Official Title:	Statistical Analysis Plan: A Long-Term, Open-Label Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Migalastat In Subjects > 12 Years of Age with Fabry Disease and Amenable *GLA* Variants
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Statistical Analysis Plan

Study Drug:
Migalastat Hydrochloride

Protocol Number: AT1001-036

Study Title:
A Long-term, Open-label Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Migalastat in Subjects > 12 Years of Age With Fabry Disease and Amenable *GLA* Variants

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Sponsor:
Amicus Therapeutics, Inc.

3675 Market Street
Philadelphia, PA 19104
Phone: +1-609-662-2000

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD		Oct 8, 2021
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
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Amicus Therapeutics Approval

PPD		Oct 8, 2021
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1. Glossary of Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
cm	Centimeters
CSR	Clinical Study Report
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ERT	Enzyme Replacement Therapy
EOT	End of Treatment
ET	Early Termination
FPHPQ	Fabry-Specific Pediatric Health and Pain Questionnaire
GLA	Gene Encoding α-Galactosidase A
HEENT	Head, Eyes, Ears, Neck and Throat
ICF	Informed Consent
ICH	International Conference on Harmonisation
LVMI	Left Ventricular Mass Index
lyso-Gb_3	Globotriaosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially Clinically Significant
PedsQL™	Pediatric Quality of Life Inventory™
PD	Pharmacodynamics
PR	PR Interval
PT	Preferred Term
QOD	Every other day
QRS	QRS Complex
QT	QT Interval

Abbreviation	Description
QTc	Corrected QT Interval
QTcB	Corrected QT Interval with Bazett's Formula
QTcF	Corrected QT Interval with Fridericia's Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	Système International
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings and Figures
WHO-DD	World Health Organization Drug Dictionary (WHO Drug Enhanced + Herbal B3 March 2018 or latest available version)

1. Introduction

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is created based on Protocol AT1001-036, Amendment 2, 19Aug2021. The purpose of this SAP is to outline the planned analyses by Syneos Health to support the completion of the Clinical Study Report (CSR). This SAP describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. The planned analyses identified in this SAP are following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines E9 (R1) Statistical Principles for Clinical Trials. They will be included in regulatory submissions and/or future manuscripts.

1.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all SDTMs, derived datasets, and tables, listings, and figures (TLFs).

1.2. Timing of Analyses

The primary analysis of safety and efficacy and/or pharmacodynamics is planned after all subjects complete the final study visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is as follows:

- to assess the long-term safety of migalastat treatment in pediatric subjects diagnosed with Fabry disease and who have variants in the gene encoding α-Galactosidase A (*GLA*) amenable to treatment with migalastat

2.1.2. Secondary Objectives

The secondary objectives of this study are as follows:

- to characterize the pharmacodynamics (PD) of migalastat in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat
- to assess the efficacy of migalastat in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat.

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

The efficacy endpoints of this study are as follows:

- change from baseline in estimated glomerular filtration rate (eGFR; Schwartz formula)
- change from baseline in urine protein and albumin levels
- change from baseline in left ventricular mass index (LVMi)
- change from baseline in Fabry-Specific Pediatric Health and Pain Questionnaire (FPHPQ) scores
- change from baseline in Pediatric Quality of Life Inventory™ (PedsQL™)

2.2.2. Pharmacodynamic Endpoints

The PD endpoint of this study is the change from baseline in plasma levels of Globotriaosylsphingosine (lyso-Gb3).

2.2.3. Safety Endpoints

The safety endpoints of this study are as follows:

- incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to discontinuation of study drug
- change from baseline in clinical laboratory test results over time
- change from baseline in vital signs over time
- change from baseline in physical examination findings over time
- change from baseline in body weight and height over time
- change from baseline in electrocardiogram (ECG) results over time

- change from baseline in echocardiogram (ECHO) parameters from baseline to Month 12/ET
- change from baseline in Tanner stage

3. Study Design

3.1. Summary of Study Design

This is a long-term, open-label, uncontrolled, multicenter study to evaluate the safety, PD, and efficacy of migalastat treatment in subjects over 12 years of age with Fabry disease and with amenable GLA variants. Subjects will enroll in this study following completion of migalastat Study AT1001-020.

Enrollment in this study should immediately follow completion of Study AT1001-020 in order to maintain the continuity of treatment. As appropriate, assessments performed at the End of Treatment visit for Study AT1001-020 will be utilized for Visit 1 (baseline) assessments for this study.

In order to monitor safety, subsequent visits for this study were initially scheduled every 3 months with monthly interim telephone contacts. Following Amendment 2, the visit schedule was changed to every 6 months, with phone contacts at intervening 3-month intervals.

