Statistical Analysis Plan

Study Drug:
Migalastat Hydrochloride

Protocol Number: AT1001-020

Study Title:
An Open-label Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of 12-Month Treatment with Migalastat in Pediatric Subjects (aged 12 to <18 years) with Fabry Disease and Amenable *GLA* Variants

Version: 1.0

Date: 20Oct2020

Based on: Protocol Amendment 4 (13Jun2019)

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Revision History

Version #	**Date** (DDMmmYYYY)	**Document Owner**	**Revision Summary**
1.0	20Oct2020	Amicus	Final Version

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

Approvals

Syneos Health Approval

Name, Title	Signature	Date (DD-Mmm-YYYY)
Amicus	Amicus *Date: Nov 6 2020 09:41 EST*	
Amicus	Amicus *Date: Nov 10, 2020 10:58 EST*	

Amicus Therapeutics Approval

Name, Title	Signature	Date (DD-Mmm-YYYY)
Amicus	Amicus	ember 2020 | 16:11 GMT

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1. Glossary of Abbreviations

Abbreviation	Description
α-Gal A	α-Galactosidase A
ADaM	Analysis Data Model
AE	Adverse Event
AT1001	Migalastat
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
cm	Centimeters
CRF	Case Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DOB	Date of Birth
ECG	Electrocardiogram
ECHO	Echocardiography
eCRF	Electronic Case Report Form
e-diary	Electronic Diary
eGFR	Estimated Glomerular Filtration Rate
ERT	Enzyme Replacement Therapy
ET	Early Termination
FABPRO-GI	Fabry Disease Patient-Reported Outcome – Gastrointestinal Signs and Symptoms
FPHPQ	Fabry-Specific Pediatric Health and Pain Questionnaire
GI	Gastrointestinal
GLA	Gene Encoding α-Galactosidase A
h	Hours
HEENT	Head, Eyes, Ears, Neck and Throat
ICH	International Conference on Harmonisation
IRT	Interactive Response Technology
ITT	Intent to Treat
kg	Kilograms

Abbreviation	Description
LCL	Lower Confidence Limit
LVMi	Left Ventricular Mass Index
lyso-Gb_3	Globotriaosylsphingosine
m	Meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
min	Minutes
PCS	Potential Clinical Significance
PedsQL™	Pediatric Quality of Life Inventory™
PGI-C	Patient Global Impression of Change
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAP	PK Analysis Plan
PR	PR Interval
PT	Preferred Term
QOD	Every other day
QRS	QRS Complex
QT	QT Interval
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
SE	Standard Error
SI	Système International
SYNH	Syneos Health
SOC	System Organ Class
SOP	Standard Operating Procedure

Abbreviation	Description
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)

2. Introduction

This Statistical Analysis Plan (SAP) is created based on Protocol Number AT1001-020, Amendment 4, 13Jun2019. The purpose of this SAP is to outline the planned analyses by Syneos Health (SYNH) 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 International Conference on Harmonisation (ICH) guidelines E9 (R1) Statistical Principles for Clinical Trials. They will be included in regulatory submissions and/or future manuscripts.

2.1. Responsibilities

SYNH will perform the statistical analyses and is responsible for the production and quality control of all tables, listings and figures (TLFs). Syneos Health will not be responsible for the pharmacokinetic (PK) analysis; it will be analyzed separately by another vendor and detailed in a PK Analysis Plan (PKAP).

2.2. Timings of Analyses

The primary analysis of safety and efficacy 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.

3. Study Objectives and Endpoints

3.1. Study Objectives

3.1.1. Primary Objectives

The primary objectives of Stage 1 are as follows:

- to characterize the PK of migalastat in adolescents with Fabry disease and to validate extrapolation of migalastat plasma exposure in adults to adolescents weighing ≥ 45 kilograms (kg) for the 150 milligrams (mg) migalastat capsule administered every other day (QOD);
- to evaluate the safety of migalastat treatment in pediatric subjects diagnosed with Fabry disease and who have variants in the gene encoding α-galactosidase A (α-Gal A) (*GLA*) amenable to treatment with migalastat.

The primary objective of Stage 2 is as follows:

- to evaluate the safety of migalastat treatment in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat.

