Official Title:	Statistical Analysis Plan for the Final CSR: An Open-Label, Fixed-Sequence, Ascending-Dose, First-in-Human Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Intravenous Infusions of ATB200 Co-Administered with Oral AT2221 in Adult Subjects with Pompe Disease
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STATISTICAL ANALYSIS PLAN
FOR THE FINAL CSR

VERSION: *Final v1.0*

DATE OF PLAN: *4 April 2024*

BASED ON:

Protocol Amendment #8 Dated: 10 January 2019

PROTOCOL NUMBER: *ATB200-02*

STUDY TITLE:

AN OPEN-LABEL, FIXED-SEQUENCE, ASCENDING-DOSE, FIRST-IN-HUMAN STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF INTRAVENOUS INFUSIONS OF ATB200 CO-ADMINISTERED WITH ORAL AT2221 IN ADULT SUBJECTS WITH POMPE DISEASE

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Term/Abbreviation	Definition
10MWT	10-meter walk test
6MWD	6-minute walk distance
AE	adverse event
AT2221	INN: miglustat; *N*-butyl-deoxynojirimycin; iminosugar that is used as an enzyme stabilizer to ATB200 (a recombinant human acid α-glucosidase)
ATB200	INN: cipaglucosidase alfa; recombinant human acid α-glucosidase (rhGAA) enzyme with optimized carbohydrate structures, including mannose 6-phosphate (M6P), to enhance uptake and delivery of active ATB200 to lysosomes
CI	confidence interval
CK	creatine kinase
CSR	clinical study report
DBL	database lock
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
FSS	Fatigue Severity Scale
FVC	forced vital capacity
GAA	human acid α-glucosidase, may be specified as either GAA enzyme activity or GAA protein
GSGC	Gait, Stairs, Gowers', Chair
Hex4	hexose tetrasaccharide
IAR	infusion-associated reaction
iCSR	interim clinical study report
IMG	immunogenicity
IV	intravenous
MEP	maximum expiratory pressure
MIP	maximum inspiratory pressure
MMT	manual muscle test
PD	pharmacodynamic or pharmacodynamics
PDLC	pre-defined limits of change

Table 1: List of Abbreviations (Continued)

Term/Abbreviation	Definition
PFT	pulmonary function test
PGIC	Physician's Global Impression of Change
PK	pharmacokinetic or pharmacokinetics
PRO	patient-reported outcome
PROMIS®	Patient-reported Outcomes Measurement Information System
PT	preferred term
QMT	quantitative muscle test
rhGAA	recombinant human acid α-glucosidase
RHS	Rotterdam Handicap Scale
R-PAct	Rasch-built Pompe-specific Activity
SAP	statistical analysis plan
SGIC	Subject's Global Impression of Change
SNIP	sniff nasal inspiratory pressure
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TUG	Timed Up and Go

2. INTRODUCTION

This statistical analysis plan (SAP) is based on Amendment 8 to Protocol ATB200-02 dated 10 January 2019. The purpose of this SAP is to describe the planned data analyses and outputs to be included in the final clinical study report (CSR) to close out the study. Most of the subjects in Study ATB200-02 are expected to transition to commercial products while a few will transition to the sponsor's expanded access program (EAP) Study ATB200-11. The expected database lock (DBL) date for the final CSR is 24 July 2024.

The study design consists of 4 stages as described in Section 5 (and represented in Table 2), and the stages are as follows:

- Stage 1 involves the administration of a single-ascending dose (SAD) of ATB200 (also referred to as cipaglucosidase alfa) alone, with focus on safety, tolerability, and pharmacokinetic (PK) assessments.
- Stage 2 involves the co-administration of multiple-ascending doses (MAD) of ATB200/AT2221 (also referred to as cipaglucosidase alfa/miglustat), with a focus on safety (including pharmacodynamics [PD]) and PK assessments.
- Stages 3 and 4 involve a fixed dosing regimen of ATB200/AT2221 co-administration to support the proof of concept and the long-term extension phase of the study (with long-term efficacy and safety assessments).

The ATB200-02 study data have been reported previously in 2 interim clinical study reports and 1 addendum. The first interim clinical study report (iCSR-1), dated 15 December 2020, was based on the data cutoff date of 19 June 2020 and focused mainly on the analyses of the study data during Stages 1 and 2, including the complete analysis of the PK data, as well as the safety and PD data collected prior to the co-administration of the fixed dosing regimen of 20 mg/kg cipaglucosidase alfa + 260 mg miglustat. An addendum to iCSR-1, dated 11 May 2021, was based on the data cutoff date of 13 November 2020. The second interim clinical study report (iCSR-2), dated 31 August 2022, focused on the analysis of long-term efficacy, PD, immunogenicity (IMG), and safety data collected during Stage 2 Period 5 through Stages 3 and 4 that were available at the time of the data cutoff date of 13 December 2021.

As this is the final CSR, the plan is to report all data for the study using summary tables and/or listings. The current SAP describes the analyses of long-term data on safety, efficacy, and PD collected from Stage 2 Period 5 through the DBL date. No new PK samples are available since iCSR-1, and therefore PK analyses from iCSR-1 will be referenced or copied into the final CSR. Similarly, safety and PD analyses for Stages 1 and 2 reported in iCSR-1 will be copied into the final CSR, unless the underlying data have changed.

This SAP has been developed in accordance with Good Clinical Practice (GCP), International Conference on Harmonisation (ICH) guideline E9 (Statistical Principles for Clinical Trials), and Amicus standard operating procedure (SOP) ATCRA-SOP-AT-008. All decisions regarding the final analyses for the CSR, as defined in this SAP document, will be made prior to the expected study DBL date.

The SAP may evolve over time to incorporate important changes, including changes that reflect feedback and comments from regulatory interaction. However, the final SAP will be finalized

and placed on file before the DBL date. The analyses and statistical methods specified in this SAP supersede those described in the study protocol.

3. STUDY OBJECTIVES

For ease of presentation, the study objectives are presented by stage.

3.1. Objectives for Stage 1

Primary objectives for Stage 1 are:

- To evaluate the safety and tolerability of single-ascending doses of intravenously (IV) infused ATB200
- To characterize the PK of single-ascending doses of IV infused ATB200

An exploratory objective for Stage 1 is:

- To evaluate PD markers (urine hexose tetrasaccharide [Hex4] and serum creatine kinase [CK])

3.2. Objectives for Stage 2

Primary objectives for Stage 2 are:

- To evaluate the safety and tolerability of single doses of IV infused ATB200 as a fixed dose, co-administered with ascending oral doses of AT2221
- To characterize the single- and multiple-dose plasma total human acid α-glucosidase (GAA) protein PK of IV infused 20 mg/kg ATB200 when co-administered with oral 130 mg or 260 mg AT2221 in enzyme replacement therapy (ERT)-experienced subjects with late-onset Pompe disease (LOPD)
- To characterize the single- and multiple-dose plasma GAA activity PD of IV infused 20 mg/kg ATB200 when co-administered with oral 130 mg or 260 mg AT2221 in ERT-experienced subjects with LOPD
- To characterize the plasma miglustat PK of single and multiple oral doses of 130 mg or 260 mg AT2221 when co-administered with IV infused ATB200 in ERT-experienced subjects with LOPD

An exploratory objective for Stage 2 is:

- To evaluate PD markers (urinary Hex4 and serum CK)

3.3. Objectives for Stages 3 and 4

Primary objectives for Stages 3 and 4 are:

- To evaluate the long-term safety and tolerability of 20 mg/kg of IV infused ATB200 as a fixed dose co-administered with oral 260 mg AT2221 in all subjects from Stage 3
- To evaluate the long-term efficacy of 20 mg/kg of IV infused ATB200 as a fixed dose co-administered with oral 260 mg AT2221 in all subjects from Stage 3
- To characterize the single- and multiple-dose plasma total GAA protein PK of IV infused 20 mg/kg ATB200 when co-administered with oral 260 mg AT2221 in ERT-naïve subjects with LOPD

- To characterize the single- and multiple-dose plasma GAA activity PD of IV infused 20 mg/kg ATB200 when co-administered with oral 260 mg AT2221 in ERT-naïve subjects with LOPD
- To characterize the plasma miglustat PK of single and multiple oral doses of 260 mg AT2221 when co-administered with IV infused ATB200 in ERT-naïve subjects with LOPD

Exploratory objectives for Stages 3 and 4 are:

- To evaluate anti-rhGAA (recombinant human acid α-glucosidase) antibodies (total and neutralizing)
- To evaluate cross-reactivity of anti-rhGAA antibodies to alglucosidase alfa
- To evaluate pro-inflammatory cytokines and other biomarkers of immune system activation
- To evaluate PD markers (urinary Hex4 and serum CK)
- To evaluate the impact of anti-rhGAA antibodies and neutralizing antibodies on plasma GAA total protein exposures, safety (adverse events [AEs] and infusion-associated reactions [IARs]), and efficacy (6-minute walk distance [6MWD] and pulmonary function tests [PFTs])

4. ENDPOINTS

4.1. Pharmacokinetic Parameters

Descriptions and definitions of the plasma PK parameters for signature peptides T09 and T50 from total GAA protein concentrations, GAA activity levels, and miglustat concentrations are provided in Section 12.4.4.1 of Protocol ATB200-02.

Noncompartmental analyses for ATB200 and AT2221 include the following:

- Stage 1 PK (derived signature peptides T09 and T50 from total GAA protein concentrations and GAA activity levels) parameters in plasma
- Stage 2 (ERT-experienced) PK (derived signature peptides T09 and T50 from total GAA protein concentrations, GAA activity levels, and miglustat concentrations) parameters in plasma
- Stage 3 (ERT-naïve) PK (derived signature peptides T09 and T50 from total GAA protein concentrations, GAA activity levels, and miglustat concentrations) parameters in plasma
- Stage 4 (ERT-experienced) long-term sparse plasma PK sampling for signature peptides T09 and T50 from total GAA protein and miglustat concentrations population PK analysis

4.2. Safety Variables

Safety analyses will be performed for the following endpoints:

- Study drug exposure and compliance
- Identification and counts of treatment-emergent adverse events (TEAEs), and treatment-emergent serious adverse events (TESAEs), including IARs
- Change from baseline in 12-lead electrocardiogram (ECG)
- Change from baseline in clinical safety laboratory evaluations, including serum chemistry, hematology, and urinalysis
- Change from baseline in physical examinations (PEs)
- Change from baseline in vital signs

4.3. Pharmacodynamic Variables

PD analyses will be performed for the following endpoints:

- Change from baseline in Hex4
- Change from baseline in CK

4.4. Efficacy Variables

Efficacy analyses will be performed for the following endpoints:

Functional measurements for ambulatory subjects:

- Change and percent change from baseline in Gowers' maneuver, 4-stair climb, 6MWD, percent predicted 6MWD, 10-meter walk test (10MWT), total score of Gait, Stairs, Gowers', Chair (GSGC), Timed Up and Go (TUG), muscle strength tests (manual muscle tests [MMT] using Medical Research Council [MRC] scale and quantitative muscle test [QMT] based on hand-held dynamometer) for both upper and lower limbs
- Change and percent change from baseline in PFTs including forced vital capacity (FVC), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and sniff nasal inspiratory pressure (SNIP) for subjects without invasive ventilatory support

Functional measurements for non-ambulatory subjects:

- Change and percent change from baseline in MMT and QMT for upper limbs only
- Change and percent change from baseline in PFTs (FVC, MIP, MEP, and SNIP [for subjects without invasive ventilatory support])

Patient-reported Outcomes (PROs):

- Change and percent change from baseline in the total score of Fatigue Severity Scale (FSS), Rotterdam Handicap Scale (RHS), Rasch-built Pompe-specific Activity (R-PAct) scale, and Patient-reported Outcomes Measurement Information System (PROMIS®) scale

Global Impression of Change:

- Physician's Global Impression of Change (PGIC) and Subject's Global Impression of Change (SGIC)

Note: Further descriptions of the efficacy variables are provided in Appendix 1.