Subjects will remain on the same dose of migalastat that they were receiving in Study AT1001-020. If a subject's weight decreases to below 43 kg, an unscheduled visit will be arranged 2 to 4 weeks later in order to monitor the subject's weight.

3.2. Subject Selection

Inclusion and exclusion criteria for this study can be found in Section 8.2 of the study protocol. Waivers of inclusion/exclusion criteria will not be granted.

3.3. Determination of Sample Size

As this study is an open-label extension of Study AT1001-020, no sample size calculation was performed.

3.4. Treatment Assignment and Blinding

As this study is an open-label extension of Study AT1001-020 and all subjects receive migalastat, no treatment assignment is conducted, and no blinding process is used for this study.

3.5. Administration of Study Medication

Migalastat will be supplied as 150-mg capsules. Migalastat capsules contain 123 mg migalastat free base, which is equivalent to 150 mg migalastat HCl. Migalastat will be administered every other day (QOD) during the treatment period. Capsules are to be taken with water at the same time of day during the QOD dosing schedule. Subjects will be instructed not to eat for at least 2 hours before and for 2 hours after administration of study drug. Water can be consumed during this period.

Study drug should not be taken on 2 consecutive days. If a dose is missed entirely for the day, the subject should take the missed dose of study drug only if it is within 12 hours of the time the dose normally is taken. If more than 12 hours have passed, the subject should resume taking study drug at the next planned dosing day and time according to the every-other-day dosing schedule.

3.6. Study Procedures and Flowchart

Table 1 details the schedule of assessments:

Table 1. Schedule of Assessments

Assessments	**Baseline**[a]	**Treatment Period**								**EOT/ ET**	**Follow-up**
Visit Interval	**Day 1**	**Month 3 (TC)**	**Month 6**	**Month 9 (TC)**	**Month 12**	**Month 15 (TC)**	**Month 18**	**Month 21 (TC)**	**Month 24**	**--**	**30-Day Safety**
Visit Window (days)	**—**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**
Informed consent/assent	X										
Inclusion/exclusion criteria	X										
Medical history	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Dosing diary[b]	X	→	→	→	→	→	→	→	X		
FPHPQ questionnaire	X		X		X		X		X	X	
PedsQL	X		X		X		X		X	X	
Complete physical examination	X		X		X		X		X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, RR, Temp)	X		X		X		X		X	X	
Body weight	X		X		X		X		X	X	
Height	X		X		X		X		X	X	
Tanner Staging	X		X		X		X		X	X	
12-lead ECG	X		X		X		X		X	X	

Table 1. Schedule of Assessments (Continued)

Assessments	Baseline[a]	Treatment Period								EOT/ ET	Follow-up
Visit Interval	**Day 1**	**Month 3 (TC)**	**Month 6**	**Month 9 (TC)**	**Month 12**	**Month 15 (TC)**	**Month 18**	**Month 21 (TC)**	**Month 24**	**--**	**30-Day Safety**
Visit Window (days)	**—**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**+6**
Chemistry (including eGFR using Schwartz formula)	X		X		X		X		X	X	
Hematology	X		X		X		X		X	X	
Plasma lyso-Gb_3, analogs, and exploratory PD biomarkers	X		X		X		X		X	X	
Urinalysis (urine protein, albumin and microalbumin levels)	X		X		X		X		X	X	
Urine pregnancy test or date of LMP (as applicable)[c]	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram (LVMi and additional parameters)	X				X				X	X	
Study treatment supply/resupply/ return	X		X		X		X		X	Xd	

Abbreviations: BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = end of treatment; ET = early termination; FPHPQ = Fabry-Specific Pediatric Health and Pain Questionnaire; HR = heart rate; LMP = last menstrual period; LVMi = left ventricular mass index; lyso-Gb_3 = Globotriaosylsphingosine; PD = pharmacodynamic; PedsQL = Pediatric Quality of Life Inventory; RR = respiration rate; TC = telephone call; Temp = body temperature
Note: Following Month 24, visits will continue every 6 months with interim telephone contacts at 3-month intervals. The assessment schedule will repeat starting from Month 3.
Note: For the purposes of this study, a month is considered to be 30 days.
[a] End of study assessments from Study AT1001-020 will be used as baseline assessments for Study AT1001-036.
[b] A dosing diary will be completed throughout the treatment period.
[c] Female subjects only; urine pregnancy tests will be conducted at each site visit. For menstruating females, date of LMP will be elicited during telephone contacts.
[d] Return of study drug only

4. Analysis Population

4.1. Enrolled Population

The enrolled population will include all enrolled subjects. All safety, PD, and efficacy analyses will be performed using the enrolled population.

