Official Title:	Final Statistical Analysis Plan for CSR: A Phase 3 Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of Intravenous ATB200 Co-Administered with Oral AT2221 in Adult Subjects with Late-Onset Pompe Disease
NCT Number:	NCT04138277
Document Date:	30 July 2025

FINAL STATISTICAL ANALYSIS PLAN FOR CSR

VERSION: Final v1.0

DATE OF PLAN: 30 July 2025

STUDY TITLE

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

PROTOCOL NUMBER: ATB200-07

Amendment 3: 10 December 2024

COMPOUNDS:

ATB200 (cipaglucosidase alfa) and AT2221 (miglustat)

INDICATION: Pompe Disease

SPONSOR

Amicus Therapeutics, Inc.
47 Hulfish Street
Princeton, NJ 08542, USA
Phone: +1 609-662-2000

SIGNATURE PAGE

This document has been prepared and reviewed by:

[redacted]

[redacted]
Director, Biostatistics
Amicus Therapeutics

Signature Date

This document has been reviewed and accepted by:

[redacted]

[redacted]
[redacted] Biostatistics & Data Management
Amicus Therapeutics

Signature Date

[redacted]

[redacted]
[redacted] Global Drug Safety
On behalf of [redacted]
Amicus Therapeutics

Signature Date

[redacted]
[redacted] Clinical Research
Amicus Therapeutics

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Table 1: List of Abbreviations

Abbreviation	Term
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	adverse event
CI	confidence interval
CK	creatine kinase
CSR	clinical study report
ECG	electrocardiogram
ERT	enzyme replacement therapy
FAS	full analysis set
FVC	forced vital capacity
GSGC	Gait, Stairs, Gowers' maneuver, and Chair test
Hex4	hexose tetrasaccharide
IAR	infusion-associated reaction
MMT	manual muscle test
OLE	open-label extension
OLE-ES	open-label extension enrolled subjects
PD	pharmacodynamic(s)
PDLC	pre-defined limits of change
PROMIS	Patient-reported Outcomes Measurement Information System
PT	preferred term
QMT	quantitative muscle test
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned data analyses and the outputs to be included in the final clinical study report (CSR) for the standalone open-label extension (OLE) Study ATB200-07. The SAP is based on Amendment 3 of the Protocol for Study ATB200-07 dated 10 December 2024.

This final SAP describes the analyses that will be performed for the final CSR for the standalone Study ATB200-07 based on a data cutoff date of 31 December 2024. All data collected through the cutoff date will be reported as summary tables and/or listings.

This SAP has been developed in accordance with Good Clinical Practice (GCP), International Council on Harmonisation (ICH) guideline E9 (Statistical Principles for Clinical Trials), and Amicus standard operating procedure (SOP) ATCRA-SOP-AT-008.

The analyses and statistical methods specified in the final SAP supersede those described in the study protocol.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to assess the long-term safety and tolerability of ATB200/AT2221 combination treatment.

2.2. Secondary Objectives

The secondary objectives of this study are as follows:

- to assess the long-term efficacy of ATB200/AT2221 combination on ambulatory function, as measured by the 6-minute walk test (6MWT)
- to assess the long-term efficacy of ATB200/AT2221 combination on pulmonary function, as measured by sitting forced vital capacity (FVC) (% predicted)
- to assess the long-term efficacy of ATB200/AT2221 combination on muscle strength
- to assess the long-term efficacy of ATB200/AT2221 combination on health-related patient-reported outcomes
- to assess the long-term efficacy of ATB200/AT2221 combination on motor function
- to assess the long-term efficacy of ATB200/AT2221 combination on overall clinical impression, as assessed by both physician and subject
- to assess the long-term efficacy of ATB200/AT2221 combination on measures of pulmonary function other than FVC (% predicted)
- to assess the long-term effect of ATB200/AT2221 combination on biomarkers of muscle injury and disease substrate
- to assess the immunogenicity of ATB200/AT2221 combination
- to characterize the pharmacokinetics of ATB200 and AT2221 using plasma total GAA protein level by signature peptide and plasma AT2221 concentration assays in subjects at sites in Japan only

2.3. Study Endpoints

Safety assessments are the primary focus for the final CSR.

2.3.1. Safety Endpoints

Safety endpoints to be evaluated include exposure, incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) including infusion-associated reactions (IARs), AEs leading to discontinuation from the study, TEAEs leading to discontinuation of study drug, TEAEs leading to death, frequency and severity of immediate and late IARs, and abnormalities noted in other safety assessments (eg, clinical laboratory tests, electrocardiograms (ECGs), vital signs).

2.3.2. Efficacy Endpoints

The protocol does not designate any particular endpoint as the 'primary' for the OLE study. For purposes of the CSR, efficacy endpoints will be split into two groups, as (1) main efficacy endpoints and (2) supportive efficacy endpoints.

2.3.2.1. Main Efficacy Endpoints

- Change from baseline in 6-minute walk distance (6MWD) which is the distance walked (in meters) in the 6MWT
- Change from baseline in sitting FVC (% predicted)

  Note: The predicted FVC values will be age-adjusted based on the subject's age at the assessment visit.
- Change from baseline in the manual muscle test (MMT) score for the lower extremities
- Change from baseline in the total score for the Patient-reported Outcomes Measurement Information System (PROMIS®) – Physical Function
- Change from baseline in the total score for the PROMIS – Fatigue
- Change from baseline in the total score for the Gait, Stairs, Gowers' maneuver, and Chair test (GSGC)

2.3.2.2. Supportive Efficacy Endpoints

Supportive efficacy endpoints include:

- Change from baseline in % predicted 6MWD (PP6MWD), where the predicted values are calculated using Enright and Sherrill 1998 reference equations
- Change from baseline 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 Gowers' maneuver of the GSGC test
  - time to rise from a chair as part of the GSGC test
  - time to complete the Timed Up and Go (TUG) test
- Change from baseline in the following variables related to muscle strength:
  - MMT score for the upper extremities
  - MMT total score (upper and lower extremities combined)
  - Proximal muscles MMT score
  - Quantitative muscle test (QMT) value (kg) for the upper extremities
  - QMT value (kg) for the lower extremities

  - QMT total value (kg) (upper and lower extremities combined)