4.5. Immunogenicity Variables

Details of IMG variables are described in a separate Modeling and Simulation Plan.

5. STUDY DESIGN

5.1. Summary of Study Design

This is an open-label, fixed-sequence, single- and multiple-ascending dose, first-in-human (FIH) study to evaluate the safety, tolerability, PK, PD, and efficacy of intravenous ATB200 alone and when co-administered with oral AT2221. The study was conducted in 4 stages and enrolled 4 cohorts as shown in Table 2.

The 4 cohorts in the study are as follows:

- Cohort 1: this cohort was planned to enroll 11 ERT-experienced ambulatory subjects defined as adults with Pompe disease who have been on ERT for 2 to 6 years prior to enrollment and are able to walk at least 200 meters in the 6-minute walk test (6MWT).
- Cohort 2: this cohort was planned to enroll 4 to 6 ERT-experienced non-ambulatory subjects defined as adults with Pompe disease who are wheelchair-bound and unable to walk unassisted and have been on ERT for ≥ 2 years prior to enrollment.
- Cohort 3: this cohort was planned to enroll 5 ERT-naïve ambulatory subjects defined as adults with Pompe disease who have never received treatment with ERT and who are able to walk at least 200 meters in the 6MWT.
- Cohort 4: this cohort was planned to enroll 6 to 8 ERT-experienced ambulatory subjects defined as adults with Pompe disease who have been on ERT for at least 7 years prior to enrollment and are able to walk at least 75 meters in the 6MWT. This cohort was added after Amendment 5 to Protocol ATB200-02.

The 4 study stages are as follows:

- Stage 1 is a 3-period, fixed-sequence, single-ascending dose PK study of ATB200 alone. Safety, tolerability, and PK were evaluated following sequential single-ascending doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg of IV infused ATB200 administered 2 weeks apart. Only subjects in Cohort 1 participated in Stage 1.
- Stage 2 is a 2-period, fixed-sequence, single- and multiple-dose PK study of 20 mg/kg ATB200 co-administered with multiple-ascending doses of AT2221. In Stage 2, safety, tolerability, and PK were evaluated following single- and multiple-ascending dose combinations: 20 mg/kg of IV infused ATB200 co-administered with 130 mg of AT2221 administered orally every 14 days (± 3 days) for 3 doses, followed by 20 mg/kg of IV infused ATB200 co-administered with 260 mg of AT2221 administered orally for 3 doses. Only subjects in Cohort 1 participated in Stage 2.
- Stage 3: Cohort 1 subjects who completed Stages 1 and 2 entered into an extension stage of the study, during which they continued on extended treatment with 20 mg/kg of IV infused ATB200 co-administered with 260 mg of AT2221 administered orally. Additionally, during Stage 3, three new cohorts – Cohorts 2, 3, and 4, were enrolled. Subjects from Cohorts 2, 3, and 4 were treated with 20 mg/kg of IV infused ATB200 co-administered with 260 mg of AT2221 administered orally every 2 weeks. The

duration of Stage 3 was 2 years, and all subjects were evaluated for safety, tolerability, PD, and efficacy. In addition, disease-relevant functional assessments were performed at regular intervals. Key messages from Stage 3 will help support the proof-of-concept based on the efficacy endpoints.

- The Stage 4 treatment period began at the end of Stage 3 and will continue as a long-term extension to provide additional safety and efficacy data until subject withdrawal, regulatory approval, or marketing authorization and/or commercialization in the participating subject's country, or study termination by the sponsor, Amicus Therapeutics (Amicus).

Table 2: Treatment Assignment by Cohort and Stage

Cohorts	Stage 1 (6 weeks)			Stage 2 (12 weeks)		Stage 3 (2 years)	Stage 4 (Until Approval)
	Period 1 Single-dose	Period 2 Single-dose	Period 3 Single-dose	Period 4 3 Multiple Doses Co-administration	Period 5 3 Multiple Doses Co-administration	Multiple Dose, 24 months, Extension Co-administration	Multiple Dose, Long-term, Extension Co-administration
Cohort 1 (n = 11)	5 mg/kg ATB200	10 mg/kg ATB200	20 mg/kg ATB200	20 mg/kg ATB200 + 130 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221
Cohort 2 (n = 4-6)	NA					20 mg/kg ATB200 + 260 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221
Cohort 3 (n = 5)	NA					20 mg/kg ATB200 + 260 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221
Cohort 4 (n = 6-8)	NA					20 mg/kg ATB200 + 260 mg AT2221	20 mg/kg ATB200 + 260 mg AT2221

Abbreviations: ATB200 = cipaglucosidase alfa; AT2221 = miglustat; NA = not applicable
Note: At least 1 of the 2 sentinel subjects will complete Stage 2, Period 5 and the safety data will be reviewed by the Safety Steering Committee (SSC) before dosing any newly enrolled subjects from Cohorts 2 and 3. The first 2 subjects from Cohorts 2 and 3 will also serve as sentinel subjects for their respective cohorts.

For details of assessments to be performed at each study visit, please refer to Table 9 through Table 15 in Protocol ATB200-02.

5.2. Definition of Study Medications

Study drugs for Stages 1, 2, 3, and 4 are defined in Table 2 above. The study drug that is being investigated is cipaglucosidase alfa co-administered with miglustat, which is also denoted as cipaglucosidase alfa/miglustat (or ATB200/AT2221). Where necessary, these denotations will be used interchangeably in this document.

- Cipaglucosidase alfa (or ATB200): a recombinant human acid α-glucosidase (rhGAA) enzyme with optimized carbohydrate structures that functions as an ERT. This is administered intravenously.
- Miglustat (AT2221): *N*-butyl-deoxynojirimycin. This is an iminosugar that functions as a selective enzyme stabilizer of rhGAA. This is administered orally.

5.3. Sample Size Considerations

5.3.1. Sample Size Justification

No formal sample size calculation was performed, as this began as a FIH study in a single cohort using a sentinel dosing scheme, and no hypothesis test was specified.

The plan was to increase the sample size as the study expanded to include additional cohorts. A sample size of between 18 to 34 subjects across 4 cohorts was considered adequate for the purposes of evaluating safety and tolerability as well as providing preliminary efficacy data in this study.

5.3.2. Sample Size Re-estimation

No formal sample size re-estimation was planned for this study.

5.4. Randomization and Stratification

Randomization and stratification are not applicable to this study, as subjects received open-label treatment.

5.5. Clinical Assessments

Study assessments were to be performed in accordance with the Schedule of Assessments as provided in Table 9 through Table 15 in Protocol ATB200-02.

5.6. Interim Analyses

No formal interim analysis (ie, one that involves some strategy for early stopping or adjustment of the testing procedure to maintain an overall type I error rate) is planned for this study. However, the protocol allowed informal interim analyses to be performed in the study as needed.

As of 31 December 2023, there have been approximately 11 different data cuts for informal interim analyses under separate SAPs to support publications, conference presentations, and regulatory submissions, including 2 interim CSRs. The DBL for this final CSR is planned for 24 July 2024.

5.7. Multicenter Studies

Because a small number of subjects were expected at each center, data from all centers were to be pooled for analysis.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

6.1. Analysis Populations

The number of subjects enrolled and the number and percentage of subjects in each analysis population will be summarized by cohort and the total.

A listing of subjects in the analysis populations will be provided and it will include the study stage and cohort. There will be no separate listings by stage.

6.1.1. All Enrolled Subjects

The All Enrolled Subjects population includes all subjects who entered the study, completed the study entry procedures, and satisfied the eligibility criteria for the study, based on the inclusion and exclusion criteria. This includes:

- All subjects enrolled into Cohort 1 (ie, entered any of the 4 study stages: Stage 1, Stage 2, Stage 3, and Stage 4).
- All subjects enrolled into Cohorts 2, 3, and 4.

The All Enrolled Subjects population will be used for subjects' accounting purposes, summary of demographic and baseline characteristics, protocol deviations, and for some data listings.

6.1.2. Safety Population

The Safety population consists of all enrolled subjects who were exposed to at least 1 dose of study medication.

- For Stage 1, this includes all Cohort 1 subjects who were administered at least one IV infusion of ATB200 as a single agent during Stage 1.
- For Stage 2, this includes all Cohort 1 subjects who entered Stage 2 and received at least one IV infusion of 20 mg/kg ATB200 co-administered with either 130 mg or 260 mg of AT2221.
- For Stages 3 and 4, this includes all Cohort 1 subjects who entered Stage 2 Period 5 and received at least one dose of the fixed therapy 20 mg/kg ATB200 + 260 mg AT2221, as well as all the subjects who were later enrolled into Cohorts 2, 3, and 4 in Stage 3 and received at least one dose of the study medication.

Safety analyses for Stages 1 and 2 were completed and reported in iCSR-1, and they will not be repeated in this SAP unless there has been a change in the underlying data. The plan is to copy the pertinent summaries from the iCSR-1 into the final CSR. This SAP describes the analysis of safety data covered in the last bulleted item, following the co-administration of the fixed therapy 20 mg/kg ATB200 + 260 mg AT2221. All safety analyses will be conducted on the Safety population, unless otherwise specified.

6.1.3. Efficacy Population

The Efficacy population consists of all enrolled subjects who took at least 1 dose of the study medication (20 mg/kg ATB200 + 260 mg AT2221 co-administration) in Stage 3 and had both a baseline and at least 1 post-baseline assessment for any efficacy endpoint as listed in Section 4.4

(including assessments on motor function tests, muscle strength tests, PFTs, PROs, and Global Impression of Change). That is:

- For Cohort 1, this includes all subjects who entered Stage 2 Period 5 and received at least 1 dose of the 20 mg/kg ATB200 + 260 mg AT2221 co-administration and had both a baseline and at least 1 post-baseline assessment for any efficacy endpoint.
- For Cohorts 2, 3, and 4, this includes all subjects who received at least 1 dose of the 20 mg/kg ATB200 + 260 mg AT2221 co-administration and had both a baseline and at least 1 post-baseline assessment for any efficacy endpoint.

All efficacy analyses will be based on this population, unless otherwise specified.

6.1.4. PK Population

The PK population includes all subjects who were exposed to at least 1 dose of study drug and completed at least 1 PK period. Detailed description of the PK population for noncompartmental analyses is provided in Section 12.4.4.1 of Protocol ATB200-02 and in a separate Modeling and Simulation Plan for the population PK analysis which will be referenced in the final CSR.

6.2. General Methodology and Presentation

6.2.1. General Methodology

There will be no inferential statistics as no hypothesis tests were planned for this study. In general, continuous variables will be summarized using descriptive statistics including the number of subjects (n), mean, standard deviation (SD), median, the first quartile (Q1), third quartile (Q3), minimum, and maximum. Unless otherwise stated, these summaries will be provided for the raw values, absolute change from baseline, and the percent change from baseline values. Where appropriate, a 95% confidence interval (CI) for the mean change from baseline will be provided for summary purposes. Categorical variables will be summarized using frequencies (counts) and percentages.

6.2.2. General Presentation of Data

6.2.2.1. Presentation of Baseline and Background Data

Demographics, baseline characteristics, medical and surgical history, and other background information such as falls history, prior medications, prior pre-infusion medications, and history of IARs will be presented by cohort (including the total). The displayed columns will include:

- Cohort 1, Cohort 2, Cohort 3, and Cohort 4
- Total (where Total = Cohort 1 + Cohort 2 + Cohort 3 + Cohort 4)

There will be no separate presentation of baseline and background data for the different stages of the study.