4.2. Protocol Deviations

Protocol deviations are defined as instances in which subjects or investigational site study personnel fail to adhere to the protocol requirements (e.g., eligibility criteria, addition or deletion of tests, dosing, duration of treatment, and/or any other aspect of the study design). Deviations are collected on the electronic Case Report Forms (eCRF). Deviations related to the COVID-19 pandemic are indicated by including “COVID-19” in the deviation details field.

A list of protocol and site deviations will be provided with the date the deviation occurs, the category (eg, inclusion/exclusion criteria, informed consent (ICF)/subject privacy, etc.), and the description of the deviation.

5. General Aspects for Statistical Analysis

This section addresses the definitions, algorithms, imputations, and conventions that apply to the analysis and handling of the data.

5.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will have text (eg, headers or footers) providing explanatory notes that cover, as appropriate: date of data extraction, date of output generation, Statistical Analysis System (SAS®) program name, and any other output-specific details that require further elaboration.

The descriptive summary statistics will be prepared for baseline, each visit, and change from baseline to each visit (if appropriate).

Row entries in post text tables are made only if data exist for at least one subject (eg, a row with all zeroes will not appear). The only exception to this rule applies to tables that summarize the study termination status of subjects (eg, reasons for not completing the study). In this case, zeroes will appear for study termination reasons that no subject satisfied. The summary tables will clearly indicate the number of subjects to which the data apply and data that is unknown or not performed will be distinguished from missing data. All data collected will be reported in data listings.

Missing dates will be imputed as described in Section 5.7. Missing AE severity and relationship will be imputed as described in Section 5.7.2. No other missing data imputation will be performed. When imputed or derived data are included in the individual subject data listings, they will be flagged.

5.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The convention will be to number tables and listings using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings. The first level number will be consistent with the corresponding CSR appendix in which the tables or listings will appear. Thus, all post text tables will have a main number level 14 and listings will have a main number level 16.

Subject accounting and final disposition, analysis populations, protocol deviations and/or violations, demographics and baseline profile will appear as the second level number (Table 14.1 series). Efficacy tables will come next (Table 14.2 series). Safety tables will be at the end (Table 14.3 series). Similar conventions will be applied to the subject data listings and figures/graphs.

For tables, the last line of the title will provide the analysis group being summarized (eg, Enrolled Population). Whether in the title or body of a table or listing, units will always be specified for all appropriate data. Metric system units will be used (eg, degrees Celsius [°C] for temperature, kg for body weight, and centimeters [cm] for height).

In general, the listings will be sorted and presented by investigational site and subject number. From left to right, the columns will include the subject number, visit number, visit name, visit date, treatment, and days relative to first dose in the study.

5.3. Data management

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) datasets will be used. All statistical and data analyses, SDTMs and Analysis Data Model (ADaM) datasets will be created

using SAS® software version 9.4 or later. The data specifications and reviewer's guide will also be created.

5.4. Data Presentation Conventions

5.4.1. Descriptive Statistics

Data will be summarized with descriptive statistics and/or response frequencies. For numerical data, descriptive statistics will include number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum. For categorical data, descriptive statistics will be categorized by frequency counts and proportions (or percentages) of the number of subjects used in the analysis. The counts for the categories of 'Missing,' 'Unknown,' or 'Not applicable' will be provided as appropriate, but the percentages will not be provided.

5.4.2. Rounding

In general, the minimum and maximum will be reported to the same number of decimal places as the data. The mean, median, and confidence intervals will be rounded to one more decimal place than the data. The SD will be rounded to two more decimal places than the data. Proportions will be reported as percentages rounded to one decimal place.

Each subject's age will be truncated to a whole number (rather than rounded).

5.4.3. p-values

Not applicable.

5.4.4. Dictionaries

The Medical Dictionary for Regulatory Activities (MedDRA, version 21.0 or later version) will be used to code AEs and medical history into system organ class (SOC) and preferred term (PT) within SOC. The enhanced version of the World Health Organization Drug Dictionary (WHO-DD, WHO Drug Enhanced + Herbal B3 March 2018, or latest available version) will be used to code all medications (prior and concomitant) to anatomical therapeutic chemical (ATC) class and preferred drug names.

5.5. Baseline Definition

For all safety, PD, and efficacy data, the baseline value is defined as the last non-missing measurement obtained on or before the administration of the first dose of study drug in Study AT1001-036 (Day 1).