- Change from baseline in the following variables from patient-reported outcome (PRO) measures:
  - Total score for the PROMIS – Dyspnea
  - Total score for the PROMIS – Upper extremities
  - Total score for the Rasch-built Pompe-specific Activity (R-PAct) Scale
- European Quality of Life (EuroQol)-5 Dimensions 5 Response Levels (EQ-5D-5L) health status which includes the categorical dimensional levels and the quantitative Visual Analogue Scale (EQ-VAS) score. That is:
  - Absolute value and categorical change in the levels of each EQ-5D-5L dimensional measure
  - Change from baseline in the EQ-VAS score
- Actual value of the subject's functional status (improving, stable, or declining) pertaining to the effects of study drug in the following areas of life, as measured by the Subject's Global Impression of Change (SGIC):
  - 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), as measured by the Physician's Global Impression of Change (PGIC)
- Change from baseline in the following measures of pulmonary function, as follows:
  - Sitting slow vital capacity (SVC) (% predicted)
  - Maximum vital capacity (VC) (% predicted), where maximum VC is defined as the larger of the sitting FVC and the sitting SVC
  - Maximal inspiratory pressure (MIP) (% predicted)
  - Maximal expiratory pressure (MEP) (% predicted)
  - Sniff nasal inspiratory pressure (SNIP) (% predicted)

2.3.3. Pharmacodynamic Endpoints

Pharmacodynamic (PD) variables are:

- Change from baseline in serum creatine kinase (CK) level
- Change from baseline in urinary hexose tetrasaccharide (Hex4) level

2.3.4. Immunogenicity Endpoints

Immunogenicity (IMG) variables are:

- Total anti-drug antibodies (ADAs), including titers
- Neutralizing antibodies (NAbs):
  - Inhibition of recombinant human acid α-glucosidase (rhGAA) binding to cation-independent mannose-6-phosphate receptor (CI-MPR)
  - Inhibition of rhGAA-mediated hydrolysis of 4-MU-glucoside
  - Inhibition of rhGAA-mediated hydrolysis of glycogen
- Anti-rhGAA cross-reactive with alglucosidase alfa
- Anti-rhGAA-specific Immunoglobulin E (IgE)

3. STUDY DESIGN

3.1. Summary of Study Design

This is a multicenter, international, OLE study of ATB200/AT2221 (heretofore referred to as cipaglucosidase alfa/miglustat) in adult subjects with late-onset Pompe disease (LOPD) who completed the randomized double-blind Study ATB200-03. Study ATB200-07 consists of a treatment period that lasts until 31 December 2024 or until study termination by the sponsor, and it includes a 30-day safety follow-up period for the end of study (EOS) or early termination (ET) assessments.

All subjects in Study ATB200-07 are to be treated with cipaglucosidase alfa/miglustat every 2 weeks. Subjects who previously received alglucosidase alfa/placebo in Study ATB200-03 were switched to cipaglucosidase alfa/miglustat in Study ATB200-07, and subjects who received cipaglucosidase alfa/miglustat in Study ATB200-03 continued on cipaglucosidase alfa/miglustat in Study ATB200-07. The first infusion visit in this study was to be scheduled approximately 2 weeks after the last visit in Study ATB200-03 in an effort to ensure continued administration of study drug on the same schedule with no gap between studies. The end of study assessment in Study ATB200-03 will be considered the baseline assessment in Study ATB200-07, as described in Section 4.4.2.

3.2. Definition of Study Drugs

The dose of miglustat is 260 mg (4 × 65-mg oral capsules) for subjects weighing ≥ 50 kg, or 195 mg (3 × 65-mg oral capsules) for subjects weighing ≥ 40 kg to < 50 kg. Miglustat is administered orally and is followed approximately 1 hour later by IV infusion of 20 mg/kg cipaglucosidase alfa (administered over a 4-hour period). Subjects are required to fast at least 2 hours before and 2 hours after administration of miglustat.

3.3. Sample Size Considerations

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

3.4. Randomization and Stratification

This is an open-label extension study, and it is uncontrolled. There is no randomization or stratification.

3.5. Clinical Assessments

Study assessments were to be performed in accordance with the Schedule of Assessments of the ATB200-07 study protocol.

Safety assessments including clinical lab tests (chemistry, hematology, urinalysis), brief physical examination (BPE), and vital signs were to be performed at Baseline Visit (for subjects who did not complete Week 52 in Study ATB200-03), and at Weeks 2, 4, 6, 12, 26, and then every 26 weeks thereafter. Assessments of Hex4 were also to be performed at Baseline Visit (for subjects who did not complete Week 52 in Study ATB200-03), and at Weeks 2, 4, 6, 12, 26, and

then every 26 weeks thereafter. Assessments of efficacy and ECG were to be performed at Baseline Visit (for subjects who did not complete Week 52 in Study ATB200-03), and at Weeks 12, 26, and then every 26 weeks thereafter.

3.6. Impact of COVID-19 Pandemic

During the conduct of the study, the pandemic caused by the SARS-CoV-2 virus (COVID-19) emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. This could result in some subjects experiencing delayed visits, missed infusions, missed assessments, and early withdrawals from the study.

Missed assessment and infusion visits due to COVID-19 related reasons were to be recorded as protocol deviations in the electronic data capture (EDC) and the reasons attributed to COVID-19. Infusions that were missed near the scheduled assessment visits (particularly at Weeks 12, 26, and every 26 weeks after Week 26) were to be examined on a case-by-case basis to determine whether catch-up infusions were needed, and if so, how many catch-up infusions were needed, prior to rescheduling the visits to perform make-up assessments.

3.7. Interim Analysis

This is an OLE study, and the protocol allowed for an informal interim analysis to be conducted for purposes of writing an interim clinical study report.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

4.1. Analysis Populations

4.1.1. OLE Enrolled Subjects

The open-label extension enrolled subjects (OLE-ES) includes all subjects who satisfied the eligibility requirements (based on the inclusion and exclusion criteria) and entered the OLE Study ATB200-07.

The OLE-ES population will be used for reporting protocol deviations and for subject accounting purposes.

4.1.2. OLE Safety Population

The open-label extension safety population (OLE-SAF) includes all subjects who took at least one dose of cipaglucosidase alfa/miglustat combination treatment in Study ATB200-07.

The OLE-SAF population will be used for reporting all safety data, demographic and baseline characteristics, disease characteristics, medical history, medications and nondrug therapies, exposure, and compliance.

4.1.3. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who entered the OLE Study ATB200-07 who had both a valid baseline and at least one post-baseline assessment, for at least 1 of the main efficacy endpoints (6MWD, FVC, MMT-lower extremities, PROMIS-Physical Function, PROMIS-Fatigue, and GSGC).