6.2.2.2. Presentation of Protocol Deviations and Concomitant Pre-infusion Medications

The presentation of protocol deviations and concomitant pre-infusion medications will be similar to that of baseline and background data in Section 6.2.2.1.

6.2.2.3. Presentation of Post-baseline Safety Data

The results of post-baseline safety analyses, including by-visit results and changes from baseline, pre-defined limits of change (PDLC) as well as concomitant medications, non-drug therapies, study drug exposure, treatment compliance, TEAEs, and TESAEs will be presented by study stage, as follows:

- Stage 1 analyses and results are presented by SAD treatment dose.
- Stage 2 analyses and results are presented by MAD treatment dose.
- Stages 3 and 4 analyses and results (starting from Stage 2 Period 5) are presented by cohort. The columns displayed will be:
  - Cohort 1, Cohort 2, Cohort 3, Cohort 4
  - Pooled ambulatory subjects (Cohort 1 + Cohort 3 + Cohort 4)
  - Total (where Total = Cohort 1 + Cohort 2 + Cohort 3 + Cohort 4)

Note: Safety analyses for Stages 1 and 2 were reported in iCSR-1 and they will not be repeated in this SAP unless there is a change in the underlying data from Stages 1 and 2. The plan is to copy the pertinent summaries from the iCSR-1 into the final CSR.

6.2.2.4. Presentation of Post-baseline Efficacy Data

Post-baseline efficacy assessments were only collected from Stage 2 Period 5 through Stages 3 and 4. Summary results, including by-visit raw values and change from baseline values, will be presented by cohort, and the columns displayed will be:

- Cohort 1, Cohort 3, Cohort 4
- Pooled ERT-experienced ambulatory subjects (Cohort 1 + Cohort 4)
- All ambulatory subjects (Cohort 1 + Cohort 3 + Cohort 4)

Note: Efficacy results for Cohort 2 (non-ambulatory subjects) will be presented separately.

6.2.2.5. Presentation of Post-baseline Pharmacodynamic Data

Analyses results for pharmacodynamic data during Stages 1 and 2 will be copied from iCSR-1 unless it is determined that the underlying data from Stages 1 and 2 have changed.

For Stages 3 and 4 (starting from Stage 2 Period 5), analyses results will be presented similarly to the presentation of efficacy data in Section 6.2.2.4.

6.3. Data Management

Data management tools and methods used in this study are in accordance with applicable Amicus standards and data cleaning procedures as defined in the Data Management Plan for this study. Clinical data were collected using an electronic case report form (eCRF). The eCRF data were entered into an electronic data capture (EDC) system that is managed by a clinical research organization (CRO). Additional protocol specified data, such as laboratory and ECG data that were collected through third party vendors were integrated with eCRF data by the CRO to create complete datasets. Datasets will be created according to Clinical Data Interchange Standards

Consortium (CDISC) standards. The most current or latest version of the Study Data Tabulation Model (SDTM, version 3.2) datasets will be used. The SDTMs, Analysis Data Model (ADaM, version 2.1) datasets, all statistical and data analyses, and summary tables will be created using SAS® software version 9.4 or later. The data specifications and reviewer's guide will also be created.

6.4. Derived and Transformed Data

6.4.1. Baseline Definition

In general, baseline assessment is defined as the last non-missing result on or prior to the administration of the first dose of study medication. Baseline definitions for different variables during specific stages of the study are provided in Table 3.

Table 3: Baseline Visit by Study Stage, Cohort, and Variable

Cohort	Assessment at Screening (V1, Days -28 to -1)	Assessment at Baseline (V2, Day 0)	Result Used as Baseline
Safety Data (including vital signs, laboratory data, ECG, PEs, etc) During Stages 1 and 2			
Cohort 1	X	X	Baseline is the last result obtained on/prior to V2; If result from V2 is unavailable, then use V1.
Note: Safety results for Stages 1 and 2 were reported in iCSR-1 and will not be repeated here.			
Safety Data During Stage 2 Period 5 and Stages 3 and 4			
Cohort 1	X	X	Baseline is the last result obtained on/prior to the start of the 20 mg/kg ATB200 + 260 mg AT2221 dose in Stage 2 Period 5. If the result from V9 is unavailable, then use V8. See Section 6.4.5.
Cohorts 2, 3, and 4	X	X	Baseline is the last result obtained on/prior to V2. If result from V2 is unavailable, then use V1.
Efficacy Data, Biomarkers, and PROs During Stage 2 Period 5 and Stages 3 and 4			
Cohorts 1, 2, 3, and 4	NA	X	Baseline will be the result obtained at V2.

Abbreviations: ECG = electrocardiogram; NA = not applicable; PEs = physical examinations (which includes brief physical examination and comprehensive physical examination); PROs = patient-reported outcomes; V = visit

6.4.2. Multiple Baseline Assessments

For continuous variables, if multiple baseline measurements were taken at the same visit, the last result prior to the first dose of study medication will be used. If it is not possible to determine the last result, then the average will be used as the baseline value for analysis purposes.

6.4.3. Change from Baseline and Percent Change from Baseline

Analysis of change from baseline will include only subjects who have assessment at both baseline and the post-baseline time point being analyzed. That is:

- Change from baseline is calculated as: Change = post-baseline result – baseline result.
- Percent change from baseline is calculated as: 100 * (Change from baseline / Baseline result).

If either the baseline or the post-baseline result is missing, the change from baseline and the percentage change from baseline are set to missing.

6.4.4. Baseline Age and Other Age Definitions

Baseline age (in years) is the subject's enrollment age calculated as: FLOOR([date of informed consent – date of birth] / 365.25), where FLOOR( ) function returns the integer part of the result.

Age (years) at Pompe disease diagnosis is calculated as: FLOOR([date of Pompe disease diagnosis – date of birth] / 365.25).

For subjects who are ERT-experienced (ie, subjects in Cohorts 1, 2, and 4), the age (years) at start of first ERT is calculated as: FLOOR([date of ERT initiation – date of birth + 1] / 365.25).

6.4.5. Study Day (Relative Day)

The reference start day is defined for Cohort 1 and for Cohorts 2, 3, and 4 as follows:

- For Cohort 1: Visit 9 (Day 85 in Stage 2, Period 5) is considered the reference start day. This is the day of first dose of the 20 mg/kg ATB200 + 260 mg AT2221 co-administration.
- For Cohorts 2, 3, and 4: The study Day 1 in each cohort is the reference start day.

There will be no Day 0. If the date of interest occurs on or after the reference start day, then the relative study day is calculated as: (date of interest – date of reference start day + 1).

Note: The appropriate reference start day should be used depending on whether the summary involves Cohort 1 or Cohorts 2, 3, and 4. For example, for Cohort 1, the relative day of the assessment at V12 will be calculated as: date of V12 – 85 + 1 (ie, Day 43).

If the date occurs before the reference start day, then study day is calculated as: (date of interest – date of reference start day). Thus, days before the reference start day will have a negative day displacement. For example, for Cohort 1, the relative day of the assessment at the efficacy baseline (V2) will be calculated as: date of baseline assessment – 85.

6.5. Analysis Visit Windows

Analysis visit windows will be used for the per-visit analyses.

6.5.1. Visit Windows for Cohort 1 Data

For the analysis of Cohort 1 data (both safety and efficacy), the visit windows in Table 4 will be used. A general formula for deriving the visit windows is given in the footnotes. A summary at the last assessed value (LAV) will be provided for the efficacy analyses.

Table 4: Visit Windows for Analysis of Cohort 1 Safety, Efficacy, and Pharmacodynamic Data

	Days Based on the Original Study Reference Start Day (Visit 2)		Days Based on the Re-scaled Reference Start Day (Visit 9)	
Visit Name	**Target Day**[a]	**Analysis Visit Windows**	**Target Day**[b]	**Analysis Visit Windows**
Baseline[c]	1	See Section 6.4.1	1	See Section 6.4.5
Visit 10	99	Day 93 – 106	15	Day 9 – 22
Visit 11	113	Day 107 – 120	29	Day 23 – 36
Visit 12	127	Day 121 – 172	43	Day 37 – 88
Month 3	217	Day 173 – 262	133	Day 89 – 178
Month 6	307	Day 263 – 352	223	Day 179 – 268
Month 9	397	Day 353 – 442	313	Day 269 – 358
Month 12	487	Day 443 – 532	403	Day 359 – 448
Month 15	577	Day 533 – 622	493	Day 449 – 538
Month 18	667	Day 623 – 712	583	Day 539 – 628
Month 21	757	Day 713 – 802	673	Day 629 – 718
Month 24	847	Day 803 – 937	763	Day 719 – 853
Month 30	1027	Day 938 – 1117	943	Day 854 – 1033
Month 36	1207	Day 1118 – 1297	1123	Day 1034 – 1213
Month 42	1387	Day 1298 – 1477	1303	Day 1214 – 1393
Month 48	1567	Day 1478 – 1657	1483	Day 1394 – 1573
Month 54	1747	Day 1658 – 1837	1663	Day 1574 – 1753
Month 60	1927	Day 1838 – 2017	1843	Day 1754 – 1933
Month X[d]	$T_{MONTH\ X}$	d1 – d2	$T_{MONTH\ X}$	d3 – d4
LAV[e]	Target day corresponding to the LAV	Visit window corresponding to the LAV	Target day corresponding to the LAV	Visit window corresponding to the LAV

Abbreviations: LAV = last assessed value; PRO = patient-reported outcome; V = visit

Note: Analysis visit windows have been presented based on both the original study reference day (as per the Study Data Tabulation Model [SDTM] datasets) and the re-scaled referenced start day (to create the Analysis Data Model [ADaMs] datasets).

[a] Cohort 1 target day starting from V2. Cohort 1 visits in Stages 3 and 4 designated as 'Month 3,' 'Month 6,' etc, are designed to ensure alignment with similarly labeled visits in Cohorts 2, 3, and 4 in order to facilitate by-visit comparisons among the cohorts. However, the target day corresponding to a Cohort 1 visit at Month X occurs at approximately (X * 30) days after Visit 12 (Day 127). For example, the target day for Month 3 is approximately at Day 3 * 30 + 127 = 217.

[b] Cohort 1 target day for Month X (starting from V9) is determined as (X * 30) + 43. For example, the target day for Month 3 is approximately at Day 3 * 30 + 43 = 133.

[c] For safety analysis by visit, baseline is taken from Visit 9 (Day 85), but for efficacy, biomarker, and PRO analyses, baseline value is taken from Visit 2 (Day 1). See Section 6.4.1 and Section 6.4.5.

[d] T_X is the target day of planned assessment visit at Month X.

- If the derivation starts from the original study day at V2, then: $T_{MONTH\ X} = (30 * X + 127)$. For example, the target day at Month 54 = $T_{MONTH\ 54} = 30 * 54 + 127 = 1747$. Target day of the assessment visit immediately before Month X is given by T_{BEFORE}. For example, $T_{BEFORE} = T_{48} = (30 * 48 + 127) = 1567$. Target day of the assessment visit immediately after Month X is given by $T_{AFTER} = T_{60} = (30 * 60 + 127) = 1927$. The visit windows are then given as d1 – d2, where $d1 = ([T_{BEFORE} + T_{MONTH\ X}] / 2) + 1$ and $d2 = (T_{MONTH\ X} + T_{AFTER}) / 2$.
- If the derivation starts from Visit 9, then target day at Month X is given by $T_{MONTH\ X} = (30 * X + 43)$. For example, the target day at Month 54 is $T_{MONTH\ 54} = 30 * 54 + 43 = 1663$. Target day of the assessment visit immediately before Month X is given by T_{BEFORE}. For example, $T_{BEFORE} = T_{48} = (30 * 48 + 43) = 1483$. Target day of the assessment visit immediately after Month X is given by $T_{AFTER} = T_{60} = (30 * 60 + 43) = 1843$. Visit windows are given as d3 – d4, where $d3 = ([T_{BEFORE} + T_{MONTH\ X}] / 2) + 1$ and $d4 = (T_{MONTH\ X} + T_{AFTER}) / 2$.