5.6. Derived and Transformed Data

5.6.1. Calculations Using Dates

5.6.1.1. Baseline Age

Age for enrolled subjects will be calculated as the truncated difference (eg, fractional part ignored) between the date of the ICF and the subject's birth date adjusted for years (ie, AGE = int[(ICF date of this study- date of birth + 1 day) / 365.25]).

5.6.1.2. Study Day

Study Day 1 denotes the day of the first dose of study drug in Study AT1001-036 and is the reference start date for all analyses in this study. Study days (or visit days) are defined relative to Day 1 unless otherwise specified. Days prior to Day 1 are negative and days after Day 1 are positive. There is no Day 0. That is,

Relative Day = (Date of Assessment) – (Date of First Dose of Study Drug) + 1, if assessment is on or after the date of first dose of study drug;

Relative Day = (Date of Assessment) – (Date of First Dose of Study Drug), if assessment is before the date of first dose of study drug.

5.6.1.3. Other Calculations Using Dates

Total duration of treatment will be calculated as the difference between the dates of last and first dose of study drug plus 1 day, regardless of any study drug interruption.

All other calculations of duration for enrolled subjects (eg, time since the primary diagnosis or age of first diagnosis) will be performed relative to the first dose of study drug and will follow the algorithm:

Duration = (Target Date – First Dose Date + 1).

5.6.1.4. Change from Baseline

For any parameter at a specific visit, change from baseline is calculated as the value of the parameter at the specific visit minus the baseline value of that parameter, as defined above.

5.6.1.5. Visit Windows

There will be no derivation for visit windows in terms of summary assessments. Nominal visits will be used for by-visit tables. For data with repeated observations at a given visit (eg, laboratory assessments), the earliest of the available non-missing values at a visit should be used in summary tables. Other observations will be considered as unscheduled visits.

5.6.1.6. Multiple Assessments

If multiple assessments are associated with a nominal visit post-baseline, the first assessment will be used.

5.7. Handling of Missing Data

5.7.1. Missing Start and Stop Dates for Adverse Events

For AEs, partially missing start dates will be imputed for the purpose of determining treatment emergence only.

Partially missing start dates will be imputed as follows:

For a missing day,

- If the month and year are equal to the month and year of the date of the first dose of study drug, then the date of the first dose of study drug will be used.
- Otherwise, the first day of the month will be used.

For a missing day and month or just missing month,

- If the year is equal to the year of the first dose of study drug, then the date of the first dose of study drug will be used.
- Otherwise, the first day of the month and the first month of the year will be used.

If the stop date is not missing and the imputed start date is after the stop date, then the stop date will be used.

If the start date is completely missing and the stop date is on or after the date of first dose of study drug, the AE will be considered a TEAE.

If both the start date and stop date are missing, the AE will be considered a TEAE.

Missing stop dates for AEs will not be imputed.

These imputations will be applied only to the AE summary tables. Listings will show the data as collected.

5.7.2. Missing Adverse Event Severity, Relationship, and Seriousness

If an AE is missing the severity or relationship to study drug, the AE will be classified under the maximum severity (ie, severe) or the maximum relationship (ie, definite), respectively. If the serious status is missing for an AE, the event will be assumed to be serious.

5.7.3. Missing Start and Stop Dates for Prior and Concomitant Medications

Partially missing medication start dates will be imputed in a similar manner as described in Section 5.7.1 for imputing missing AE start dates. Missing stop dates for medications will not be imputed. If when using these rules, the imputed start date is after the stop date, then the start date will be left as missing and the medication will be considered a concomitant medication for the purpose of the analysis.

5.7.4. Missing Exposure Dates

A subject's first dose date will be obtained from the first (earliest) dosing diary log record that contains a non-missing date of study drug dosing.

- If the month and day is missing, and the year is the same as the ICF date, the month and days will be imputed as the same date of ICF. Otherwise, January will be imputed for missing months and the 1st of the month will be imputed for missing days.
- If the days are missing and the month and year is the same as the ICF date, the days will be imputed as the same date of ICF. Otherwise, the first of the month will be used.
- If the end date of the last dose is missing, the last dose date will be imputed by adding 2 multiplied by the number of doses dispensed from the last non-missing dispensation date.

5.7.5. Missing Baseline and Demographic Data

If partial dates are present for demographic or baseline data, the following general method will be used to handle them.

- For any missing days or months, the first day of the month or the first month of the year will be used. If the imputed dates are prior to the ICF date, they will be set as the same date of ICF.
- If a year is missing and no other information is available, the date should be set to missing. (Note that missing year of the date of birth is not allowed in the study.)
- For date of diagnosis of Fabry disease, no imputation will be done.