The FAS population will be used for reporting all efficacy and PD data.

4.2. Presentation by Treatment Group

Presentation of treatment group in the analysis outputs for the CSR will be as follows:

1. Cipaglucosidase alfa/miglustat–Cipaglucosidase alfa/miglustat: subjects treated with cipaglucosidase alfa/miglustat in Study ATB200-03 and continued cipaglucosidase alfa/miglustat in Study ATB200-07.
2. Alglucosidase alfa/placebo–Cipaglucosidase alfa/miglustat: subjects treated with alglucosidase alfa/placebo in Study ATB200-03 and switched to cipaglucosidase alfa/miglustat in Study ATB200-07.

Where appropriate, these 2 treatment groups will be presented together with the overall treatment group (which combines [1] and [2]) so that all 3 treatment groups are displayed in the results presentation.

4.3. Subgroups

4.3.1. Planned Subgroups of Interest

At the time of entering Study ATB200-07, all subjects had at least one year of treatment with enzyme replacement therapy (ERT). Nonetheless, the previous ERT status of the subjects prior to entering the pivotal Study ATB200-03 remains a subgroup of interest in the analysis of the standalone data from Study ATB200-07.

The planned subgroups of interest Study ATB200-07 are the prior ERT status groups, which are defined as follows:

- ERT-experienced: subjects in the OLE study who had been previously treated with ERT prior to their participation in the randomized double-blind Study ATB200-03
- Previously ERT-naïve: subjects in the OLE study who had not been previously treated with ERT prior to their participation in the randomized double-blind Study ATB200-03

In particular, the 6 main efficacy endpoints specified in Section 2.3.2.1 as well as the % predicted 6MWD among others, will be presented by the prior ERT status subgroups.

4.3.2. Other Subsets of Subjects

Additionally, the following subsets of subjects will be used for the analyses indicated below, unless otherwise stated. The baseline indicated below refers to the baseline result in Study ATB200-07.

- Baseline % predicted FVC categories: $< 85\%$, $\geq 85\%$.

  This will be used to summarize % predicted FVC overall and by ERT status.

4.4. Data Handling

4.4.1. Study Day

For the purposes of analysis, the date of first dose of study drug (First Dose Date) in ATB200-07 is designated as Day 1 and it will serve as the reference start date. The following relative days are considered:

- Total duration of treatment (ie, exposure) will be calculated as: (last dose date prior to data cutoff – first dose date) + 1.
- If the date of interest occurs on or after the first dose date, then study day will be calculated as: (date of interest – first dose date) + 1.
- If the date of interest occurs prior to the first dose date, then study day will be calculated as: (date of interest – first dose date).

4.4.2. Baseline Definition

In general, baseline is defined as the last available value on or prior to the administration of the first dose of study drug in Study ATB200-07. This is the case for all endpoints unless otherwise specified.

Note that:

- For subjects who completed Week 52 in Study ATB200-03, the results from the last visit in Study ATB200-03 were to serve as baseline values in ATB200-07. These data may already be available in the EDC system for Study ATB200-07.
- If the result from Week 52 of Study ATB200-03 was missing, then that assessment was to be performed at the Baseline Visit in Study ATB200-07 on or before the first dose date. For the 6MWD and % predicted 6MWD, 2 such assessments may be performed: if 2 assessments were performed, then the average is to serve as the baseline result; otherwise, the single value is to serve as the baseline result.
- If a subject had a change in the use of an assistive device that was used to perform the 6MWD during the Study ATB200-03, then the 6MWD was repeated in ATB200-07 (on or prior to the first dose date) to re-establish the baseline result.
- For all other endpoints (apart from the 6MWD and % predicted 6MWD), if there is more than one baseline value for a subject, the latest value (ie, last in chronological order) will be used.

4.4.3. Change and Percent Change from Baseline

Change from baseline is calculated as: Value at a visit – Baseline value.

Percent change from baseline is calculated as:

100*(Value at a visit – Baseline value) / Baseline value.

4.4.4. Baseline Age

Baseline age (years) for subjects in ATB200-07 is calculated as:

FLOOR ([date of informed consent in ATB200-07 – date of birth] / 365.25),

where the FLOOR ( ) function returns the integer part of the result.

4.5. Analysis Visit Windows

Analysis visit windows will be used for all by-visit analyses.

4.5.1. Visit Windows for By-visit Safety Analysis

By-visit safety endpoints including clinical laboratory and vital signs, BPE, and ECG as well as PD will be analyzed based on the by-visit safety windows in Table 2.

Table 2: Visit Windows for By-visit Safety Data

Study Visit	Target Day	Analysis Visit Window
Baseline[a]	1	Baseline
Week 2	15	Day 2 – Day 22
Week 4	29	Day 23 – Day 36
Week 6	43	Day 37 – Day 64
Week 12	85	Day 65 – Day 134
Week 26	183	Day 135 – Day 274
Week 52	365	Day 275 – Day 456
Week 78	547	Day 457 – Day 638
Week 104	729	Day 639 – Day 820
Week 130	911	Day 821 – Day 1002
Week 156	1093	Day 1003 – Day 1184
Week 182	1275	Day 1185 – Day 1366
Week 208	1457	Day 1367 – Day 1548
Week 234	1639	> Day 1548

Abbreviation: 6MWT = six-minute walk test
[a] In general, baseline is derived as the last assessment on or prior to the first dose date in Study ATB200-07. For most subjects, the baseline value will be the assessment from Week 52 in ATB200-03. For subjects who did not complete Week 52 in Study ATB200-03, baseline assessments are to be performed at the Baseline visit. If a subject has a change in the use of an assistive device that was used to perform the 6MWT during Study ATB200-03, then the 6MWT is to be repeated at the Day 1 Visit.

4.5.2. Visit Windows for Efficacy Analysis

Efficacy endpoints and PRO measures will be analyzed based on the efficacy visit windows in Table 3.

