol or site deviations that impact the analyses of the primary endpoints or the integrity of the study, and took only the study drug to which they were randomized. This population will be analyzed according to the planned treatment groups. The per-protocol population may be used in supportive/sensitivity analyses of the primary and/or key secondary endpoints.

Pharmacokinetic population(s) will be described in a separate modeling and simulation plan.

15.3.2. Statistical Methods

15.3.2.1. Randomization

The following 2 factors have been identified as design stratification variables:

1. baseline 6MWD (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters)
2. ERT status (ERT-experienced, ERT-naïve)

These 2 factors form 6 factorial combinations (ie, levels, strata).

A centralized block randomization procedure will be used to balance the above factors, 1) to reduce bias and increase the precision of statistical inference, and 2) to allow various planned and unplanned subset analyses. The block randomization scheme will be performed for each of the 6 strata. The randomization ratio is 2:1 ATB200/AT2221 to alglucosidase alfa/placebo, fixed.

15.3.2.2. Missing Data Handling

Missing data may be imputed using methods of multivariate imputation by chained equations. Both missing-at-random and missing-not-at-random patterns will be considered and their impacts on robustness of the primary and/or key secondary analysis results will be assessed with a tipping point analysis. Further details of the approach will be provided in the full SAP.

Similarly, missing attributes for AEs will be imputed with the worst possible outcome, for summary purposes.

15.3.2.3. Efficacy Analyses

For functional assessments, screening results will serve as the baseline values. For 6MWD, the 2 values for 6MWD obtained at screening will be averaged to get the baseline value. For FVC, the higher of the 2 screening values will be the baseline value, and baseline values for all other pulmonary function tests (SVC, MIP, MEP, and SNIP) will be those obtained at the same visit during which the higher value for FVC was obtained.

15.3.2.3.1. Analyses of the 6MWT

The primary efficacy endpoint (ie, change from baseline to Week 52 in 6MWD) will be analyzed using a parametric analysis of covariance (ANCOVA) model to compare between the new treatment and the control. This model would typically adjust for baseline 6MWD (as a continuous covariate), and the 2 factors used to stratify randomization: ERT status (ERT-naïve vs. ERT-experienced) and baseline 6MWD (75 to < 150 meters, 150 to < 400 meters, ≥ 400 meters). However, the baseline 6MWD cannot be used in the model twice (both as a continuous and a categorical variable) due to the expected high point-biserial correlation between them. Thus, the 6MWD continuous variable will remain in the model but the categorical 6MWD will be removed. The ANCOVA model then has terms for treatment, baseline 6MWD (continuous), and ERT status (categorical).

Additionally, potential treatment-by-covariate interactions (ie, TREATMENT-by-ERT-STATUS and TREATMENT-by-BASELINE 6MWD continuous) will be examined. If an interaction term is statistically significant (eg, $p < 0.10$, 2-sided), and there is logical biological interpretation, then the interaction term can potentially be added in the final ANCOVA model that will be used for the primary endpoint analysis. The data would then be analyzed based on the ANCOVA model, and all the relevant estimates (eg, LS means for each treatment group, LS means difference, 95% confidence intervals [CIs] for the LS mean difference, and p-value for comparing between the 2 treatment groups) would be provided.

To support the interpretation of clinical benefit, a composite subject-level response will be defined based on the totality of the treatment outcome data. Subjects will be classified by an ordinal response variable consisting of significant improvement, moderate improvement, or minor/no improvement based on treatment outcomes.

This defines a hierarchical ordinal categorical response variable, for which a continuation logit model will be used to perform separate logistical regression analyses adjusting for baseline factors like duration of prior alglucosidase alfa, gender, and mutation type. The results of these separate logistic regression analysis are then pooled to test the overall null hypothesis that treatment with ATB200/AT2221 is more effective than alglucosidase alfa with respect to either the positive response (ie, significant improvement) or the negative response (ie, minor/no improvement).

Details of the methodology with regards to the definition of improvement criteria, intergroup comparisons, test against the overall null hypothesis, and use of assistive devices while performing the 6MWT will be provided in the SAP.

15.3.2.3.2. Key Secondary Endpoint Analyses

Key secondary endpoints will be analyzed according to the hierarchical order as specified in Section 15.1.2, using stepwise closed testing procedure to control the type I error rate. Key secondary and other secondary endpoints will be analyzed separately with a similar method used for the primary endpoint analysis.

15.3.2.3.3. Other Secondary Endpoint Analyses

15.3.2.3.3.1. Functional Assessments

Endpoints for motor function tests, muscle strength tests, and pulmonary function tests will be summarized by treatment group and visit. In addition, the change from baseline to Week 52 for each endpoint measure will be analyzed and compared between the 2 treatment groups using similar analysis as for the primary endpoint.