6. Demographic, Other Baseline Characteristics and Medication

6.1. Subject Disposition and Withdrawals

Frequency counts and percentages of all subjects who are enrolled but do not take study drug, and subjects who are enrolled and complete the study drug/study or discontinue study drug/study early will be presented. All subjects who discontinue from the study will be identified, and their reason for discontinuation in the study will be reported. The denominators for the percentage calculations will be the number of subjects in the enrolled population.

The following frequencies (number and percentage) will be displayed:

- Subjects in the enrolled population
- Subjects who completed the study
- Subjects who discontinued early overall and by reason

A listing of all study subjects, whether they discontinued the study or not, and the reasons for study discontinuations will be provided for the enrolled population.

6.2. Demographic and Other Baseline Characteristics

Demographic and baseline data will be summarized by means of descriptive statistics: continuous variables as mean, SD, median, minimum, and maximum, and categorical variables as frequencies and percentages, based on the enrolled population. Demographic data will include age, sex, race, ethnicity, reproductive potential, height, body weight, and body mass index (BMI). Baseline characteristics will include number of years since diagnosis of Fabry disease, previous use of enzyme replacement therapy (ERT), and previous and current use of angiotensin-converting enzyme inhibitors, renin inhibitors, and angiotensin receptor blockers. The following calculations will be utilized:

- Age = (ICF date - date of birth + 1) / 365.25 and truncated to complete years. Age at entry into this study will be re-calculated based on the date of birth recorded in Study AT1001-020
- Weight (in kg) = weight (in pounds) *0.4536
- Height (in cm) = height (in inches) * 2.54
- BMI (kg/m2) = weight(kg)/[(height(cm)/100)^2], where m=meters.
- Number of years since diagnosis of Fabry disease = (ICF date of this study - date of diagnosis of Fabry disease + 1) / 365.25 and rounded to 1 decimal.
- For any missing days or months, years will be used for the calculation: Number of years since diagnosis of Fabry disease = (year of ICF date of this study – year of date of diagnosis of Fabry disease)
- For missing years, number of years will be missing.
- A month will be defined as 30 days
- ERT status is defined as ERT naïve at baseline and ERT experienced; ERT status is determined based on the subject's ERT status in Study AT1001-020.

All demographic and baseline characteristic data will also be listed.

6.3. Medical History

A summary table of the number and percentage of subjects for medical history by SOC and PT will be produced for subjects in the enrolled population. Medical history will be sorted alphabetically by SOC and PT within the same SOC using the MedDRA coding dictionary, version 21.0, or later version. For the summary tables, a subject may appear more than once if he/she has more than one medical history coded under different SOC or PT categories. However, the subject will be counted only once in the overall category. A by-subject listing with coded SOC and PT along with eCRF term will also be provided.

6.4. Concomitant Medications

Medications will be classified as prior (started prior to the first dose of study treatment in the 036 study) and concomitant (continued past or started on or after the first dose of study treatment in the 036 study). Medications starting after the last dose of study drug will not be considered as concomitant but will be flagged as post medications on the listing. All concomitant medications will be summarized.

All prior and concomitant medications will be classified using the ATC classification coded terms and preferred drug names from the WHO-DD.

Summaries of prior and concomitant medications will be presented separately in tabular form using the level 4 ATC term as an upper classification level and the preferred drug name as a lower classification level. All medications will be summarized and sorted alphabetically by level 4 ATC term and preferred drug name within a given level 4 ATC term. The summary will consist of the frequency and percentage of subjects in the enrolled population who used the medication at least once.

For each subject, the medication will be counted only once within a level 4 ATC term and only once under a given preferred drug name. A subject may appear more than once if he/she has more than one concomitant medication coded under different ATC terms or preferred drug names; however, the subject will be counted only once in the overall category.

A by-subject listing with coded terms will also be provided along with calculated study day.

7. Efficacy

Observed values and changes from baseline for each efficacy endpoint in Section 3.2.1 will be summarized by subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced), with descriptive statistics at each scheduled time point based on the enrolled population. Mean plots including standard error bars at each visit for the numerical observed values and changes from baseline of the indicated laboratory assessments, ECHO results and subject questionnaires will be provided by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall, if feasible.

7.1. Laboratory Assessments

Efficacy analyses will include summaries of observed and change from baseline values for eGFR, urine protein, and urine albumin for scheduled visits by subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced), indicated in Section 4.6. By-visit summary will also include the last post-baseline values.

The eGFR will be calculated using the 2009 Schwartz formula for creatinine clearance.

A by-subject listing will be presented for each laboratory test.

7.2. Echocardiography

A summary table of observed and change from baseline values in numerical ECHO results will be provided at each scheduled visit by subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced). By-visit summary will also include the last post-baseline values.