3.1.2. Secondary Objective(s)

The secondary objectives are as follows:

Stage 1:

- Not applicable.

Stage 2:

- 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 evaluate the efficacy of migalastat in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat;
- to evaluate the relationship between exposure to migalastat and response.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

Efficacy endpoints are as follows:

- change in estimated glomerular filtration rate (eGFR) from baseline to Months 3, 6, and 12/Early Termination (ET), and annualized rate of change from baseline
- change in urine protein and albumin levels from baseline to Months 3, 6, and 12/ET
- change in left ventricular mass index (LVMi) and other echocardiogram (ECHO) parameters from baseline to Month 12/ET
- change in gastrointestinal signs and symptoms and pain from baseline to Month 12/ET, as measured by e-diary (electronic diary) responses (Short Fabry Disease Patient-Reported Outcome – Gastrointestinal Signs and Symptoms [FABPRO-GI] and Pain Questionnaire for Clinical trials [24-hour version])
- mean Patient Global Impression of Change (PGI-C) values at Months 3, 6 and 12/ET

- change in Fabry-Specific Pediatric Health and Pain Questionnaire (FPHPQ) scores from baseline to Month 12/ET
- change in Pediatric Quality of Life Inventory™ (PedsQL™) scores from baseline to Month 12/ET

3.2.2. Pharmacodynamic Endpoints

Pharmacodynamic endpoint is as follows:

- change in plasma levels of lyso-Gb_3 (Globotriaosylsphingosine) from baseline to Months 3, 6, and 12/ET.

3.2.3. Safety Endpoints

Safety endpoints are as follows:

- incidence of treatment-emergent adverse events (TEAEs), Serious Adverse Events (SAEs), and adverse events (AEs) leading to discontinuation of study drug
- changes in clinical laboratory test results from baseline over time
- changes in vital signs from baseline over time
- changes in physical examination findings from baseline over time
- changes in body weight and height from baseline over time
- changes in 12-lead electrocardiogram (ECG) results from baseline over time
- changes in ECHO parameters from baseline to Month 12/ET
- change in Tanner stage from baseline to Month 12/ET
- use of concomitant medications

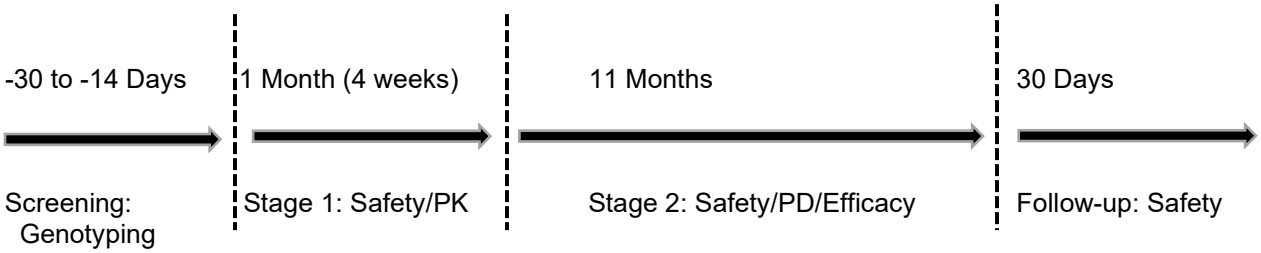
4. Study Design

4.1. Summary of Study Design

This is a Phase 3b, 2-stage, open-label, uncontrolled, multicenter study to evaluate the safety, PK, PD, and efficacy of migalastat treatment in pediatric subjects 12 to < 18 years of age and weighing ≥ 45 kg (99 pounds) with Fabry disease and with amenable *GLA* variants. Subjects must be either naïve to enzyme replacement therapy (ERT) or have stopped ERT at least 14 days at the time of screening.

The study will consist of 2 stages. Stage 1 will be a treatment period of approximately 1 month (4 weeks); Stage 2 will be a treatment period of 11 months and a 30-day (untreated) safety follow-up period. There will be no break in treatment between Stages 1 and 2. Prior to Stage 1, there will be a screening period lasting at least 14 days and up to 30 days (or more, if *GLA* genotyping is required). The study will consist of a screening period up to 30 days, a 12-month treatment period, and a 30-day safety follow-up period, for a total of approximately 14 months.