15.3.2.3.3.2. Patient-Reported Outcomes and Physician's Global Impression of Change

The mITT population 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 (descriptive scores), and PROMIS instruments will be summarized by treatment group and visit. The change from baseline to Week 52 in the total scores will be analyzed using an ANCOVA to compare between the 2 treatment groups.

Each item of the Subject Global Impression of Change will be summarized by treatment group and visit. Additionally, the response scale for each item at Week 52 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 Physician's Global Impression of Change will be summarized by treatment group and visit.

15.3.2.3.3.3. Biomarker Analyses

The mITT population will be used for biomarker analyses involving CK or urinary Hex4. Specific analyses include but not limited to intergroup comparisons of ATB200/AT2221 to alglucosidase alfa/placebo, description of relationships between biomarkers, and mediation analysis to establish surrogacy of biomarkers for clinical or patient-reported outcome endpoints with intergroup comparisons.

15.3.2.4. Pharmacokinetic Analyses

15.3.2.4.1. Population Pharmacokinetic Analysis (ERT-experienced Subjects)

Population PK analyses for repeated-measures endpoints will be conducted with NONMEM software, Version 7.3 or higher (ICON Development Solutions, Hanover, MD). Data from the current study will be added to the existing data set for Study ABT200-02, and the previously developed population PK models will be used as the starting point for updated analyses. The models will be refined as necessary to describe ATB200 and AT2221 disposition given the updated data set (eg, testing alternative structural models, random effects structure, covariate models).

The effects of demographic and clinical factors on variability of ATB200 and AT2221 pharmacokinetics will be investigated throughout the modeling process. Covariate effects to be investigated include, but are not limited to, body size, ERT status (ERT-experienced, ERT-naïve), gender, age, and the presence of antidrug Abs.

Exposure-response relationships will also be explored. Initially, plots of PD endpoints versus ATB200 exposures will be constructed to investigate potential exposure-response correlations. Any potential relationships will be explored further using longitudinal and/or landmark exposure-response analyses to characterize the effects of ATB200 exposure on PD endpoints. Additional details will be provided in a separate modeling and simulation plan to be finalized prior to population PK and PK/PD modeling, and a separate report will be provided to summarize all modeling analyses.

15.3.2.4.2. Noncompartmental Pharmacokinetic Analysis (ERT-naïve Subjects)

Plasma PK parameters will be computed by noncompartmental analysis with Phoenix® WinNonlin® version 8.0 or higher. For the purpose of calculating PK parameters, values below the limit of quantification (BLQ) will be set to 0 when a BLQ occurs before the first measurable concentration. If a BLQ occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLQ will be treated as "missing". If a BLQ value occurs at the end of the blood sampling interval (after the last quantifiable concentration) it will also be treated as "missing". For descriptive statistics of plasma concentration data, all BLQs will be set to 0 and included in designated statistical calculations. Pharmacokinetic analyses performed on preliminary quality checked concentration data will use nominal time points; PK analyses performed on final concentration data will use actual time points. Pharmacokinetic endpoints are described in Section 15.1.4.

15.3.2.5. Safety Analyses

Safety analyses will be based the safety population. Safety data will be summarized using counts and percentages for categorical data and descriptive statistics (mean, standard deviation, median, minimum, maximum) for continuous data.

Exposure to study drug will be summarized using descriptive statistics.

Summaries of AEs will include an overall summary of incidence and summaries by relationship and by severity. Summaries and/or listings will be provided for deaths, SAEs, and AEs leading to discontinuation. Infusion-associated reactions in the ATB200/AT2221 arm will be compared in frequency to the alglucosidase alfa/placebo group in this study. 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).

15.3.2.6. Immunogenicity Analyses

The effect of immunogenicity results on efficacy, pharmacokinetics, and safety will be explored.

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 Conference on 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.

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 www.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 International Council on Harmonisation/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 IRBs/IECs/REBs according to timelines specified by individual IRB/IEC/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, European Union [EU] Directive 95/46/EC, EU Directive 94/45/EC, and the General Data Protection Regulation (GDPR) (EU) 2016/679]). The subject will be informed that representatives of Amicus, the IRB/IEC/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. 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.

16.3.4. 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.

16.3.5. 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.

17. REFERENCES

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APPENDIX 1. 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 et al 2006

APPENDIX 2. 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 to 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

Abbreviation: QTcB = QT interval for corrected heart rate

[a] Reference value: baseline or initial visit value, as appropriate.