[e] LAV represents the result obtained from the subject's last visit of assessment. Summary at the LAV will only be provided for the efficacy analyses.

Efficacy data will be summarized at: Baseline (Visit 2), Visit 12, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, and every 6 months thereafter in Stage 4. Safety data will be summarized at: Baseline (Visit 9), Visit 10, Visit 11, Visit 12, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, and every 6 months thereafter in Stage 4.

6.5.2. Visit Windows for Cohorts 2, 3, and 4 Data

For Cohorts 2, 3, and 4, the visit windows in Table 5 will be used for analyses of safety and PD markers, and Table 6 for the efficacy data.

Table 5: Visit Windows for Analyses of Cohorts 2, 3, and 4 Safety and Pharmacodynamic Data

Visit Name	Target Day	Visit Windows
Baseline	NA	Baseline is Visit 2
Day 1	1	Day 1 is Visit 3
Week 2	15	Day 2 – 22
Week 4	29	Day 23 – 60
Month 3	91	Day 61 – 136
Month 6	181	Day 137 – 226
Month 9	271	Day 227 – 316
Month 12	361	Day 317 – 406
Month 15	451	Day 407 – 496
Month 18	541	Day 497 – 586
Month 21	631	Day 587 – 676
Month 24	721	Day 677 – 811
Month 30	901	Day 812 – 991
Month 36	1081	Day 992 – 1171
Month 42	1261	Day 1172 – 1351
Month 48	1441	Day 1352 – 1531
Month 54	1621	Day 1532 – 1711
Month 60	1801	Day 1712 – 1891
Month X[a]	$T_{MONTH\ X}$	d1 – d2

Abbreviation: NA = not applicable

[a] Target day of planned assessment visit at Month X is denoted $T_{MONTH\ X}$ and it is given by $T_{MONTH\ X} = (30 * X + 1)$. For example, the target day at Month 54 = $T_{MONTH\ 54} = 30 * 54 + 1 = 1621$. Target day of assessment visit immediately before Month X is given by T_{BEFORE}. For example, $T_{BEFORE} = T_{48} = (30 * 48 + 1) = 1441$. Target day of assessment visit immediately after Month X is given by T_{AFTER}. For example, $T_{AFTER} = T_{60} = (30 * 60 + 1) = 1801$. The visit windows are then given as d1 – d2, where $d1 = ([T_{BEFORE} + T_{MONTH\ X}] / 2) + 1$ and $d2 = (T_{MONTH\ X} + T_{AFTER}) / 2$.

Table 6: Visit Windows for Analyses of Cohorts 2, 3, and 4 Efficacy Data

Visit Name	Target Day	Visit Windows
Baseline	NA	NA (Baseline is Visit 2)
Month 3	91	Day 61 – 136
Month 6	181	Day 137 – 226
Month 9	271	Day 227 – 316
Month 12	361	Day 317 – 406
Month 15	451	Day 407 – 496
Month 18	541	Day 497 – 586
Month 21	631	Day 587 – 676
Month 24	721	Day 677 – 811
Month 30	901	Day 812 – 991
Month 36	1081	Day 992 – 1171
Month 42	1261	Day 11872– 1351
Month 48	1441	Day 1352 – 1531
Month 54	1621	Day 1532 – 1711
Month 60	1801	Day 1712 – 1891
Month X[a]	$T_{MONTH\ X}$	d1 – d2
LAV	Target day corresponding to the LAV	Visit window corresponding to the LAV

Abbreviations: LAV = last assessed value; NA = not applicable

[a] Target day of planned assessment visit at Month X is denoted $T_{MONTH\ X}$ and it is given by $T_{MONTH\ X} = (30 * X + 1)$. For example, the target day at Month 54 = $T_{MONTH\ 54} = 30 * 54 + 1 = 1621$. Target day of assessment visit immediately before Month X is given by T_{BEFORE}. For example, $T_{BEFORE} = T_{48} = (30 * 48 + 1) = 1441$. Target day of assessment visit immediately after Month X is given by T_{AFTER}. For example, $T_{AFTER} = T_{60} = (30 * 60 + 1) = 1801$. The visit windows are then given as d1 – d2, where $d1 = ([T_{BEFORE} + T_{MONTH\ X}] / 2) + 1$ and $d2 = (T_{MONTH\ X} + T_{AFTER}) / 2$.

6.6. Multiple Assessments in a Visit Window

Data from both scheduled and unscheduled visits as well as early termination (ET) visits that are within 30 days of the last ATB200 infusion visit will be considered in determining values for specified visit windows. Assessments from ET visits that are more than 30 days from the last ATB200 infusion will not be used.

No rules will be implemented for reassigning/remapping missing visits due to COVID-19 related reasons to address delayed visits.

If multiple assessments (eg, from scheduled and unscheduled visits, as well as ET visits that are within 30 days of the last ATB200 infusion visit) 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 average value will be used.

6.7. Completion of Study

The Study Completion page in the eCRF was designed to cover the entire study duration so that an answer of "Yes" to the question "Did the subject complete the study?" defines a completer for the study. It is checked "No" for subjects who withdraw from the study, and the checkbox is expected to remain blank for subjects who are ongoing in the study. Therefore, in order to determine the study completion/discontinuation during different stages of the study, the study dose administration records and the duration of exposure should be used together to make that determination.

Unless otherwise stated, completion during the 4 stages of the study is defined as follows:

- Stage 1 completers refer to the Cohort 1 subjects who completed Stage 1 of the study.
- Stage 2 completers refer to the Cohort 1 subjects who completed Stage 2 of the study.
- Stage 3 completers include all subjects who completed Stage 3 (24 months treatment with 20 mg/kg ATB200 + 260 mg AT2221 co-administration).
- Stage 4 completers (ie, also referred to as 'study completers') include all subjects who continued in the study until they transitioned to commercial product or until study closeout by the sponsor during Stage 4.

  Note: The plan is to consider those subjects who were moved into an ongoing EAP study due to unavailability of commercial product in their home countries as study completers.

The study completion summary will be included in the overall disposition summary table.

7. STUDY POPULATION

7.1. Subject Disposition

The count and percentage of subjects who entered, who completed, or who discontinued prematurely from the study during Stage 1, Stage 2, Stage 3, and Stage 4 and the reasons for discontinuation will be presented. The summary will be conducted on the All Enrolled Subjects population and will include:

- Number of subjects who entered Stage 1 and the number of subjects who completed Stage 1 (presented by SAD treatment dose)
- Number of subjects who entered Stage 2 and the number of subjects who completed Stage 2 (presented by MAD treatment dose)

  Note: The summaries for the above items were previously reported in iCSR-1 and will not be repeated in this SAP, as the data are not expected to change. For the final CSR, the plan is to copy the pertinent summaries from iCSR-1.
- Number of subjects who entered Stage 3 (presented by cohort, including the total):
  - Number of subjects who completed Stage 3
  - Number of subjects who discontinued study prematurely in Stage 3
  - Reasons for discontinuation during Stage 3
- Number of subjects who entered Stage 4 (presented by cohort, including the total):
  - Number of subjects who completed Stage 4 (ie, study completers)
  - Number of subjects who discontinued study prematurely in Stage 4
  - Reasons for discontinuation during Stage 4
- Overall number of subjects who completed the study:

  Note: This is based on the checkboxes marked “Yes” in the study completion page of the eCRF, and it should be equal to the number of Stage 4 completers.
  - Overall number of subjects who discontinued study prematurely
  - Reasons for study discontinuation overall

A listing of all disposition data will be provided in subject-level data listings. There will be no separate listings by stage.

7.2. Screened Subjects and Screen Failures

The number of subjects screened and the number who passed/failed screening will be presented overall in a single column (ie, the total column) in the disposition table. Demographic data for screen failures will be provided in individual subject-level data listings.

7.3. Protocol Deviations

Protocol deviation data are collected from the clinical research associates' monitoring reports and consolidated into a deviation log at PRA International (now ICON), and then transferred to Amicus for review on an ongoing basis. According to the protocol deviation plan for the study, deviations are classified as either important or not important. Important protocol deviations will be summarized cumulatively across all study stages by deviation type, based on the All Enrolled Subjects population using the methodology described in Section 6.2.1, and presented by cohort as outlined in Section 6.2.2.2. A subject-level data listing of all protocol deviations will be provided showing, among other items, the cohort in which the subject belongs, deviation type/code, deviation date, deviation description, and whether or not the deviation was classified as an important deviation (Y/N).

7.4. Demographic and Baseline Characteristics

The baseline and demographic characteristics and other related baseline information will be summarized on the All Enrolled Subjects population using the methodology described in Section 6.2.1 and presented by cohort as outlined in Section 6.2.2.1. A listing of all baseline information will be provided. Demographic and baseline characteristics to be presented in the summary table include:

- Age (at informed consent date in years), both as a continuous parameter and by categories of 18 to 64, and ≥ 65
- Sex
- Race
- Ethnicity (for sites in US only)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2). BMI will be calculated as body weight (kg)/body height^2 (m^2).

The following Pompe disease history information will be summarized with descriptive statistics for the All Enrolled Subjects population.

- Number and percentage of subjects with more than 2 years of experience of ERT (Y/N)
- Frequency of ERT infusion
- Dose of ERT
- Duration of ERT infusion

The following information related to falls history will be summarized with descriptive statistics for the All Enrolled Subjects population:

- Number of falls in the past 30 days (prior to enrollment date)
- Number of falls in the past 1 year (prior to enrollment date)
- Change in the rate of falling in the past 1 year (decreased, no change, increased)

7.5. Listing of Subjects' Inclusion and Exclusion Criteria

A listing of subjects' inclusion and exclusion criteria will be provided showing which specific eligibility criteria were met/not met.

7.6. Medical History and Surgical History

All adverse events (AEs) and surgical history that occurred prior to the first dose of study medication in Stage 1 (ie, before Stage 1 Period 1) will be considered as medical history. Medical history will be summarized on the All Enrolled Subjects population based on the methodology described in Section 6.2.1 and presented as outlined in Section 6.2.2.1. There will be no separate summaries for each stage of the study.

Past IARs and medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 23.0 into system organ class (SOC) and preferred term (PT). Medical history will then be summarized by SOC and by PT within each SOC for the Safety population, with both the SOCs and the PTs within the SOCs sorted by decreasing frequency in the total column. A listing of medical history will be provided and will include the investigator verbatim as well as the PTs and SOCs. Past IARs will be presented in a similar fashion but will be summarized by SOC, PT, and severity.

Note: Medical and surgical history summaries and listings were previously reported in iCSR-1 and will not be repeated in this SAP unless there has been a change in the underlying data. If there has been a change in the underlying data, then the changes in medical history will be identified in the data listings. Otherwise, for the final CSR, the plan is to copy the pertinent summaries from iCSR-1.

7.7. Prior and Concomitant Medications and Non-drug Therapies

Prior medications and non-drug therapies are defined as medications and non-drug therapies taken or occurring prior to the first dose of the study medication. These will be summarized 2 ways, as follows:

- Prior medications and non-drug therapies that were taken or occurring prior to the first dose of study medication (before Stage 1 Period 1). Note: These were reported in iCSR-1 and will not be repeated in this SAP, as the results are not expected to change.
- Prior medications and non-drug therapies that were taken or occurring prior to the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study medication (in Stage 2 Period 5, Visit 9).