A by-subject listing will be presented for each ECHO parameter, including LVMi measurement, and other cardiac parameters, such as ejection fraction, fractional shortening, left ventricular internal diameter end diastole and end systole, midwall fractional shortening, and wall thickness.

7.3. Subject Questionnaires

7.3.1. Fabry-Specific Pediatric Health and Pain Questionnaire

The FPHPQ includes questions about Fabry disease-specific symptoms (eg, sweating, pain, dizziness and tiredness, heat and cold intolerance, swollen eyelids, gastrointestinal symptoms, feeling thirsty, difficulty hearing, ringing, or buzzing noise in the ears, and ability and enjoyment to participate in sports). The frequency of these symptoms will be rated using a 5-point Likert scale (1=Always, 2=Often, 3=Sometimes, 4=Seldom, 5=Never). Pain severity is measured on an 11-point scale, numeric responses are given for onset of pain and school days missed, and yes/no questions are posed about difficulty hearing and other problems not specifically mentioned.

Descriptive summaries will be provided for the FPHPQ observed and change from baseline scores by visit and subgroup ie, sex (male, female), ERT status (ERT naïve, ERT 6+ months ago), and overall if feasible. Unscheduled visits will not be included. By-visit summary will also include the last post-baseline values.

A by-subject listing of FPHPQ scores will be provided.

7.3.2. Pediatric Quality of Life Inventory

The PedsQL™ is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. It consists of 23 items and includes

questions about physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items) relative to the prior 7 days, using a 5-point scale (0=Never, 1=Seldom, 2=Sometimes, 3=Often, 4=Always). Both parents or legally-authorized representatives and subjects complete the appropriate version of the PedsQL™ independently of one another. Parents or legally-authorized representatives and subjects may self-administer the questions after introductory instructions are given by study site personnel.

PedsQL™ scoring procedure is as listed below:

Step 1: Transform Score:

Item scores are reversed and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

Step 2: Calculate Scores:

Score by Dimensions:

- If more than 50% of the items in the scale are missing, the scores should not be computed.
- Mean score = Sum of the items over the number of items answered.
- Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales;
- Physical Health Summary Score = Physical Functioning Score;
- Total Score: Sum of all the items over the number of items answered on all the scales.

Descriptive summary tables will be provided for the PedsQLTM observed and change from baseline of psychosocial, physical, and total scores by visit and subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible. By-visit summary will also include the last post-baseline values.

For both the teen report and the parent of teen report, a by-subject listing of PedsQLTM scores for each single question as well as psychosocial, physical, and total scores will be provided.

8. Analysis of Pharmacodynamics

8.1. Primary PD Endpoint and Analysis

The PD endpoint is change in plasma levels of lyso-Gb3. Descriptive summaries will be provided for the observed and change from baseline values to Month 6, and Month 12 by sex (male and female), ERT status (ERT naïve, ERT experienced), and overall based on the enrolled population.

A by-subject listing will also be provided.

9. Safety

The analysis population used for safety analyses will be the enrolled population. Safety will be assessed on the basis of extent of exposure, incidence of TEAEs, SAEs and AEs leading to discontinuation, clinical laboratory data, vital signs including body weight and height, ECG parameters, physical examinations, and Tanner stage.

9.1. Extent of Exposure and Drug Compliance

The duration of study drug exposure (in both days and months) and the number of doses of study drug exposure will be summarized for the enrolled population.

> Duration of Exposure = end date of last dosing administration – start date of first dosing administration + 1Average Dose QOD = [Total dose received/ (Duration of exposure + 1)] * 2.
>
> Drug Compliance (%) = Average Dose QOD/Planned Dose QOD (ie, 150 mg)

Drug Compliance will be summarized using descriptive summaries. The number and percentage of subjects with Drug Compliance <80%, ≥80% will be summarized.

A detailed listing of exposure to study drug and drug compliance will be presented.

9.2. Adverse Events

A TEAE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment and that begins on or after the date of the first dose of study drug in the 036 study.

Treatment-related TEAEs are defined as TEAEs that have an Investigator-defined relationship to treatment of “Definite”, “Probable” or “Possible”. Events with an investigator-defined relationship of “Unrelated” or ”Unlikely Related” are considered as not related to treatment.

Serious TEAEs are defined as TEAEs that have a “yes” response to the eCRF question “Event Serious?”. Serious adverse events are categorized as “Death”, “Life-threatening”, “Requires/Prolongs Hospitalization”, “Disability/ Incapacity”, “Congenital Anomaly/Birth Defect” or “Important Medical Event or Reaction”.