Table 3: Visit Windows for Efficacy and Patient-reported Outcome Data

Week	Target Day	Analysis Visit Window
Baseline[a]	1	Baseline
Week 12	85	Day 2 – Day 134
Week 26	183	Day 135 – Day 274
Week 52	365	Day 275 – Day 456
Week 78	547	Day 457 – Day 638
Week 104	729	Day 639 – Day 820
Week 130	911	Day 821 – Day 1002
Week 156	1093	Day 1003 – Day 1184

Table 3: Visit Windows for Efficacy and Patient-reported Outcome Data (Continued)

Week	Target Day	Analysis Visit Window
Week 182	1275	Day 1185 – Day 1366
Week 208	1457	Day 1367 – Day 1548
Week 234	1639	> Day 1548

Abbreviation: 6MWT = six-minute walk test
[a] In general, baseline is derived as the last assessment on or prior to the first dose date in Study ATB200-07. For most subjects, the baseline value will be the assessment from Week 52 in Study ATB200-03. For subjects who did not complete Week 52 in Study ATB200-03, baseline assessments are to be performed at the Baseline Visit. If a subject has a change in the use of an assistive device that was used to perform the 6MWT during ATB200-03, then the 6MWT is to be repeated at the Day 1 Visit.

4.5.3. Multiple Assessments in a Visit Window

For the CSR, the usual windowing rules for handling multiple assessments will be followed for both safety and efficacy by-visit data. No active rule for reassigning/remapping missing visits due to COVID-19 related reasons to address delayed visits will be implemented.

If multiple assessments (from both scheduled and unscheduled visits) occur in the same visit window, the value closest to the planned target visit day will be used for that visit. If 2 values are equidistant from the target day or occur on the same day but at different times, the last assessment in chronological order will be used. If the 2 assessments have the same date and time, then the larger value will be used.

4.6. Handling of Missing Data for Efficacy and Safety Endpoints

4.6.1. Imputation for Missing Baseline Values

Subjects are expected to have baseline values for safety and efficacy assessments in Study ATB200-07 and so no rule for baseline imputation is needed, unless otherwise specified.

4.6.2. Imputation for Missing Post-baseline Values

Missing post-baseline values (whether efficacy or safety) will not be imputed.

4.7. Missing AE Attributes

Adverse events with missing attributes will be imputed with the worst possible outcome, for summary purposes. For example, if an adverse event (AE) is missing relationship to study drug, it will be imputed as being ‘related’ to the study drug; if an AE is missing the severity level, it will be imputed as being ‘severe.’

Nonetheless, in the data listings, the actual observed values will be reported. That is, if the response is missing, it will show as missing in the data listings.

4.7.1. Missing or Partial AE Onset or Medication Start Date

Complete dates are very important to correctly describe safety events such as TEAEs and designation of unique AE occurrences. When dates are completely missing or partially missing, they will be imputed.

The following algorithm will be used to impute partial or missing AE start dates:

1. If year is not missing and is after the year of first application of study drug:
   - If month is missing, then month will be imputed as January.
   - If day is missing, then day will be imputed as the first of the month.
2. If year is not missing and is the same as the year of the first application of study drug:
   - If month is missing, then impute the month as the month of the first application of study drug.
   - If day is missing but month is the same as the month of first application of study drug, then impute day as the first day of study drug application.
   - If day is missing but month is after the month of first application of study drug, then impute day as the first of the month.
3. If year is missing, then impute the year as the year of the first application of study drug:
   - If month is missing, then impute the month as the month of the first application of study drug.
   - If day is missing, then impute the day as the day of the first application of study drug.
4. If the start date is completely missing, but the AE is either ongoing or the stop date is after the first date of drug application, then impute the start date as the first application of study drug.
5. If using the above rules, the stop date is before the start date, then leave the start date missing and assume that the AE is treatment-emergent for the purpose of the analysis.

No imputations will be applied to AE stop dates.

4.7.2. Missing or Partial Medication Stop Date

References to year and month are the year and month of the stop date:

1. If year and month are known and study medication stopped during that month and year, use the stop date of study medication.
2. If year and month are known and informed consent was provided during that month and year, use the date of informed consent.
3. If year and month are known and study medication stopped after the date of informed consent and not in the month that medication stopped, use the last day of the month.
4. If year and month are known and are prior to the month of informed consent, use the first day of the month.

5. If only year is known and study medication stopped during that year, use the stop date of study medication.
6. If only year is known and study medication stopped after that year, use December 31st of that year.
7. If only year is known and study medication stopped prior to that year, use the first day of the year.
8. Should any of the previous stop dates be created before a start date, either a complete date or an imputed one, use the (imputed) start date instead of the date that would otherwise be created.
9. Otherwise, if stop date is unknown, leave as missing.

5. CHARACTERISTICS OF STUDY POPULATION

Unless otherwise stated, the discussion of characteristics of study population will pertain solely to Study ATB200-07.

5.1. Subject Disposition

Disposition will focus on Study ATB200-07 only, and it will be presented by the treatment groups described in Section 4.2 and overall. The presentation will include the number of subjects who enrolled in the OLE study (OLE-ES), the number and percentage of subjects in the FAS, and the OLE safety population, number and percent of subjects who completed the study (based on the 'Yes' check box on the eCRF), and who discontinued the study early. The categories classifying the subjects' study completion status are derived from the end of study electronic case report form (eCRF) page. The number and percent of subjects by reason of discontinuation will also be presented. As much as possible, any discontinuation with reason due to 'other' will be queried and re-categorized appropriately, by medical review.

5.2. Demographic and Baseline Characteristics for ATB200-07

Demographic and baseline characteristics will be summarized for the OLE enrolled subjects (OLE-ES) population with the descriptive statistics: n, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum (for continuous variables) and counts (number of observations) and percentage (for categorical variables), and presented by treatment group and overall.

5.2.1. Demographics

- Categorical: Sex; race; region; and prior ERT status (ERT-experienced or previously ERT-naïve) as at the baseline in Study ATB200-03. The regions are pooled as follows: North/South America, Europe, Asian Pacific
- Continuous: Age at informed consent in ATB200-07; weight; height; and body mass index (BMI)

  In addition, age at informed consent will be summarized as a categorical variable with the categories:

  ≥ 18 to < 35 years, ≥ 35 to < 50 years, ≥ 50 to < 65 years, ≥ 65 years

5.2.2. Baseline Characteristics

- Continuous: 6MWD; FVC (sitting % predicted); CK; Hex4; age at first dose of prior ERT treatment (years) before entering Study ATB200-03 (for subjects who are ERT-experienced as defined in Section 4.3.1); and the duration of the prior ERT treatment (for subjects who are ERT-experienced as defined in Section 4.3.1)
- Categorical:
  - Age at first dose of prior ERT treatment (years) categorized:

    < 18 years, ≥ 18 to < 35 years, ≥ 35 to < 50 years, ≥ 50 years
  - Subjects with history of falls (Y, N) at the baseline in Study ATB200-07;

- Subjects with history of IARs (Y, N) at the baseline in Study ATB200-07;
- Prior pre-infusion medications versus no prior pre-infusion medications at the baseline in Study ATB200-07.