Figure 1: Study Design



Safety assessments include monitoring AEs, clinical laboratory tests, vital signs, physical examinations, body weight and height, 12-lead ECGs, ECHOs, Tanner staging of sexual development, and use of concomitant medications. Sparse blood samples for determination of plasma migalastat concentrations and PK analysis will be collected. The PD biomarker to be evaluated in this study is lyso-Gb_3 levels in plasma. Blood samples will also be collected for exploratory biomarkers.

Efficacy assessments include eGFR, urine protein and albumin levels, ECHO parameters, and subject questionnaires (FABPRO-GI and Pain Questionnaire, PGI-C, FPHPQ, and PedsQL™). The key ECHO parameter considered for efficacy is LVMi. In addition, ejection fraction, fractional shortening, left ventricular internal diameter end diastole and end systole, midwall fractional shortening, and wall thickness will be assessed. Echocardiograms will be read centrally.

A Data Monitoring Committee (DMC) will operate according to a charter that includes operational and logistical procedures for the DMC. The DMC will monitor and evaluate all available safety data from this study by reviewing summaries of safety data on a regular basis, evaluating risk/benefit where possible, identifying any clinically relevant trends through the study, and assessing whether it is safe for the subject and/or study to continue.

4.2. 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.

4.3. Determination of Sample Size

A sample size of at least 7 to 10 subjects per age/weight group is required for statistical comparison with adult exposure based on 2 methods described by Wang et al. 2012.

First, assuming the final plasma clearance estimates and inter-individual variability of 28.5% (Migalastat Abbreviated Report of the Simulations of Migalastat in Pediatric Patients with Fabry Disease, 16 October 2016), a sample size of 7 subjects is adequate to achieve at least 80% power for a study design with rich PK sampling intended for non-compartmental analysis.

Second, according to the sample size calculation for a study with sparse/rich PK sampling intended for population PK analysis, (e^(-t(0.975,df)×〖SE〗_LCL),e^(t(0.975,df)×〖SE〗_LCL)) [SE= Standard Error, LCL=Lower Confidence Interval] should be within the pre-defined criteria of (0.6, 1.4), where SE_LCL is the standard error for log-transformed pediatric clearance that relates to weight, and t (0.975, df) is the 97.5% upper quantile values from t distribution corresponding to the sample size. Mathematically, SE_LCL was approximately equal to the relative standard error of untransformed clearance, 0.16. Therefore, a sample size of approximately 10 subjects is adequate to achieve the pre-defined boundary of (0.6, 1.4).

4.4. Randomization

As all subjects receive migalastat in this study, no randomization to treatment will be performed. Randomization will be used for sparse PK sampling as described below. The timing of PK samples was determined using optimal sampling theory using PopED and mrgsolve software packages in R using a D-optimality algorithm.

Subjects will be randomly assigned 1:1:1 to 1 of 3 PK sampling groups using interactive response technology (IRT). Four blood samples for determination of migalastat concentrations in plasma will be collected in one 24-hour period between Day 15 and Day 30 following initiation of study drug administration. Blood sampling for PK is relative to migalastat administration. Each subject will have 4 PK samples collected at the times specified in Table 2 according to their randomized PK sampling group assignment.

Table 1. Sparse Pharmacokinetic Sampling

PK Sampling Group[a]	Time Post-dose			
	Sample 1	Sample 2	Sample 3	Sample 4
1	1 hour (h) to 1h 15 minutes (min)	1h 30min to 2h	5h to 5h 30min	6h 30min to 7h
2	1h to 1h 15min	2h 45min to 3h 15min	5h 15min to 5h 45min	10h 45min to 11h 15min
3	3h 15min to 3h 45min	3h 45min[b] to 4h 15min	8h 15min to 8h 45min	8h 45min[b] to 9h 15min

[a] Sample should NOT be taken at the same time as the previous sample. Samples should be taken approximately 15 minutes apart at a minimum.

4.5. Administration of Study Medication

One migalastat 150 mg capsule will be administered with water every other day continuously for 12 months during Stages 1 and 2 of the study. Subjects should take study drug at the same time of day during the every other day dosing schedule and not eat for at least 2 hours before and after administration.