Concomitant medications and non-drug therapies include medications with onset dates on or after the first dose of study medication, medications with onset dates prior to the first dose of study medication without a stop date, or medications with a stop date after the first dose of study medication. A single medication or therapy may be both concomitant and prior. These will be summarized by study stage, as follows:

- For Stage 1: Concomitant medications and non-drug therapies with onset dates on or after the first dose of study medication Stage 1, which will be presented by the SAD treatment dose
- For Stage 2: Concomitant medications and non-drug therapies with onset dates on or after the first dose of study medication Stage 2, which will be presented by the MAD treatment dose
- For Stages 3 and 4: Concomitant medications and non-drug therapies with onset dates on or after the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study medication (in Stage 2 Period 5)

Prior and concomitant medications and non-drug therapies will be coded to indication-specific Anatomical Therapeutic Chemical (ATC) classification and preferred name using the World Health Organization Drug Dictionary (WHODD, 01 MARCH 2020 DDE B3) and then summarized by level 4 ATC and preferred name using number and percentage of subjects on the Safety population. The summary will be based on the methodology described in Section 6.2.1 and presented as outlined in Section 6.2.2.3.

Medications and non-drug therapies will be sorted alphabetically by ATC and preferred name within ATC. Subjects with multiple occurrences of a medication in ATC and preferred name will only be counted once within each ATC and preferred name. Because medications are coded to ATC by indication, preferred names may appear under multiple ATCs.

A listing of all medications, both prior and concomitant, will be presented. Any abbreviations and codes will be clearly explained on each page of the listing. The listing will be sorted by cohort (and/or treatment dose) and subject identifier and will include level 4 ATC name, preferred name, reported medication name, dose, route of administration, dosing frequency, start date/study day, end date/study day, indication, and period of medication (prior only, concomitant only, prior and concomitant). Investigator verbatim as well as coded terms will be included in the listings. Non-drug therapies will be similarly listed.

7.8. Prior and Concomitant Pre-infusion Medications

Pre-infusion medications are medications administered to subjects prior to infusion with ATB200 to prevent IARs. Both prior pre-infusion medication (taken before the first dose of cipaglucosidase alfa IV infusion study drug) as well as concomitant pre-infusion medications taken 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 cumulatively by cohort (including total) for the Safety population.

For the prior pre-infusion medication summary, the presentation will include a row for the number (n) and percentage (%) of subjects who used any prior pre-infusion medications.

For concomitant pre-infusion medications (taken during study), the presentation will include rows for the:

- Number (n) and percentage (%) of subjects who used concomitant pre-infusion medications.
- Number (n) and percentage (%) of subjects who continued with their prior pre-infusion medications.
- Number (n) and percentage (%) of subjects who initiated at least 1 pre-infusion medication during the study (regardless of whether they had received that medication in the past).

A listing of all pre-infusion medications will be provided, and this display will include columns for subject ID, Cohort, ATC Level 4/drug name/report name, start date and time relative to original study Day 1, end date and time relative to original study Day 1, and dose (unit)/route/frequency. Flags will be added to this listing to indicate whether the medication was:

- Only used as a prior pre-infusion medication,
- Used as a concomitant pre-infusion medication,
- Used as both prior and concomitant pre-infusion medication, and
- Used as a concomitant pre-infusion medication that was initiated during the study (regardless of whether it had been used in the past) but not as a prior pre-infusion medication that continued on to become a concomitant medication.

8. PHARMACOKINETIC AND IMMUNOGENICITY EVALUATION

8.1. Pharmacokinetic Analysis

This SAP does not cover the evaluation of PK data. Noncompartmental PK-related analyses were described in Section 12.4.4.1 of Protocol ATB200-02, and population PK-related analyses were described in a separate Modeling and Simulation Plan and reported in iCSR-1. These included the noncompartmental analyses, including treatment or population comparisons or dose proportionality assessments of primary PK parameters and population PK analysis from plasma total GAA protein by signature peptides T09 and T50 (as measured by liquid chromatography coupled to tandem mass spectrometry [LC-MS/MS method]) and plasma AT2221 (as measured by LC-MS/MS assay).

No PK samples have been collected in this study since iCSR-1, so the pertinent summaries from the previous iCSR-1 will be copied into the final CSR with reference to the relevant Modeling and Simulation Plan in the CSR.

8.2. Immunogenicity Analysis

This SAP does not cover the evaluation of IMG data. The analysis of IMG data including the evaluation of anti-rhGAA antibodies (total and neutralizing), cross-reactivity of anti-rhGAA antibodies to alglucosidase alfa, pro-inflammatory cytokines, and other biomarkers of immune system activation, as well as the impact of anti-rhGAA antibodies on PK, PD, safety, and efficacy, will be covered in a separate Modeling and Simulation Plan.

9. EFFICACY EVALUATION

9.1. Statement of the Null and Alternative Hypotheses

No hypothesis testing was planned for this study.

9.2. Multiple Comparisons/Multiplicity

No adjustment for multiplicity is planned for this study.

9.3. Adjustments for Covariates/Prognostic Variables

No adjustments for covariates are planned in the statistical analyses.

9.4. Analysis of Efficacy Variables

All efficacy analyses will be conducted on the Efficacy population using the summary statistics defined in Section 6.2.1 and presented as described in Section 6.2.2.4. By-visit summaries will be based on the analysis visit windows defined in Section 6.5, which includes summary at baseline, every 3 months in Stage 3, and every 6 months in Stage 4. All efficacy data will be listed in subject-level data listings. See Appendix 1 for the description of the endpoints as well as the derivation of the % predicted 6MWD, % predicted MIP, % predicted MEP, % predicted SNIP, and the total scores for the FSS, RHS, MMT, R-PAct, GSGC, and the PROMIS scales.

9.4.1. Motor Function Tests

Motor function tests (MFTs) will be summarized for all ambulatory subjects (that is, Cohorts 1, 3, and 4). The time in seconds (s) that the subject takes to accomplish each task (ie, Gowers' maneuver, 10MWT, 4-stair climb, chair test, and TUG) will be summarized. The assigned functional scores, which indicate the level of difficulty with which the subject performed the task, will be analyzed as continuous variables. The actual score, absolute change, and percent change from baseline in the test scores will be summarized.

The GSGC score will be analyzed as a continuous variable. The actual score, absolute change, and percent change from baseline will be summarized.

The 6MWD and % predicted 6MWD will be summarized for the actual value, absolute change, and percent change from baseline value. A listing of the data for each MFT including individual scores and summary scores will be provided.

9.4.2. Muscle Strength Tests

The MMT summary scores will be provided for the following:

- Body part (shoulder, elbow, knee, and hip)
- Proximal muscles (shoulder and hip)
- Body side (lower, upper)
- Total MMT

Ambulatory subjects were expected to perform all muscle tests, while non-ambulatory subjects were to perform only the upper body muscle tests.

The MMT score at each visit is calculated only if the subject has the corresponding test scores for all applicable muscle groups. The MMT scores will be analyzed as continuous variables at each scheduled visit. The actual score and absolute change from baseline in the MMT scores will be summarized. No percent change from baseline analysis will be performed for the MMTs. A listing of the data for all MMT scores (including individual scores and summary scores) will be provided.

The QMTs will be summarized for the body part, proximal muscles, body side, and total. The actual value, absolute change, and percent change from baseline in the QMT values will be presented. A listing of the data for all QMTs including individual scores and summary scores will be provided.

9.4.3. Pulmonary Function Tests

Pulmonary function tests including sitting and supine FVC, percent predicted FVC, MEP, percent predicted MEP, MIP, percent predicted MIP, SNIP, and percent predicted SNIP will be summarized for ambulatory subjects and for non-ambulatory subjects without invasive ventilatory support. The actual (absolute) value, absolute change, and percent change from baseline in each PFT will be summarized at each visit.

Note: For this study, the spirometer's software has already been programmed to display the correct spirometry predicted values for the subject's age at each session. This means, for example, that the sitting % predicted FVC values are already age-adjusted.

A listing of the lower limit of normal (LLN) values for MIP and MEP for each subject at different time points will be provided. This listing will help identify subjects who had values below the LLN but recovered due to treatment, by having increasing MIP and MEP values above the LLN.

9.5. Patient-reported Outcomes

For each PRO instrument including R-PAct scale, RHS, FSS, and PROMIS scales, the total score is obtained by summing up the individual scores. Summaries will be provided at baseline, Visit 12 and every 3 months in Stage 3, and every 6 months in Stage 4. The actual total score, absolute change, and percent change from baseline in the total score at each visit will be summarized at each visit. The PROMIS scale was introduced in the middle of the study and so baseline scores will not be available. A subject listing of each individual PRO will be provided.

9.6. Global Impression of Change

The SGIC and PGIC were only administered at post-baseline visits in Stages 3 and 4, starting from Month 3. Each answer connotes a change in the subject's status at the current visit relative to baseline. A ternary response variable is created as: "Improved" = score of 5 or higher, "No change" = score of 4, or "Declining" = score of 3 or lower. The number and percentage of subjects with the ternary response will be summarized at each visit.

9.7. Handling of Dropouts or Missing Data

The efficacy and safety analysis will be based on observed values. However, summary at the LAV will be provided for the efficacy analyses (see Section 6.5).

9.8. Examination of Subgroups

Apart from the analysis by cohort, no other subgroup analyses will be conducted due to the small number of subjects enrolled in each study cohort.

10. SAFETY EVALUATION

All safety evaluations will be conducted on the Safety population using the summary statistics defined in Section 6.2.1 and presented as described in Section 6.2.2.3. By-visit safety summaries will be performed using the analysis visit windows defined in Section 6.5. Unscheduled visits will be included in all summaries, including the summaries that evaluate the PDLCs.

10.1. Missing Adverse Event Onset Date, Intensity, and Relationship

10.1.1. Missing or Partial Adverse Event Onset Date or Medication Start Date

Complete dates will be imputed from partial dates of AEs and medications solely for the purpose of defining treatment emergence for AEs and prior/concomitant status for medications. Dates will be defined using the hierarchy of derivations below.

Algorithm for imputing missing or partial AE or medication start date:

1. If year is not missing and is after the year of first application of study drug:

   If month is missing, then impute month as January.

   If day is missing, then impute day 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 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 month as the month of the first application of study drug.

   If day is missing, then impute 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 AE is treatment-emergent for the purpose of the analysis.

10.1.2. Missing or Partial Medication Stop Date

References to month are the 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 created be 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.

No imputations will be applied to AE stop dates.

10.1.3. Missing Intensity and Relationship

If intensity is missing for any AE or TEAE, then its intensity will be classified as "severe" in the summary tables. If the assessment of relationship of the TEAE to study drug is missing, it will be classified as "related" in the summary tables.

However, 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.

10.2. Extent of Exposure and Compliance

The extent of exposure (duration of treatment) is defined as the number of days on treatment.

For Stages 1 and 2, duration will be calculated as (date of last dose – date of first dose + 1) / 30.4. The duration of exposure and compliance during Stages 1 and 2 were reported in iCSR-1 and will not be repeated here, as the data are not expected to change.

From Stage 2 Period 5 through Stages 3 and 4, duration is calculated as:
Duration (months) = (date of last dose in ATB200-02 as of the data cutoff date – date of first dose of 20 mg/kg ATB200 + 260 mg AT2221 study drug [in Stage 2 Period 5] + 1) / 30.4.

The study drug exposure and compliance starting from the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug in Stage 2 Period 5 will be summarized for ATB200 and AT2221 separately. Dose completion, treatment duration, and treatment compliance will be tabulated. A frequency distribution for the number of treated subjects and descriptive statistics for the duration of treatment (months) and compliance will be provided. The number and percentages of subjects will be tabulated by the extent of exposure categorized into months as: < 6, 6 to < 12, 12 to < 18, 18 to < 24, 24 to < 30, 30 to < 36, and ≥ 36.