For partial dates involving age at diagnosis and age at first dose of prior ERT treatment, missing day will be imputed as '01,' and missing month will be imputed as 'JANUARY.'

The demographic and baseline characteristics summary will also be presented by the prior ERT status (ERT-experienced versus previously ERT-naïve).

5.2.3. Medical History

The AEs from Study ATB200-03 together with medical history collected for Study ATB200-07 will constitute the complete medical history for the OLE Study ATB200-07. Medical history will be coded using version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA) into system organ class (SOC) and preferred term (PT). The frequency of subjects with medical history will be summarized on the OLE safety population by SOC and PT and presented by treatment group and overall.

5.2.4. Prior and Concomitant Medications and Nondrug Therapies

Prior medications/nondrug therapies are defined as any medication or nondrug therapy that a subject receives prior to the start of the study drug. Concomitant medications/nondrug therapies are defined as those that (a) a subject receives prior to first dose of study drug and continues after the first dose of study drug, or (b) those medications and nondrug therapies that are initiated after the first dose of study drug. Medications/nondrug therapies that are initiated after the last dose of study drug will not be considered as concomitant medications.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (Global B3, March 2020). The number and percentage of subjects receiving prior medication, and number and percentage of subjects receiving concomitant medication will be summarized by anatomical therapeutic chemical (ATC) class of level 4 and preferred drug name for the OLE safety population and presented by treatment group. The summary results will be presented in order of decreasing frequency of the most common medication administered to the overall treatment group.

In addition to the summary of prior and concomitant medications, the pre-infusion medications will also be summarized. Both prior pre-infusion medication (ie, pre-infusion medications taken before the first dose of cipaglucosidase alfa IV infusion study drug) and pre-infusion medications during the study (ie, those that start on or after the first dose of study drug but before the last dose of study drug) will be summarized by treatment group and overall, for the OLE safety population.

A listing of all pre-infusion medications will be provided, and this display will include columns for subject ID, prior ERT status, ATC Level 4/drug name/report name, start date and time relative to Day 1, end date and time relative to Day 1, dose (unit)/route/frequency, 'taken before start date?,' and 'taken during start date?.'

Separate listings will be provided for all prior and concomitant medications, and all prior and concomitant nondrug therapies.

5.2.5. Baseline Physical Examination

Overall assessment of baseline physical exam (categorized as normal, abnormal, or not performed) will be summarized by number and percentage, together with post-baseline data.

5.2.6. Baseline Vital Signs

Baseline vital signs including systolic and diastolic blood pressures (mmHg), heart rate (pulse [beats/min]), respiratory rate (breaths/min), and body temperature (°C) will be summarized using descriptive statistics, together with post-baseline data.

5.3. Exposure and Treatment Compliance

Study drug exposure will be summarized for the cipaglucosidase alfa/miglustat combination treatment rather than separately for cipaglucosidase alfa and miglustat. All analyses will be based on the exposure during Study ATB200-07 only.

Analyses will be presented by treatment groups Cipaglucosidase alfa/miglustat–Cipaglucosidase alfa/miglustat, Alglucosidase alfa/placebo–Cipaglucosidase alfa/miglustat, and overall, as defined in Section 4.2. The duration of treatment (ie, extent of exposure), in months, will be calculated as (date of last dose in ATB200-07 – date of first dose in ATB200-07 + 1) / 30.4, and summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

In addition, the duration of treatment will be categorized into the exposure intervals below and summarized using number and percentages of subjects:

≤ 3 months, > 3 to ≤ 6 months, > 6 to ≤ 9 months, > 9 to ≤ 12 months, > 12 to ≤ 18 months, > 18 to ≤ 24 months, > 24 to ≤ 36 months, > 36 to ≤ 48 months, > 48 months to ≤ 60 months, and > 60 months.

Additionally, a summary of the duration of treatment (exposure) will be provided by prior ERT status.

5.3.1. Study Compliance

Compliance will be provided separately for cipaglucosidase alfa and miglustat. For each subject taking cipaglucosidase alfa, compliance will be calculated based on the number of infusions as well as the actual infusion dose administered.

Compliance based on infusion dose is calculated as:

100*(total infusion dose administered [mg] / total infusion dose planned or intended [mg]).

Compliance based on number of infusions is calculated as:

100*(number of infusions administered / number of infusions planned or intended),

where the number of infusions planned is obtained as: (subject's last date in ATB200-07 as of the data cut-off date – date of first infusion + 14) / 14.

Compliance for each subject taking miglustat will be calculated as:

100*(total dose administered [mg] / planned dose [mg]).

Dose compliance rate will be classified as under-compliance: < 80%, within compliance: (80%, 120%), and over-compliance: > 120%.

6. ANALYSIS OF EFFICACY AND PHARMACODYNAMICS

6.1. Analysis of Efficacy Endpoints

No formal hypotheses are planned to be tested. Unless otherwise specified, only descriptive statistics will be presented. Any inferential statistics will be presented for summary purposes.

Efficacy endpoints are described in Section 2.3.2. Continuous variables will be summarized using descriptive statistics for the actual values and for the change from baseline. A 95% confidence interval (CI) for the mean change from baseline will be included for summary purposes. That is:

- For the Actual values (ie, baseline or visit values): the summary will present n, mean, SD, median, Q1, Q3, minimum, and maximum.
- For change from baseline values: the summary will present n, mean, SD, 95% CI, median, Q1, Q3, minimum, and maximum.

Categorical variables will be summarized using counts and percentages. Efficacy analysis will be performed on the FAS population (as defined in Section 4.1.3), and it will be presented by visit and by treatment group (and overall, if appropriate). Line plots of the mean ± standard error (SE) of the change from baseline over time will be provided for the 6MWD and % predicted FVC (see Section 2.3.2.1 for clarification).

6.2. Analysis of Pharmacodynamics (Biomarker) Endpoints

The pharmacodynamics endpoints are Hex4 and CK (as described in Section 2.3.3), which are considered biomarkers of muscle injury. These will be analyzed using descriptive statistics (n, mean, SD, 95% CI, median, Q1, Q3, minimum, and maximum) for the actual values, change and percent change from baseline, and presented by visit and by treatment group. Analysis will be conducted on the FAS population.