4.6. Study Procedures and Flowchart

The below table details the schedule of assessments:

Table 2. Schedule of Assessments

Assessments	Screening[a]	Treatment Period														Treatment Period
		Stage 1			Stage 2											
	Day -30 to -14	Baseline[b] Day 1	Day 15-30	Month 1	Month 2 (TC)	Month 3	Month 4 (TC)	Month 5 (TC)	Month 6	Month 7 (TC)	Month 8 (TC)	Month 9	Month 10 (TC)	Month 11 (TC)	Month 12/ET	30-Day Safetye
Window (days)	—	—		±3	±3	±3	±3	±3	±6	±6	±6	±6	±6	±6	±6	+6
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Informed consent/assent	X															
Inclusion/exclusion criteria	X	X														
Demography	X															
Medical history	X	X														
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirmatory *GLA* Genotyping	X															
Confirmation of amenable *GLA* variant	X															
Dosing diary		X	→	→	→	→	→	→	→	→	→	→	→	→	X	
FABPRO-GI and Pain Questionnaire		X	→	→	→	→	→	→	→	→	→	→	→	→	X	
FPHPQ questionnaire		X		X		X			X			X			X	
PedsQL™		X		X		X			X			X			X	
PGI-C						X			X			X			X	
Complete physical examination	X	X				X			X						X	

Table 2. Schedule of Assessments (Continued)

Assessments	Screening[a]	Treatment Period														Treatment Period
		Stage 1			Stage 2											
	Day -30 to -14	Baseline[b] Day 1	Day 15-30	Month 1	Month 2 (TC)	Month 3	Month 4 (TC)	Month 5 (TC)	Month 6	Month 7 (TC)	Month 8 (TC)	Month 9	Month 10 (TC)	Month 11 (TC)	Month 12/ET	30-Day Safety[e]
Window (days)	—	—		±3	±3	±3	±3	±3	±6	±6	±6	±6	±6	±6	±6	+6
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Brief physical examination			X	X								X				
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, RR, Temp)	X	X	X	X		X			X			X			X	
Body weight	X	X	X	X		X			X			X			X	
Height	X	X		X		X			X			X			X	
Tanner Staging		X							X						X	
12-Lead ECG	X	X							X						X	
Chemistry (including eGFR using Schwartz formula)	X	X				X			X						X	
Hematology		X							X						X	
Plasma lyso-Gb_3 and analogs		X				X			X						X	
Exploratory PD biomarkers		X							X						X	
PK blood samples			X[c]						X						X	
Urinalysis (urine protein and albumin or microalbumin levels)	X	X		X		X			X						X	

Table 2. Schedule of Assessments (Continued)

Assessments	Screening[a]	Treatment Period														Treatment Period
		Stage 1			Stage 2											
	Day -30 to -14	Baseline[b] Day 1	Day 15-30	Month 1	Month 2 (TC)	Month 3	Month 4 (TC)	Month 5 (TC)	Month 6	Month 7 (TC)	Month 8 (TC)	Month 9	Month 10 (TC)	Month 11 (TC)	Month 12/ET	30-Day Safety[e]
Window (days)	—	—		±3	±3	±3	±3	±3	±6	±6	±6	±6	±6	±6	±6	+6
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Urine pregnancy test or date of LMP (as applicable)[d]	X	X		X	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[b]		X		X			X			X			X	

Abbreviations: BP = blood pressure;HR = heart rate; LMP = last menstrual period; RR = respiration rate; TC = telephone call; Temp = body temperature

[a] For subjects without a documented *GLA* variant, screening procedures will be suspended until such time that a confirmed, amenable variant is determined.

[b] All baseline assessments must be completed BEFORE the first dose of migalastat is administered.

[c] Blood samples for plasma migalastat concentrations will be taken during one 24-hour period between Day 15 and 30 following initiation of study drug administration.

[d] Female subjects only

[e] Only for subjects who do not enroll in a long-term extension study

5. Analysis Population

5.1. Safety Population

The safety population will include all subjects who receive at least 1 dose or partial dose of study drug. All safety and PD analyses will be performed using the safety population.