An overall summary of TEAEs, will be tabulated, including the number and percentage of subjects reporting, by sex and overall:

- TEAEs
- Treatment-related TEAEs
- SAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death

The number of events and incidence rates will also be provided in the overall summary table. Incidence rate is calculated as: total events divided by the total patient years of exposure. Total patient years of exposure are the sum of the duration of exposure in years for all subjects.

Further, the following TEAE summaries will be provided by sex and overall:

- Any TEAEs by SOC and PT
- Any TEAEs by PT
- Treatment-related TEAEs by SOC and PT
- TEAEs by severity, by SOC and PT
- Serious TEAEs by SOC and PT
- Any non-serious TEAE by PT

When presenting summaries by SOC and PT, subjects are counted only once within each SOC and PT. TEAEs will be presented alphabetically by SOC and PT.

When presenting summaries by PT, subjects are counted only once in each PT. TEAEs will be presented in the order of descending frequency in the overall group.

When presenting summaries by severity, if a subject has more than one event within a given SOC or PT at different severities, the maximum severity will be tabulated. For example, if a subject had two events with the same PT, but one was moderate and the other severe, the severe TEAE will be included in the tabulation.

Subject listings will be provided for all AEs, TEAEs leading to discontinuation of study drug, TEAEs with an outcome of death, and SAEs.

9.3. Laboratory Evaluations

Clinical laboratory test values (hematology, serum chemistry, and urinalysis) and changes from baseline will be summarized by each visit and subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible for the enrolled population. By-visit summary will also include the last post-baseline values.

In addition, the following clinical summaries will be presented:

- Tables summarizing the frequencies and percentages of potential clinically significant (PCS; see Table 2) abnormalities at any time. The summary will indicate the number of subjects with PCS-low or PCS-high values at any time during treatment with migalastat but will not be presented by visit. PCS abnormalities will be determined both by investigator assessment and derivation from lab alert ranges provided by Amicus. PCS abnormalities that occur at unscheduled visits will be included.
- Tables displaying shifts from baseline to each assessment time-point, including the last post-baseline assessment, in laboratory test values from normal to high or low using normal range including eGFR, urine protein, and albumin.

Unscheduled visits will be included in PCS summaries and when determining the worst post-baseline assessment.

By-subject safety laboratory listings will be generated incorporating information and assessment results obtained from the designated laboratory which provided normal range and reported out of range flags. All laboratory results in Système International (SI) units will be presented in data listings. Tests will be listed in alphabetical order within their respective panels (hematology, serum chemistry, and urinalysis). Abnormal values will be flagged.

Table 2. Laboratory Potentially Clinically Significant Values

Chemistry		**Hematology**	
Alkaline Phosphatase	≥ 3 x Upper Limit Normal	Hemoglobin	≤11.5 g/dL (male) ≤9.5 g/dL (female)
AST	≥ 3 x Upper Limit Normal		
ALT	≥ 3 x Upper Limit Normal	Hematocrit	≤37% (male) ≤32% (female)
BUN	≥ 30 mg/dL		
Creatinine	≥ 2.0 mg/dL	RBC count (absolute)	<3.8 10^6/uL or > 5. 5 10^6/uL
CPK	≥ 2 x Upper Limit Normal	White blood cells	<4.5 10^3/uL or >13.5 10^3/uL
Gamma glutamyl transferase	≥ 2 x Upper Limit Normal	Neutrophils	≤ 15%
Lactate dehydrogenase	≥ 300 U/L	Eosinophils	>0.7 10^3/uL
Glucose	≥ 100 mg/dL (fasting) ≥ 200 mg/dL (non-fasting)	Platelet count	≤75 10^3/uL or ≥750 10^3/uL
		Urinalysis Parameter	
Chloride	< 95 mmol/L or > 110 mmol/L	Protein	Increase of ≥ 2 units
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL	Albumin or microalbumin	Increase of ≥ 2 units
Magnesium	<1.4 mg/dL or > 2.7 mg/dL	Glucose	Increase of ≥ 2 units
Phosphorous	<2 mg/dL or >6 mg/dL		
Potassium	<3 mmol or > 6 mmol		
Protein, total	<5 g/dL or > 9 g/dL		
Sodium	< 130 mmol/L or > 150 mmol/L		
Uric Acid	≥ 10.5 mg/dL (male) ≥ 8.5 mg/dL (female)		

9.4. Vital Signs, Body Weight and Height

Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), height, and weight will be assessed at the scheduled visits specified in Section 4.6.

A summary table of observed and change from baseline values will be provided at each scheduled visit for the enrolled population, from baseline at Month 3, Month 6, Month 9, and Month 12 and by each subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible for the enrolled population. By-visit summary will also include the last post-baseline values.