Line plots of mean ± SE of the change (and percent change) from baseline over time will be provided for the PD endpoints (CK and Hex4).

6.3. Subgroup Analysis

The following analyses will be provided by visit and by prior ERT subgroups (as defined in Section 4.3.1) with the total.

- Summary of the main efficacy endpoints: 6MWD, % predicted FVC, MMT-lower extremities, PROMIS-Physical Function, PROMIS-Fatigue, and GSGC total score

  In addition, line plots of mean ± SE of the change from baseline over time will be provided for the 6MWD and % predicted FVC only.
- Summary of PD endpoints: Hex4 and CK

  In addition, line plots of mean ± SE of the change (and percent change) from baseline over time will be provided for the PD endpoints (CK and Hex4).
- Summary of exposure

- Summary of AEs: AE overview, TEAEs by SOC and PT, treatment-emergent serious adverse events (TESAEs) by SOC and PT, IAR overview, and IAR-TEAEs by SOC and PT
- Summary of demographics and baseline characteristics: demography (sex, age at informed consent)
- Summary of disposition: overall disposition table showing populations, number and percentage of subjects discontinuing the study, and reasons for discontinuation

Additional subgroup analyses based on the subsets of subjects defined in Section 4.3.2 will be conducted for the 6MWD and % predicted FVC, as described in Section 4.3.2.

7. ANALYSIS OF SAFETY

7.1. Safety Summary Statistics

Safety analyses will be performed on the OLE safety population. Safety data will be summarized using counts (number) and percentages for categorical data. Continuous data will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum). No formal statistical tests will be performed.

7.2. Analysis of Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using MedDRA version 23.0.

Summaries of AEs and SAEs will be focused on treatment-emergent adverse events (TEAEs) pertaining to Study ATB200-07 only. These are defined as any event that started or changed in the severity on or after the first dose of study drug in Study ATB200-07.

As stated in Section 5.2.3, AEs from ATB200-03 will be part of the medical history for ATB200-07. However, if those AEs worsened (or increased in severity) on/after first dose in ATB200-07, they will be considered as TEAEs for ATB200-07. For AEs occurring on Day 1 of ATB200-07, if the start time of the event is missing or if it occurred after the administration of the first dose of study drug, the event will be considered a TEAE.

In general, adverse events that occur more than 30 days from the last dose of study drug will not be counted as treatment-emergent. Therefore, if a subject permanently discontinues study drug and then gets an AE, the event will be considered as a TEAE only if it is within the TEAE tabulation period (in days) calculated as [(last dose date of study drug + 30 days) – first dose date + 1] from the last dose date.

7.2.1. Summary of Treatment-emergent Adverse Events

7.2.1.1. Overall Summary of TEAEs

The overall summary of TEAEs (ie, the AE overview table) will be presented by treatment group and overall, and will include the following events:

- Treatment-emergent adverse events (ie, any TEAE)
- TEAEs leading to study drug discontinuation
- TEAEs related to study drug (ie, treatment related TEAEs)
- TEAEs related to study drug and leading to study drug discontinuation
- Treatment-emergent serious adverse events (ie, any TESAEs)
- TESAEs leading to study drug discontinuation
- TESAEs related to study drug (ie, treatment related TESAEs)
- TESAEs related to study drug and leading to study drug discontinuation
- Deaths

7.2.1.2. Specific Summaries of TEAEs

The number and percentage of subjects with TEAEs will be summarized in 2 ways as follows:

- by SOC and PTs, where the SOCs are ordered alphabetically and PTs within each SOC are sorted in order of decreasing frequency in the overall treatment group. A subject will be counted only once within the same SOC and within the same PT.
- by only PTs, where the PTs are sorted in order of decreasing frequency in the overall treatment group.

A summary of TEAEs by system organ class, preferred term, and severity will also be presented, where each TEAE will be counted under its maximum severity rating only.

The number and percentage of subjects with TEAEs leading to study drug discontinuation, TEAEs related to study drug (ie, treatment related TEAEs), TEAEs related to study drug and leading to study drug discontinuation, TESAEs, TESAEs leading to study drug discontinuation, TESAEs related to study drug (ie, treatment related TESAEs), TESAEs related to study drug and leading to study drug discontinuation, and death will be summarized by SOC and PT. All AEs will be provided in a listing that will include the subject identifier, SOC, PT, and the reported term, date of onset and study day, date of resolution and study day, the seriousness, the severity, the relationship to each individual study drug (for TEAEs), duration, the action taken, and the outcome. All TEAEs will be flagged in the listing. Additionally, subject data listings of deaths, SAEs, AEs leading to study drug discontinuation will be provided.

7.2.2. TEAEs Reported as Infusion-associated Reactions

For any AE, the reporting investigator is requested to enter on the AE eCRF whether the AE is deemed to be an infusion-associated reaction (IAR) and determine the relationship to each of the study drug components.

7.2.2.1. Overall Summary of TEAEs Reported to be IAR

An overall summary table of TEAEs reported to be IARs (ie, IAR-TEAEs) will be provided. This IAR overview table will present the number and percentage of subjects who had: any IAR-TEAE; any IAR-TEAE leading to study drug discontinuation; any IAR-TESAE; any IAR-TESAE leading to study drug discontinuation; and any IAR-TEAE leading to death).

7.2.2.2. Specific Summaries of IAR-TEAEs

To further characterize TEAEs considered by the reporting investigator to be IARs, specific summaries of TEAEs reported as IARs will be provided, where feasible. That is, the number and percentage of subjects who experienced any IAR-TEAEs, IAR-TEAE leading to study drug discontinuation, IAR-TESAE, IAR-TESAE leading to study drug discontinuation, and IAR-TEAE leading to death will be presented by SOC and PT within each SOC, and by treatment group and overall. A subject will be counted only once within the same SOC and within the same PT. A summary of IAR-TEAEs will also be presented by severity (mild, moderate, severe) and by relationship to each treatment component (cipaglucosidase alfa and miglustat) as well as for the combination treatment (cipaglucosidase alfa/miglustat).

Listings of treatment-emergent IAR-TEAEs, serious IAR-TEAEs, IAR-TEAEs leading to study drug discontinuation, and IAR-TEAE related deaths will be provided.