5.2. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all enrolled subjects. All efficacy analyses will be performed using the ITT population.

5.3. Pharmacokinetic Population

The Stage 1 PK population will include all subjects who have a complete set of sparse PK samples from the single day of collection at steady-state between Day 15 and Day 30 of Stage 1.

The final PK population will include all subjects with at least one quantifiable concentration and a known weight and eGFR. All final PK analyses will be performed using the final PK population.

The PK analysis will be included in a separate PKAP.

5.4. Protocol Deviations

Protocol deviations are defined as instances in which subjects or investigational site study personnel fail to adhere to the protocol requirements (eg, 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).

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

6. General Aspects for Statistical Analysis

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

6.1. 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 6.7. Missing AE intensity and relationship will be imputed as described in Section 6.7.2. 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.

6.2. 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, Intent-to-treat 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.

6.3. 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.

6.4. Data Presentation Conventions

6.4.1. 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.

6.4.2. 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).

6.4.3. p-values

Not applicable.

6.4.4. 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.

6.5. Baseline Definition

For all safety 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.

6.6. Derived and Transformed Data

6.6.1. Calculations Using Dates

6.6.1.1. Baseline Age

Age for enrolled subjects will be calculated as the truncated difference (eg, fractional part ignored) between the date of the informed consent and the subject's birth date (DOB) adjusted for years (ie, AGE = int[(Visit 1 – DOB) / 365.25]).

6.6.1.2. Study Day

There is no Day 0. Study Day 1 denotes the day of the first dose and is the reference start date for all safety 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. 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.

6.6.1.3. 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.

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).

6.6.1.4. Change from Baseline

The change from baseline will be calculated as the post-baseline visit value minus the baseline value (the value prior to or on the date of first administration of the study drug).

6.6.1.5. Visit Windows

There will be no derivation for visit windows in terms of summary assessments. Nominal visits will be used for by-visit tables. There is visit mapping rule only for monthly average scores of FABPRO-GI and Pain Questionnaire, see Section 8.3.1 for details.

6.6.1.6. Multiple Assessments

If multiple assessments including assessments at the unscheduled visit, are associated with a nominal visit post-baseline, the last assessment will be used.

6.7. Handling of Missing Data

6.7.1. 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,

- 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 adverse events will not be imputed.

6.7.2. Missing Adverse Event Intensity and Relationship

If an AE is missing the intensity or relationship to study drug, the AE will be classified under the maximum intensity (ie, severe) or the maximum relationship (ie, definite), respectively.

6.7.3. 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 6.7.1 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.

7. Demographic, Other Baseline Characteristics and Medication

7.1. 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 ITT population.

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

- Subjects in the ITT population
- Subjects in the safety population
- Subjects in the PK population
- Subjects who completed the study
- Subjects who discontinued early overall and by reason

In addition, the number of screened subjects and screen failures will be provided.

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

7.2. 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 ITT population. Demographic data will include age (continuous and categorical), gender, 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 ERT, and previous and current use of angiotensin-converting enzyme inhibitors, renin inhibitors, and angiotensin receptor blockers. The following calculations will be utilized:

- Age = (informed consent date - date of birth + 1) / 365.25 and truncated to complete years
- Weight (in kg) = weight (in pounds) *0.4536
- Height (in cm) = height (in inches) * 2.54
- BMI (kg/m^2) = weight(kg)/[(height(cm)/100)^2], where m = meters
- Number of years since diagnosis of Fabry disease = (informed consent date - 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 informed consent date – 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 and ERT experienced.

All demographic and baseline characteristic data will also be listed, including the protocol version (captured in eCRF) under which the subject was screened and the date of informed consent.

7.3. 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 safety 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 verbatim Case Report Form (CRF) term will also be provided.

7.4. Prior and Concomitant Medications

Medications will be classified as prior (started prior to the first dose of study treatment) and concomitant (continued past or started on or after the first dose of study treatment).

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 safety subjects 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 days.

Prior ERT will be summarized by preferred drug name for the safety population.

8. Efficacy

Observed values and changes from baseline for each efficacy endpoint in Section 3.2.1 will be summarized with descriptive statistics at each scheduled time point based on the ITT 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.