The incidence rates of PCS vital sign values and changes from baseline (Table 3), by parameter, will be summarized. The summary will indicate the number and percentage of subjects with PCS-low and PCS-high values at any time during treatment and will not be presented by visit.

A by-subject listing will be provided for each vital sign parameter.

Table 3. Vital Signs Potentially Clinically Significant Values

Parameter	Baseline PCS Criterion	Post-Baseline PCS Criterion
Heart Rate	≥100 bpm (high) ≤60 bpm (low)	≥100 bpm and CFB ≥15 (high) ≤60 bpm and CFB ≤-15 (low)
Diastolic Blood Pressure	≥83 mmHg (high) ≤64 mmHg (low)	≥83 mmHg and CFB ≥15 (high) ≤64 mmHg and CFB ≤-15 (low)
Systolic Blood Pressure	≥131 mmHg (high) ≤110 mmHg (low)	≥131 mmHg and CFB ≥20 (high) ≤110 mmHg and CFB ≤-20 (low)
Weight	NA	Percent CFB ≥7% (high) Percent CFB ≤-7% (low)

*CFB = change from baseline

9.5. Electrocardiogram Results

A summary table of observed and change from baseline values in ECG results will be provided at each scheduled visit for the enrolled population. A summary table displaying shifts in interpretation from baseline to each assessment time-point, including the last post-baseline assessment, will be provided by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible. By-visit summary will also include the last post-baseline values.

A by-subject listing will be provided, including each ECG parameter: heart rate (beats per minute [bpm]), PR interval [msec], QRS interval [msec], QT interval mean [msec], QTc (QTcF or QTcB) [msec] and interpretation. QTc=corrected QT interval, QTcF = corrected QT interval with Fridericia's formula, and QTcB = corrected QT interval with Bazett's formula.

9.6. Physical Examination

Complete physical examination, including HEENT (Head, Eyes, Ears, Neck and Throat), Respiratory, Cardiovascular, Dermatological, Lymph Nodes, Gastrointestinal, Neurological, Thyroid, Musculoskeletal and other assessments, will be conducted at baseline and each scheduled visit. A categorical summary table will be provided of the physical examination findings at each scheduled visit for the enrolled population by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible. By-visit summary will also include the last post-baseline values.

A by-subject listing will be presented for each body system.

9.7. Tanner Stage

A summary table of assessment results in Tanner stage will be provided at each scheduled visit by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible for the enrolled population. By-visit summary will also include the last post-baseline values.

A by-subject listing will be presented for each Tanner stage parameter, including pubic hair development, breast development, and genital development.

10. Reference List

Online source for PedsQL™ scoring:

http://www.lsebn.nhs.uk/website/X13911/files/20%20scoring_PedsQL_v13[1].pdf

11. Interim Analyses

No interim analyses are planned.

12. Changes from Analysis Planned in Protocol

As the subjects who receive at least 1 dose or partial dose of study drug will coincide with enrolled subjects in this study, the safety and intent-to-treat population have been removed and replaced with a single “enrolled population. All PD and safety analyses will be conducted on the enrolled population.

No other changes are planned from the analyses described in the protocol amendment 1 (24JUN2019),

13. Programming Considerations

All TLFs and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

One SAS® program can create several outputs.

Each output will be stored in a separate file.

Output files will be delivered in Word format or portable document format (pdf).

Numbering of TLFs will follow ICH E3 guidance

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TLFs will be produced in landscape format on A4/American letter size, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch blank margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

  Amicus Therapeutics
  Protocol: AT1001-020
- All output should have the Data Cut-off Date at the top right of each page.

- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page. Each table should have the relevant listing number containing the raw data as a footer.

13.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering convention will be followed. A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is centered. The analysis population is identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Enrolled Population)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the total column.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis population sizes will be presented for each column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis population.

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and

- Numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- The summary tables will clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

- Units will be included where available

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.

- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and SD are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. P-values less than 0.001 will be presented as <0.001. If a p-value is less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis population who have an observation will be the denominator. Percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are presented by the body system, treatment class, or SOC, PT, assuming all terms are coded. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject is included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. Listing Conventions

- Listings will include days relative to the initiation of treatment as applicable.

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

13.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.

- Subject specific footnotes are avoided, where possible.

- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (ie, 'Program: myprogram.sas Listing source: 16.x.y.z').

14. Quality Control

SAS® programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health Standard Operating Procedure (SOP) Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Quality Deliveries (SDTM, ADaM, TLF) (3908) describes the quality control procedures that are performed for all SAS® programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.