7.2.2.3. Summary of Infusions and IARs for All Subjects and for Subjects with IARs

A summary of total infusions and infusions associated with IARs will be provided for all subjects as well as for subjects with IARs. This summary will include the following:

- Summary for all subjects:
  - Overall total number of infusions administered during ATB200-07
  - Overall total number of infusions associated with IARs
  - Overall percentage of infusions associated with IARs, where the percentage is calculated as: total number of infusions associated with IARs / total number of infusions administered
- Summary for subjects with IARs:
  - Total number of infusions in subjects with IARs
  - Number of infusions associated with IARs in subjects with IARs
  - Percentage of infusions associated with IARs in subjects with IARs, where the percentage is calculated as: total number of infusions associated with IARs in subjects with IARs / total number of infusions in subjects with IARs

For this summary, any infusion suspected by the reporting investigator as leading to an IAR is considered an 'infusion associated with IAR.'

7.2.2.4. Analysis of Subjects with IARs and Time to First IAR-TEAE

For subjects with IAR-TEAEs, a summary table will be provided displaying the following:

- Summary of IAR-TEAEs by subjects with IARs:
  - the number and percentage of subjects with IAR-TEAEs
  - total number of IAR-TEAEs
  - the number of subjects who experienced 1, 2, 3, 4 to 6, 7 to 10, 11 to 19, and ≥ 20 IARs in each treatment group and overall
- Time to first IAR-TEAE for subjects with IARs:
  - the time (in weeks) from the first dose of study drug to the onset of the first TEAE that is an IAR (ie, IAR-TEAE) will be calculated for each subject as:

    Time to first IAR-TEAE (Weeks) = (date of the first IAR-TEAE – date of first dose of study drug in ATB200-07 + 1) / 7.
  - The calculated times will be summarized as a continuous variable and included in the same table.

In addition, a listing displaying the number of infusions and infusions that were associated with IARs by each individual subject who had an IAR will be provided. For each subject, this listing

includes subject ID, whether or not pre-infusion medication was given, number of infusions received, number of infusions that were associated with IARs, percentage of infusions associated with IARs, a chronological listing of the number of IARs corresponding to (or associated with) each infusion, and time to first IAR.

7.2.2.5. Analysis of IARs by Onset Intervals

The IARs will also be analyzed by onset intervals categorized as follows:

- 1 to 3 days, 4 to 7 days, 8 to 14 days, 15 to 28 days, 29 days to ≤ 3 months, > 3 months to ≤ 6 months, > 6 months to ≤ 12 months, > 12 months to ≤ 2 years, > 2 years to ≤ 3 years, > 3 years to ≤ 4 years, and > 4 years.

The event rates and changes in severity over time (over these intervals) will be summarized for each treatment group. This analysis will further describe the clinical characteristics of IARs and help determine whether the IARs disappear over time or appear late.

7.2.2.6. Analysis by Time After Infusion Start

IARs and anaphylactic reactions will be analyzed by the time after infusion start. Based on protocol descriptions of immediate-type IARs and late-type IARs, the following time after infusion start will be used:

- 0 to < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 12 hours, 12 to < 24 hours (1 day), 1 to < 4 days (96 hours).

The event rates and changes in severity over time (over these intervals) will be summarized to help describe the clinical characteristics of IARs and anaphylactic reactions.

7.3. Clinical Safety Laboratory Data

Laboratory data will be presented using the Système International (SI) unit. Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be presented for the absolute visit values, change from baseline, and percent change from baseline to post-baseline visits by treatment group and overall, and by visit, starting at the Baseline visit. Summaries will be presented by the specific lab parameters within the domains of clinical chemistry, hematology, and urinalysis.

Line plots of mean ± SE of the change from baseline and percent change from baseline over time will be provided for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by treatment group and overall. Similar line plots will also be provided by prior ERT status.

Additionally, a summary of the number and percentage of subjects with treatment-emergent or newly-occurring laboratory values that meet pre-defined limits of change (PDLC) at any post-baseline visit will be presented by treatment group and overall. The PDLC criteria are provided in Table 4. If a subject has even 1 post-baseline value that meets the PDLC criteria for any particular lab parameter, then all values of that parameter for that subject will be listed.

Table 4: Pre-defined Limits of Change Criteria for Clinical Safety Laboratory Data

Laboratory Test	Parameter for ANY Value and LAST Value
Chemistry	
Albumin	Composite: < LLN and > 25% decrease from BL
Bilirubin	Composite: > ULN and > 25% increase from BL
	Absolute Value: > 2X ULN
Bicarbonate	Absolute Value: < 16 mEq/L
Calcium	Composite: > ULN and > 10% increase from BL
Phosphorus	Composite: < LLN and > 25% decrease from BL
	Composite: > ULN and > 25% increase from BL
Potassium	Composite: < LLN and > 15% decrease from BL
	Composite: > ULN and > 15% increase from BL
Sodium	Composite: < LLN and decrease > 5 mEq/L or more from BL
	Composite: > ULN and increase > 5 mEq/L or more from BL
Uric Acid	Male: absolute value ≥ 624.6 μM
	Female: absolute value ≥ 505.6 μM
	Composite: < LLN and > 25% decrease from BL
	Composite: > ULN and > 25% increase from BL
ALT	Absolute Value: > 3X ULN
	Absolute Value: > 5X ULN
	Absolute Value: > 8X ULN
AST	Absolute Value: > 3X ULN
	Absolute Value: > 5X ULN
	Absolute Value: > 8X ULN
ALT > 3X ULN and Tbili > 2X ULN	Composite: ALT > 3X ULN and Tbili > 2X ULN (with the Tbili elevation > 2 X ULN within 30 days of the ALT elevation > 3X ULN)
AST > 3X ULN and Tbili > 2X ULN	Composite: AST > 3X ULN and Tbili > 2X ULN (with the Tbili elevation > 2X ULN within 30 days of the AST elevation > 3X ULN)
CK	Absolute CK ≥ 2X ULN or 2X baseline value

Table 4: Pre-defined Limits of Change Criteria for Clinical Safety Laboratory Data (Continued)