Compliance for each subject taking ATB200 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/kg] / total infusion dose planned or intended [mg/kg]) starting from the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug in Stage 2 Period 5.

Compliance based on the number of infusions is calculated as:

> 100 * (number of infusions administered / number of infusions planned or intended) starting from the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug in Stage 2 Period 5.

Compliance for each subject taking AT2221 will be calculated as:

> 100 * (total dose administered [mg] / total dose scheduled or planned dose [mg]) starting from the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug in Stage 2 Period 5.

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

10.3. Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs whose onset occurs after receiving the study medication. Treatment-emergent AEs that occurred during Stages 1 and 2 have been reported in iCSR-1 and will not be repeated here unless the underlying data have changed.

The SAP describes the events that occurred starting from the administration of 20 mg/kg ATB200 + 260 mg AT2221 in Stage 2 Period 5 through Stages 3 and 4. Events which occur more than 30 days after the last dose of study medication will not be considered as treatment-emergent. Adverse events with an unknown date of onset and a stop date after the start of the study period or unknown will be included as TEAEs. Any AE with a start date equal to the date of first dose, where the time of the AE cannot definitively place the start of the AE prior to the first dose, will be considered as treatment-emergent. If any AE records contain only partial dates, these will be handled by imputation as described in Section 10.1.1. All AEs will be provided in data listings, and those that are treatment-emergent will be flagged in the listings.

Adverse events will be summarized using number and percentage as described in Section 6.2.1. Incidence rate of AEs by patient-years of exposure will also be summarized.

10.3.1. Summary of Treatment-emergent Adverse Events

An overall summary of TEAEs table will be presented, and it will include the following events:

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

In addition, summary tables will be presented for each of the individual events listed above. The number and percentage of subjects who experienced TEAEs will be presented by SOC and by PT within SOC, and separately by PT only. The SOCs will be sorted alphabetically, and the PTs will be sorted by descending frequency within the SOCs based on the total column. A subject will be counted only once within the same SOC and within the same PT.

The cumulative number and percentage of subjects with TEAEs will be summarized by intensity (mild, moderate, severe), and by relationship to study drug ('related' versus 'not related'). If a subject experienced more than 1 TEAE within different intensity or relationship categories within the same SOC/PT, only the worst case (worst intensity and related TEAE) will be reported.

All AEs (including TEAEs and non-TEAEs) 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 intensity, the relationship to each individual study drug (for TEAEs), duration, the action taken, and the outcome. All TEAEs will be flagged in the listing.

Separate listings will also be generated for deaths, serious adverse events (SAEs), and discontinuations due to TEAEs.

10.3.2. TEAEs Reported as Infusion-associated Reaction

For any AE, the reporting investigator is requested to enter onto the AE eCRF whether the AE is deemed to be an IAR and determine its relationship to each of the study drug components (ATB200 and AT2221).

To further characterize TEAEs considered by the reporting investigators to be IARs, a summary table of TEAEs reported as IARs will be provided. The number and percentage of subjects who experienced IARs will be presented by SOC and by PT within SOC. A subject will be counted only once within the same SOC and within the same PT.

A summary of IARs will also be presented for relationship to each treatment component (ATB200 and AT2221) as well as for the co-administration. Additional summary outputs (tables and/or plots) will be provided to describe the clinical characteristics of the IARs by treatment group, including the event rates, changes in intensity over time, and time to first IAR (as described in Section 10.3.3.2). The IAR summary will also be presented by prior history of IARs (yes/no).

A listing that includes treatment-emergent IARs, serious IARs, IAR-related deaths, and IARs leading to study drug discontinuation will be provided. 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-medication was given, number of infusions received, number of infusions that were

associated with IARs, percentage of infusions associated with IARs, and a sequential/horizontal listing of the number of IARs corresponding to (or associated with) each infusion.

A summary of the number of subjects with TEAEs that are IARs (ie, IAR-TEAEs), the total number of IARs, and the number of subjects with 1, 2, 3 to 4, or ≥ 5 IARs will be presented.

To characterize the overall number of infusions associated with IARs during the study, the following will be summarized:

- For all subjects (regardless of whether they experienced an IAR), the overall total number of infusions administered during the study, and the number and percentage of infusions administered that were associated with IARs;
- For subjects who experienced IARs, the total number of infusions administered, and the number (and percentage) of infusions administered that were associated with IARs.

10.3.3. Additional Analysis of IARs

10.3.3.1. Analysis by Onset Intervals

The onset intervals (in months), defined relative to the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug, will be: ≤ 6, > 6 to ≤ 12, > 12 to ≤ 18, > 18 to ≤ 24, and > 24. For Cohort 1 subjects, the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug happened in Stage 2 Period 5.

The event rates and changes in intensity over time (over these intervals) will be summarized. This analysis will further describe the clinical characteristics of IARs, and it can help determine whether the IARs disappear over time or appear late.

10.3.3.2. Analysis of Time to First IAR-TEAE

The number of subjects with IARs and the onset dates of the IARs are already available in the database. For each of these subjects, the time (in weeks) starting from the first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug to the onset of the first TEAE that is an IAR (ie, IAR-TEAE) will be calculated as: Time to first IAR-TEAE (weeks) = (date of the first IAR-TEAE while using the 20 mg/kg ATB200 + 260 mg AT2221 dose – date of first dose of the 20 mg/kg ATB200 + 260 mg AT2221 study drug + 1) / 7.

This analysis does not include subjects who have no IARs. The calculated times will be summarized as described in Section 6.2.1 to obtain the mean time to the first IAR-TEAE.

10.3.3.3. Analysis by Time After Infusion

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

- 0 to < 2 hours, 2 to < 6 hours, 6 to < 12 hours, 12 to < 24 hours (1 day), 1 to < 4 days (96 hours), or the time just before the next dose of study drug.

The event rates and changes in intensity over time (over these intervals) will be summarized as described in Section 6.2.1. This analysis will help to describe the clinical characteristics of IARs and anaphylactic reactions.

10.3.4. Describing Relationship to Study Drug

For each AE entered on the AE eCRF, the reporting investigator was asked to assess the relationship to both infusion drug (ATB200) and capsule (AT2221). The relationship to each study drug will be presented by 2 categories:

- "related," which includes possibly related, probably related, and definitely related, as reported by the investigator
- "not-related," which includes unrelated and unlikely related, as reported by the investigator

To describe the overall relationship to study drug, 2 approaches will be presented:

1. Based on the pooling into one designation of the 2 individual relationships to ATB200 and AT2221:
    a. If the 2 categories of the individual relationships are discordant (ie, "related" to one and "not related" to the other), the pooled designation will be considered "related."
    b. If the 2 categories of the individual relationships are concordant (ie, "related" to both, or "not related" to both), the pooled designation will be concordant with the individual categories.
2. Based on the assessment of causality to the individual component, yielding these possible combinations:
    a. "related" to ATB200 – "related" to AT2221
    b. "related" to ATB200 – "not related" to AT2221
    c. "not related" to ATB200 – "related" to AT2221
    d. "not related" to ATB200 – "not related" to AT2221

10.4. Clinical Laboratory Evaluation

Laboratory data will be collected and processed via a central laboratory, QLab, and presented in standard international (SI) units. Lab data will be summarized using the descriptive statistics described in Section 6.2.1 and presented based on the descriptions in Section 6.2.2.3. Clinical laboratory results collected during Stages 1 and 2 have been reported in iCSR-1 and will not be repeated here unless the underlying data have changed. These results will be referenced in the final CSR.

The rest of this section describes the analysis of laboratory data collected during Stage 2 Period 5 through Stages 3 and 4. The clinical lab parameters are presented in Table 7.

Table 7: Clinical Laboratory Parameters

Serum Chemistry	
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
Hematology	
Platelet count	Automated WBC differential
Red blood cell count	Neutrophils
WBC count (absolute)	Lymphocytes
Hematocrit	Monocytes
Hemoglobin	Eosinophils
	Basophils
Urinalysis	
Color	Ketones
Appearance	Blood
Specific gravity	WBC
pH	Nitrite
Protein	Bilirubin
Glucose	Microscopy of sediment
Urine hexose tetrasaccharide (Hex4)	

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

Quantitative laboratory results will be summarized for hematology, serum chemistry, and selected urinalysis parameters. The actual values, absolute change from baseline, and percent change from baseline will be summarized. Figures of mean (± SE) absolute change from baseline will be plotted for ALT and AST, and the mean ± SD values at baseline will be indicated in a legend for the plots.

Laboratory results will be presented in an appendix data listing for each lab panel (chemistry, hematology, and urinalysis). The listing will include the stage, cohort, treatment dose, subject, visit, and parameter. Laboratory values outside of the normal range will be flagged. Categorical urinalysis findings and urine pregnancy results will be presented in appendix data listings only.

The percentage of subjects with specific treatment-emergent laboratory values (ie, lab values collected after the first dose in Stage 2 Period 5) that meet the PDLC criteria shown in Table 8 by parameter will be summarized altogether (over the duration from first dose in Stage 2 Period 5 through Stages 3 and 4 to the DBL date), not by visit. The incidence rates of PDLCs will be presented. Unscheduled visits will be included in evaluating the PDLC summary.

A listing will be provided of subjects meeting the PDLC criteria. If a subject has at least 1 post-baseline value that meets the PDLC criteria for any lab parameter, then all values of that parameter for that subject will be listed. For the PDLCs, it is possible for subjects to appear in both categories for any parameter.

Table 8: 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 mM
	Female: absolute value ≥ 505.6 mM
	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

Table 8: Pre-defined Limits of Change Criteria for Clinical Safety Laboratory Data (Continued)

Laboratory Test	Parameter for ANY Value and LAST Value
Chemistry (Continued)	
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
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
Eosinophils	Absolute value: > 10%

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; CK = creatine kinase; LLN = lower limit of normal; Tbili = total bilirubin; ULN = upper limit of normal

10.5. Pharmacodynamic Markers

Pharmacodynamic parameters (CK and urine Hex4) will be analyzed separately from the other safety lab parameters. The baseline for the PD parameters will be the original study baseline at Visit 2 (as defined in Section 6.4.1). The PD summaries for Stage 1 and for Stage 2 have been reported in iCSR-1 and will not be repeated in this SAP unless the underlying data have changed. Otherwise, the pertinent summaries will be copied from iCSR-1 into the final CSR.

The analysis of PD data collected during Stage 2 Period 5 through Stages 3 and 4 to the DBL date will be reported. Subjects with both baseline and at least 1 post-baseline assessment will be analyzed on the Efficacy population. Figures of the mean (± SE) absolute change from baseline will be plotted for CK and urine Hex4. The mean ± SD values at baseline will be indicated in a legend for the plots. Additionally, all PD data will be presented in subject data listings.

10.6. Vital Signs

Vital signs (ie, sitting systolic blood pressure, sitting diastolic blood pressure, pulse rates, body temperature, weight, and height) will be summarized using the summary statistics defined in Section 6.2.1 and presented as described in Section 6.2.2.3. The summary will include the actual value and change from baseline. Vital signs results for Stages 1 and 2 have been reported in

iCSR-1 and will not be repeated in this SAP unless the underlying data have changed. Otherwise, the final CSR will reference the results in iCSR-1.

Vital signs data collected during Stage 2 Period 5 through Stages 3 and 4 to the DBL date will be analyzed on the Safety population. Per the schedule of assessments, vital signs were monitored at 0, 1, 4, 6, 12, and 24 hours after the infusion for Stage 3. Therefore, the analysis of vital signs will include summaries at these monitoring time points.