Laboratory Test	Parameter for ANY Value and LAST Value
Hematology	
Hemoglobin	Male: absolute value ≤ 11.5 g/dL
	Female: absolute value ≤ 9.5 g/dL
	Change: ≥ 2 g/dL decrease from BL
	Change: ≥ 2 g/dL increase from BL
Platelets	Absolute value: ≤ 75 x 10^9/L
	Absolute value: ≥ 700 x 10^9/L
	Composite: > ULN and increase > 25% from BL
	Composite: < LLN and > 25% decrease from BL
White Blood Count	Composite: < LLN and > 25% decrease from BL
	Composite: > ULN and > 50% increase from BL
Eosinophils	Absolute value: > 10%

Abbreviations: BL = baseline; LDH = lactate dehydrogenase; LLN = lower limit of normal; PDLC = pre-defined limit of change; SGOT (AST) = serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT (ALT) = serum glutamic pyruvic transaminase (alanine aminotransferase); Tbili = total bilirubin; ULN = upper limit of normal

Supportive data listings for all laboratory results will be generated by laboratory type (hematology, serum chemistry, and urinalysis). Subject data listings will include the type of visit (eg, scheduled test, retest, or unscheduled), age, sex, laboratory test, test units, laboratory test result, and the laboratory standard normal ranges adjusted as appropriate for age and sex, if available. Laboratory values outside of the normal range will be flagged in the data listings.

Results of urine pregnancy tests will be presented in a listing only.

7.4. Analysis of Vital Signs, ECG, and Physical Examination Data

7.4.1. Vital Signs

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for the baseline, value at each visit, and change from baseline at each visit will be presented for vital signs by treatment group and overall, for systolic blood pressure, diastolic blood pressure, heart rate, and body weight at each visit starting at baseline.

The number and percentage of subjects with treatment-emergent vital signs results at any post-baseline visit meeting the PDLC criteria in Table 5 will be summarized. The incidence rates of PDLC for vital signs results will be summarized (altogether, not by visit).

A listing will present all values for a subject and vital sign parameter if at least 1 post-baseline value for that subject and parameter meets the PDLC criterion.

Table 5: Pre-defined Limits of Change Criteria for Vital Signs

Vital Sign	Criteria
Pulse rate	≥ 120 bpm at any time post-dose and ≥ 15 bpm increase from baseline at any time post-dose
	≤ 50 bpm at any time post-dose and ≥ 15 bpm decrease from baseline at any time post-dose
Systolic blood pressure	≥ 180 mm Hg at any time post-dose and ≥ 20 mm Hg increase from baseline at any time post-dose
	≤ 90 mm Hg at any time post-dose and ≥ 20 mm Hg decrease from baseline at any time post-dose
Diastolic blood pressure	≥ 105 mm Hg at any time post-dose and ≥ 15 mm Hg increase from baseline at any time post-dose
	≤ 50 mm Hg at any time post-dose and ≥ 15 mm Hg decrease from baseline at any time post-dose
Weight	Change: > 5% increase from BL
	Change: > 5% decrease from BL

Abbreviations: bpm = beats per minute; mm Hg = millimeters mercury; PDLC = pre-defined limit of change

7.4.2. Electrocardiograms

Electrocardiogram data, including heart rate [HR] (beats/min), PR interval [PR] (msec), QRS duration (msec), QT interval (msec), QTcB interval (msec), QTcF interval (msec), and R-R interval [RR] (msec), will be summarized at baseline.

For quantitative ECG values, descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for the baseline, value at each visit, and change from baseline at each post-baseline visit will be presented by treatment group and overall, and by visit.

The number and percentage of subjects with treatment-emergent (or newly-occurring) ECG results at any post-baseline visit meeting the PDLC criteria in Table 6 will be summarized. The summary will indicate the number and percentage of subjects with PDLCs at any time during the study and will not be presented by visit. Unscheduled visits will be included in this summary. It is possible for subjects to appear in both categories for any parameters. A listing will present all values for a subject and ECG parameter if at least 1 post-baseline value for that subject and parameter meets the PDLC criterion.

Additionally, the number and percentage of subjects with the following overall ECG result will be presented:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

Table 6: Pre-defined Limits of Change Criteria for ECG Values

ECG Parameter	Criteria
PR interval (msec)	< 120 msec or ≥ 210 msec
QRS duration (msec)	≤ 50 msec or > 120 msec
QTcF interval (msec) and QTcB interval (msec)	Absolute post-baseline QTcB, QTcF, and uncorrected QT interval: > 450 msec > 480 msec > 500 msec
	Change from baseline for QTcB, QTcF, and uncorrected QT: > 30 msec; > 60 msec

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; msec = millisecond; PDLC = pre-defined limit of change; QTcB = QT interval for corrected heart rate (based on Bazett's formula: $QT/(RR^{1/2})$); QTcF = QT interval for corrected heart rate (based on Fridericia's formula: $QT/(RR^{1/3})$)

7.4.3. Physical Examination

Complete physical exams are performed in ATB200-07 at Screening/Baseline and EOS/ET visit. Brief physical exams are performed at Weeks 2, 4, 6, 12, 26, and every 26 weeks thereafter. Baseline physical examination results will be presented for each body system/category examined. The number and percentage of subjects judged to be normal, abnormal, or not performed will be summarized.

Further, the results of the physical examinations will be summarized by visit for subjects in the OLE safety population who had an examination post-baseline. Each site/system will be summarized with respect to being normal or abnormal or not performed.

The supportive data listing will include the information collected on the eCRF (eg, body system/category, result of the observation [eg, normal or abnormal] or not performed, and any investigator comment).

7.5. Analysis of Immunogenicity

A summary of available immunogenicity results for subjects treated with ATB200/AT2221 in the OLE Study ATB200-07 will be provided. The summary will include results for the following:

- Total ADA, including titers, as available (which will be assessed using the ATB200 assay).
- NAbs (inhibition of rhGAA-mediated hydrolysis of 4-MU glucoside, inhibition of rhGAA-mediated hydrolysis of glycogen, and/or inhibition of rhGAA binding to CI-MPR, as available), GAA cross-reactivity (anti-rhGAA antibodies cross-reactive to alglucosidase alfa, as available), which will be assessed regardless of treatment arm. Screen/confirm analysis only will be performed (ie, no titers will be assessed with the GAA assay).
- Anti-rhGAA IgE, as available (which will be assessed as needed).

No analysis assessing the impact of immunogenicity on safety, efficacy, PK or PD will be performed for this final CSR.

8. REFERENCES

Enright, P. L. and D. L. Sherrill (1998). “Reference equations for the six-minute walk in healthy adults.” Am J Respir Crit Care Med 158(5 Pt 1): 1384-1387.