The incidence rates of values exceeding the PDLC criteria for vital signs defined in Table 9 by parameter will be summarized altogether (over the duration from first dose in Stage 2 Period 5 through Stages 3 and 4 to the DBL date), not by visit. Unscheduled visits will be included in evaluating the PDLC summary. All vital signs data will be presented in data listings.

Table 9: Pre-defined Limits of Change Criteria for Vital Signs

Vital Sign	Criteria
Pulse (Heart 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: BL = baseline; bpm = beats per minute; mm Hg = millimeters mercury

10.7. Electrocardiogram Variables

Quantitative ECG results will be summarized for the actual value and absolute change from baseline values using the descriptive statistics described in Section 6.2.1 and reported per the descriptions in Section 6.2.2.3.

Electrocardiogram results for Stages 1 and 2 have been reported in iCSR-1 and will not be repeated in this SAP unless the underlying data have changed. Otherwise, the final CSR will reference the results in iCSR-1. Electrocardiogram data collected during Stage 2 Period 5 through Stages 3 and 4 to the DBL date will be analyzed on the Safety population.

For categorical ECG data, frequency counts and percentages will be presented. The number and percentage of subjects with ECG interpretations (recorded as: Normal/Abnormal, Not clinically significant/Abnormal, Clinically significant) as well as the specific clinical findings for the abnormal ECGs will be presented.

The incidence rates of values exceeding PDLC for ECG intervals defined in Table 10 by parameter will be summarized altogether (over the duration from first dose in Stage 3 to the data cutoff date), not by visit. Unscheduled visits will be included in evaluating the PDLC summary. For the PDLCs, it is possible for subjects to appear in both categories for any parameter. All ECG data, including the interpretation of normal/abnormal and the specific clinical findings for the abnormal ECGs will be presented in data listings.

Table 10: Pre-defined Limits of Change Criteria for Electrocardiogram Values

ECG Parameter	Criteria	
PR interval (msec)	< 120 msec or ≥ 210 msec	
QRS duration (msec)	≤ 50 msec or > 120 msec	
QTcB interval (msec)	Change from baseline for QTcB and uncorrected QT: ≤ 30 msec or > 30 msec; ≤ 40 msec or > 40 msec	
	Absolute post-baseline QTcB and uncorrected QT interval: ≤ 450 msec or > 450 msec ≤ 480 msec or > 480 msec ≤ 500 msec or > 500 msec	
QTcF interval (msec)	Change from baseline for QTcF and uncorrected QT: ≤ 30 msec or > 30 msec; ≤ 40 msec or > 40 msec	
	Absolute post-baseline QTcF and uncorrected QT interval: ≤ 450 msec or > 450 msec ≤ 480 msec or > 480 msec ≤ 500 msec or > 500 msec	
Ventricular rate (bpm)	A decrease from reference ≥ 15 bpm, and an absolute value < 50 bpm	An increase from reference ≥ 15 bpm, and an absolute value > 120 bpm

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; msec = millisecond; PR = PR interval (measured from the beginning of the P wave to the beginning of the QRS complex in ECG tracing); QRS duration = duration of the QRS complex; QT interval = a measure from the start of the Q wave to the end of the T wave in the heart's electrical cycle; QTcB = QT interval for corrected heart rate (using Bazett's formula: $QT/RR^{1/2}$); QTcF = QT interval for corrected heart rate (using Fridericia's formula: $QT/RR^{1/3}$)

10.8. Physical Examination

No data on physical examination (PE) during Stages 1 and 2 were available to be reported in iCSR-1. All PE data, including data for Stages 1 and 2 (if available), will be summarized on the Safety population using the descriptions in Section 6.2.1 and presented as described in Section 6.2.2.3.

Both comprehensive physical examinations (CPE) and brief physical examinations (BPE) data collected during Stage 2 Period 5 through Stages 3 and 4 to the DBL will be summarized by body system. The number and percentage of subjects with overall assessment of CPE judged to be normal, abnormal, or not done will be summarized. For both CPE and BPE, the results of the

clinical significance categorized as ‘Clinically significant’ and ‘Not clinically significant’ will be summarized.

Further, the results of the physical examinations will be summarized for subjects who had examination at both baseline and post-baseline. Each site/system will be summarized with respect to being normal, abnormal, or not performed. The number and percentage of subjects judged to have ‘improved’ (ie, changed from abnormal at baseline to normal), ‘worsened’ (ie, changed from normal at baseline to abnormal), or remained unchanged from baseline to each post-baseline visit will be presented.

Supportive data listings will be provided that include the information collected on the eCRF (eg, body system/category, result of the observation [eg, normal, abnormal, or not performed], description of abnormal findings, and any investigator comment). Additionally, for observations related to safety, a listing of subjects with laboratory values, vital signs, and ECG values meeting the PDLCs, as well as abnormal PE values, will be provided (per ICH E3 Section 14.3.4).

11. CHANGES TO THE STATISTICAL METHODOLOGY PRESENTED IN THE PROTOCOL

Table 11: Changes from the Statistical Analysis Plan That Was Presented for the Second Interim CSR

Protocol Section/Existing Contents	SAP Section/Revision Text	Reason for Change
7.1; 7.2; 7.3 Objectives and Purpose	3.1; 3.2; 3.3 The bulleted items in the objectives were revised for accuracy and clarity.	For clarification
12.4.1 Intent-to-Treat Population: includes all enrolled subjects. Other populations may be defined in the SAP.	6.1.1; 6.1.3; 6.1.4 The SAP uses 'All Enrolled Subjects' population, but no ITT population. The SAP also includes Efficacy and PK populations.	(1) For clarity (2) There may be improper usage of the term ITT analyses, as the study was not randomized.
12.4.4.2; 12.4.4.5 Analyses are organized for: (1) Individual Cohorts, and overall; (2) Combined Cohorts 1, 3, and 4 (for ambulatory subjects); and (3) Combined Cohorts 1 and 4 (for ERT-experienced subjects)	General The SAP is organized as one document with three sub-studies based on the different stages in the study design (Stage 1, Stage 2, and Stages 3 and 4). However, the presentation of results for Stages 3 and 4 is consistent with the way analyses are organized in the protocol.	Organization of SAP is designed to meet the needs of the interim CSR.
12.4.4.2; 12.4.4.3 Summary statistics specified are: n, mean, SD, median, minimum, and maximum.	6.2 The first quartile (Q1) and third quartile (Q3) have been added to the summary statistics.	Q1 and Q3 can help in understanding the data distribution.
12.4.4.3 Safety Analyses	10.1; 10.3 Additional details have been provided for the safety analyses so as to align them to the ongoing pivotal Study ATB200-03.	For clarification and consistency
12.4.4.3 – Safety Analyses Shift changes and shift tables are described for vital signs, clinical labs, ECG based on PCS values in Protocol Appendix 2.	10.4; 10.5; 10.6 No more shift tables. Shift changes are now based on the use of PDLC. Although the PDLC criteria are similar to the PCS, they are not exactly the same.	To keep some level of consistency with Study ATB200-03.

Abbreviations: CSR = clinical study report; ECG = electrocardiogram; ERT = enzyme replacement therapy; ITT = intent-to-treat; PCS = potentially clinically significant; PDLC = pre-defined limits of change; PK = pharmacokinetic; SAP = statistical analysis plan; SD = standard deviation

12. GENERAL PROGRAMMING INFORMATION

12.1. General

All programmed table, figure, and listing outputs, unless specified otherwise, will be generated using the SAS version 9.4 or later. The programmed outputs will be similar to the format/appearance of the table and listing shells. However, space/formatting limitations may dictate changes in the programmed output. The footnotes specified in the table and listing shells may be changed as necessary for clarifying table entries or the explanation of algorithms or methods used for producing the entries. Significant changes in footnotes will be discussed prior to their implementation.

12.2. Format of Tables/Listings

Tables and listings should be produced in landscape mode and centered horizontally. Required margins are 1 inch for the top, left, right, and bottom margins. All outputs should have a 3-line header at the upper left margin:

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Other important formats for the tables and listings include the following:

- All outputs should have a 1-line footer with explanatory notes that include the date of data extraction, SAS program name including the path that generates the output, and the date and time the output was produced at the lower left margin of the footer. Tables will have the report listings for the data analyses presented in the table identified at the lower left margin, and listings will have the source eCRF identified.
- Tables and listings should be internally paginated in relation to the total length for that table or listing (ie, Page n of N, where n is the page number within the table or listing, and N is the total number of pages for that table or listing).
- The table, figure, and listing numbering will be based on the ICH Guideline E3. A number should identify each table/listing, and the table designation (eg, Table 1) should be centered above the title. A decimal system (eg, x, x.y, x.y.z) should be used to identify tables/listings with related contents. The title should be centered and in mixed-case characters.
- The title and table/listing designation should be single-spaced but are separated from the content of the table/listing by a space and a solid underline. The study population and/or subgroup (eg, Safety population) should be identified on the line immediately following the title.
- Column headings should be in initial upper-case characters. For numeric variables, the unit should be included in the column heading when appropriate.

- Footnotes should be single-spaced but separated by an underline and a space from the text of the table/listing. The notes should be aligned vertically by the left vertical border of the table/listing. Numeric references, which can be confused with data, should not be used; asterisks and other non-numeric symbols should be used to refer to footnotes.
- The dictionary (eg, MedDRA, WHO-DRUG) and the dictionary version numbers should be identified in the footnotes to the tables/listings for data coded with a dictionary. The source of the information (eg, Printed on CRF) should be identified if the data were not coded using a dictionary.
- For summarizations of categorical data, an Unknown or Missing category should be added to any variable for which information is not available for all subjects. However, only the number of unknown or missing subjects will be presented, and percent will be based on non-missing data.
- Individual data listings will be sorted and presented by treatment group, patient number, and visit date.

12.3. Data Formats

Unless otherwise specified, means and medians will be rounded and presented to 1 decimal place more than the raw (or actual measured) data and standard deviations to 2 decimal places more than the raw data. Minimum and maximum values will be presented to the same number of decimal places as the raw data.

Data in columns will be formatted as follows:

- Alphanumeric values will be center-aligned (in mixed upper and lowercase).
- Numerical data will be decimally aligned.
- Fractional data should be presented with the zero to the left of the decimal point (eg, 0.54).

Unless otherwise specified, percentages should be presented to 1 decimal place. Less than signs (ie, '<') should be presented as appropriate (eg, 0.04% should be presented as < 0.1%, not 0.0%).

Dates will be presented in DDMONYYYY format. Dates with partial missing data will be presented with a dash (ie, '-') for the missing data (eg, --JAN2005).

13. 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.

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Merkies, I. S., P. I. Schmitz, F. G. Van Der Meche, J. P. Samijn, and P. A. Van Doorn (2002). "Psychometric evaluation of a new handicap scale in immune-mediated polyneuropathies." Muscle Nerve 25(3): 370-377.

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APPENDIX 1. DESCRIPTIONS AND DERIVATIONS OF EFFICACY ENDPOINTS

1. Pulmonary function tests (PFTs):
   - Sitting forced vital capacity (FVC): maximum FVC (L) and percent predicted FVC (%)
   - Supine forced vital capacity: maximum FVC (L) and percent predicted FVC (%)
   - Maximum inspiratory pressure (MIP) (cm of water [cm H_2O])
   - Maximum expiratory pressure (MEP) (cm of water [cm H_2O])
   - Sniff nasal inspiratory pressure (SNIP) (cm of water [cm H_2O])
   - The percent predicted values of MIP, MEP, and SNIP will be calculated as:

     % predicted = (actual result / predicted result) * 100.

     The predicted results are obtained using the following reference equations: Uldry and Fitting, 1995 for MIP, MEP, and the lower limit of normal (LLN), and Evans and Whitelaw, 2009 for the SNIP values.

Table 12: Predicted Equations for MIP, MEP, and SNIP

PFT	Male	Female
MIP	120 – (0.41 x Age in years)	108 – (0.61 x Age in years)
MIP LLN	62 – (0.15 x Age in years)	62 – (0.50 x Age in years)
MEP	174 – (0.83 x Age in years)	131 – (0.86 x Age in years)
MEP LLN	117 – (0.83 x Age in years)	95 – (0.57 x Age in years)
SNIP	126.8 – (0.42 x Age in years)	94.9 – (0.22 x Age in years)

Abbreviations: LLN = lower limit of normal; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PFT = pulmonary function test; SNIP = sniff nasal inspiratory pressure

2. Manual muscle testing (MMT):
   - Right/left shoulder adduction
   - Right/left shoulder abduction
   - Right/left elbow flexion
   - Right/left elbow extension
   - Right/left hip flexion – ambulatory patients only
   - Right/left hip abduction – ambulatory patients only
   - Right/left hip adduction – ambulatory patients only
   - Right/left knee flexion – ambulatory patients only
   - Right/left knee extension – ambulatory patients only

Each manual muscle testing is evaluated on a scoring scale from 0 to 5: 0 = no muscle movement; 1 = visible muscle movement, but no movement at the joint; 2 = movement at the joint, but not against gravity; 3 = movement against gravity, but not against added resistance; 4 = movement against resistance, but less than normal; 5 = normal strength.

- Upper body muscle groups include right/left shoulder abduction, right/left shoulder adduction, right/left elbow flexion, and right/left elbow extension with the total score ranging from 0 – 40, based on these 8 muscle groups. That is,
  Upper = Shoulder + Elbow.
- Lower body muscle groups include right/left hip flexion, right/left hip abduction, right/left hip adduction, right/left knee flexion, and right/left knee extension with the total score ranging from 0 – 50, based on these 10 muscle groups. That is,
  Lower = Hip + Knee.
- Proximal body muscle groups include right/left hip flexion, right/left hip abduction, right/left hip adduction, right/left shoulder abduction, and right/left shoulder adduction with the total score ranging from 0 – 50, based on these 10 muscle groups. That is, Proximal = Shoulder + Hip.
- Total MMT score ranges from 0 – 90 based on all 18 muscle groups, and it will be analyzed as a continuous variable. Higher scores indicate less disease impact on muscle functions. That is, Total = Upper + Lower.

  Note: If there are many instances of missing testing scores (ie, if ≥ 50% of the testing scores [at least 9 out of 18] are missing), then the total will be normalized to 100%. That is, the total score will be prorated as: Total = (Mean of all available scores) x 18.

  Note: The right/left hip adduction muscle group was added later in the study, and so it will not appear in MMT summaries provided at earlier time points in Stage 3. For example, the lower body score at the earlier time points will range from 0 – 40 (based on 8 muscle groups) and the total MMT score at the earlier time points will range from 0 to 80 (based on 16 muscle groups).

  Ambulatory subjects were expected to perform all the muscle tests for both lower and upper body, while non-ambulatory subjects were to perform the muscle tests for only upper body.
- Body parts are shoulder, elbow, knee, and hip.

  Note: Each body part is the sum of its corresponding 4 muscle groups,
  eg, shoulder = right/left shoulder abduction + right/left shoulder adduction.

3. Quantitative muscle tests (QMTs) using hand-held dynamometer (in kg):
   - Right/left shoulder adduction
   - Right/left shoulder abduction
   - Right/left elbow flexion
   - Right/left elbow extension
   - Right/left hip flexion – ambulatory patients only

- Right/left hip adduction – ambulatory patients only
- Right/left hip abduction – ambulatory patients only
- Right/left knee flexion – ambulatory patients only
- Right/left knee extension – ambulatory patients only

Note: The muscle tests involving the upper body, lower body, total, and the proximal body (made up of the 5 moves from shoulder + hip) will be summarized.

4. Six-minute walk distance (6MWD) is the distance in meters (m) walked in the 6-minute walk test. It was performed by only ambulatory subjects.
   - Percent predicted 6MWD is calculated as:

     % predicted 6MWD = (actual 6MWD / predicted 6MWD) * 100

     (rounded up or down based on standard rounding rules), where the predicted values are derived for males and females using Enright equations (Enright and Sherill, 1998) as follows:

     Males: 6MWD = (7.57 x Height in cm) – (5.02 x Age in years) – (1.76 x Weight in kg) – 309 m

     Females: 6MWD = (2.11 x Height in cm) – (5.78 x Age in years) – (2.29 x Weight in kg) + 667 m

     Height is measured at the Screening visit. Weight is weight at same date that the 6MWD was measured. If weight was not measured at that date, then the weight measurement closest to the given date will be used. Age is the age at the 6MWD assessment, and it is calculated as: FLOOR([age at assessment – birthdate] / 365.25).
5. Gait, Stairs, Gowers', Chair (GSGC) total score is obtained by adding up the scores attributed to each of the following 4 functional tests:
   - Gait test is based on the 10-meter walk test (10MWT). This is scored as: 1 = normal; 2 = mild waddling, lordosis, and/or toe walking; 3 = moderate waddling, lordosis, and/or toe walking; 4 = severe waddling, lordosis, and/or toe walking; 5 = walks only with assistance (ie, braces, cane, crutches); 6 = stands, but unable to walk; 7 = confined to wheelchair.
   - Stairs test is based on the subject climbing 4 stairs. It is scored as: 1 = climbs four stairs without assistance; 2 = supports one hand on thigh; 3 = supports both hands on thighs; 4 = climbs stairs in upright position but with aid of railing; 5 = climbs while clinging to the railing with both hands; 6 = climbs only a few steps; 7 = unable to climb steps.
   - Gowers' maneuver test is based on the subject lying down on the floor, then rising from the floor to get to a standing position. This is scored as: 1 = normal; 2 = butt first maneuver, one hand on floor; 3 = butt first maneuver, two hands on floor; 4 = unilateral hand support on thigh; 5 = bilateral hand support on thighs; 6 = arises only with aid of an object (table, chair, etc); 7 = unable to rise.

- Chair test is based on the subject arising from a sitting position in a chair to a standing position. This is scored as: 1 = normal; 2 = with wide base and/or difficulty but without support; 3 = with support on one thigh; 4 = with support on both thighs; 5 = with support on arms of chair or on a table; 6 = not possible.

GSGC was performed by ambulatory subjects only. The total GSGC score ranges from 4 (normal performance) to 27 (worst performance).

6. Other motor function tests – ambulatory subjects only

   For each of these motor function tests, the actual time (in seconds [s]) that the subject takes to perform the test and the assigned score (which indicates the level of difficulty with which the patient performed this task) are recorded for analysis.

   - Gowers' maneuver test is based on the patient lying down on the floor, then rising from the floor to get to a standing position. The time is measured in seconds (s) and assigned the test score.
   - 10-meter walk test (10MWT) is based on the time it takes the subject to walk 10 meters. The score from this test is used as the Gait score in GSGC.
   - 4-stair climb is based on the subject climbing 4 stairs.
   - Timed Up and Go (TUG) test represents the time it takes the subject to stand up from the chair, walk to the line on the floor (about 3 meters), turn around, walk back to the chair, and sit down, all at the regular pace.

7. Rasch-built Pompe-specific Activity (R-PAct) consists of 18 questions, each scored on a scale from 0 = 'no,' 1 = 'yes, but with difficulty,' to 2 = 'yes, without difficulty.'

   The 'summed raw score' or total score ranges from 0 to 36, with higher values representing lower level of disease impact on the muscles. The total score will be calculated simply by summing up the observed scores across the 18 items. The total score is analyzed as a continuous variable.

8. Rotterdam Handicap Scale (RHS): This consists of 9 questions, each scored on a scale from 1 = 'unable to perform task' to 4 = 'able to perform task independently or completely.'

   The total score ranges from 9 to 36, with higher values representing lower level of handicap. The total score is obtained as the sum of the individual scores, and it will be analyzed as a continuous variable. The instrument will be scored using the traditional 50% response rule, described as follows:

   If a score of '0 = not applicable' is provided, it is interpreted as a missing response or an unanswered question.

   If ≥ 50% of the questions were answered (ie, at least 5 out of 9 responses are available), the total score is obtained as: Total = ([Sum of all available scores] x 9) / (9 – [Number of missing items]) = (Mean of all available scores) x 9 (Merkies, Schmitz et al. 2002).

   Otherwise (ie, if less than or equal to 4 out of 9 questions were answered), the total score will be considered missing ('.').

9. Fatigue Severity Scale (FSS): This consists of 9 questions, each scored on a scale from 1 = 'completely disagree' to 7 = 'completely agree.'

   The total score ranges from 9 to 63, with higher values representing higher level of fatigue due to the disease condition. The total score is obtained as the sum of the individual scores, and it will be analyzed as a continuous variable. The 50% response rule will be applied.

   If at least 5 out of 9 item responses are available, the total score will be calculated as: Total = ([Sum of all available scores] x 9) / (9 – [Number of missing items]) = (Mean of all available scores) x 9. Otherwise, the total is considered missing.

10. PROMIS® Short Forms:

    - PROMIS – Physical Function Short Form 20a (v2.0) consists of 20 questions. The first 14 questions are each scored on a scale from 1 to 5 as follows: 1 = unable to do; 2 = with much difficulty; 3 = with some difficulty; 4 = with a little difficulty; 5 = without any difficulty; the next 6 questions are each scored on a scale from 1 to 5 as follows: 1 = cannot do; 2 = quite a lot; 3 = somewhat; 4 = very little; 5 = not at all.

      The total score ranges from 20 – 100, with higher scores indicating more mobility.

    - PROMIS – Fatigue Short Form 8a consists of 8 questions, each scored on a scale from 1 to 5 as follows: 1 = not at all; 2 = a little bit; 3 = somewhat; 4 = quite a bit; 5 = very much; and 2 questions, each scored on a scale from 1 to 5 as follows: 1 = never; 2 = rarely; 3 = sometimes; 4 = often; 5 = always.

      The total score ranges from 8 – 40, with higher scores indicating more fatigue.

    - PROMIS – Upper Extremity Short Form 7a consists of 7 items each scored on a decreasing scale from 1 to 5 as follows: 1 = unable to do; 2 = with much difficulty; 3 = with some difficulty; 4 = with a little difficulty; 5 = without any difficulty.

      The total score ranges from 7 – 35, with higher scores indicating less disability in the upper extremity.

    - PROMIS – Dyspnea Severity Short Form 10a consists of 10 questions each scored on a scale from 0 to 3 as follows: 0 = no shortness of breath; 1 = mildly short of breath; 2 = moderately short of breath; 3 = severely short of breath.

      The total score ranges from 10 – 50, with higher scores indicating greater shortness of breath.

      The total score of each PROMIS instrument is obtained by summing up the individual scores, and it will be analyzed as a continuous variable.

11. Global impression of change

    - SGIC: The Subject's Global Impression of Change involves 8 questions assessing each of the following functional areas:
      – overall physical wellbeing
      – effort of breathing

  - muscle strength
  - muscle function
  - ability to move around
  - activities of daily living
  - energy level
  - level of muscular pain

  Each of the 8 functional items is scored on a 7-point rating scale as follows: 1 = very much worse; 2 = much worse; 3 = worse; 4 = no change; 5 = improved; 6 = much improved; 7 = very much improved.

  For each functional item, a ternary response is defined as: “Improved” = item response of 5 or higher, ‘No change’ = item response of 4, or “Declining” = item response of 3 or lower.

- PGIC: The Physician’s Global Impression of Change (PGIC) is based on a single question that is scored on a 7-point rating scale, similarly to the SGIC.

  A ternary response is created from the responses, defined as: “Improved” = response of 5 or higher, “No change” = response of 4, or “Declining” = response of 3 or lower.