8.1. Laboratory Assessments

Efficacy analyses will include summaries of observed and change from baseline values for the eGFR, urine protein and albumin for scheduled visits, indicated in Section 4.6. Scheduled visits will only be included for by-visit summary.

Annualized rate of change from baseline of eGFR will be included in the summary table. Annualized rate of change from baseline of eGFR is defined as change from baseline to last visit divided by the duration from baseline to the last visit (Last assessment date – First dose date +1) and multiplied by 365.25.

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

8.2. Echocardiography

A summary table of observed and change from baseline values in numerical echocardiography results will be provided at each scheduled visit.

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.

8.3. Subject Questionnaires

8.3.1. Electronic Diary (FABPRO-GI and Pain Questionnaire for Clinical Trials [24-hour version])

Subjects are asked to complete daily diary entries at approximately the same time of day (preferably in the evening before bed time) beginning on Day 1 and for the duration of the study. Diary entries will include completion of the short FABPRO-GI and Pain Questionnaire.

The FABPRO-GI and Pain Questionnaire for Clinical Trials (24-hour version) consists of 4 questions regarding gastrointestinal signs and symptoms and 2 questions regarding pain relative to the past 24 hours. Subjects will record the frequency and consistency of stools using the Bristol Stool Scale, a pictorial chart and descriptive text for 7 types of stool, ranging from Type 1 (separate hard lumps, like nuts – hard to pass) through Type 7 (watery, no solid pieces – entirely liquid). Subjects will also rate the severity of their worst occurrence of diarrhea, constipation, tummy pain, and overall pain from 0 (none) to 10 (worst possible); for tummy pain, subjects will indicate the location of any tummy pain using a diagram.

Descriptive summary tables will be provided for observed monthly average scores of e-diary responses for FABPRO-GI and Pain Questionnaires for Clinical Trials (24-hour version) by subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible.

e-diary responses will include:

1) Monthly average of worst tummy pain in past 24 hours score based on the tummy pain question in the FABPRO-GI and Pain Questionnaire for Clinical Trials (24-hour version) with its 0 to 10 scale (0 = no pain, 10 = worst possible pain)
2) Monthly average of overall pain in past 24 hours score in the (FABPRO-GI and Pain Questionnaire for Clinical Trials (24-hour version) with its 0 to 10 scale (0 = no pain, 10 = worst possible pain)
3) Monthly average of daily ratings of severity will be assessed separately for each of the following items: diarrhea and constipation.

Visit mapping:

FABPRO-GI and Pain questionnaires are assessed daily. For each subject, there are scheduled visits at Month 1, 3, 6, 9 and 12/ET. The closest date to the date of the scheduled visits are mapped to the corresponding visits. If there are multiple dates at the same distance to the scheduled date, the later date will be assigned to the scheduled visit.

Monthly averaged scores:

The monthly average score is calculated as the sum of the total scores of each test from 30 day prior to the scheduled dates of Month 1, 3, 6, 9 and 12/ET divided by the number of days when actual assessments were done. If there are more than 6 days of missing assessments, then the total score for the monthly scheduled visit is set as missing, since less than 80% assessments are available.

A by-subject listing of responses from FABPRO-GI and Pain Questionnaires for Clinical Trials (24-hour version) will be provided.

8.3.2. Patient Global Impression of Change

The PGI-C consists of 4 questions regarding diarrhea, abdominal (tummy) pain, overall pain, and daily living to be answered using a 7-point scale. Descriptive by visit summary tables at Month 3, 6 and 12/ET will be provided for observed PGI-C scores and average of overall Gastrointestinal (GI) symptoms scores. Categorical summary of improved and worsened status for each question at Month 3, 6 and 12/ET will also be summarized by visit and subgroup, ie, sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible. Improved status includes “Much better”, “Better” and “A little better”; Worsened status includes “A little worse”, “Worse” and “Much worse”; “The same” will be categorized separately.

A by-subject listing of PGI-C Questionnaires will be provided.

8.3.3. 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 (0=Never, 1=Seldom, 2=Sometimes, 3=Often, 4=Always). Pain intensity 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. There are 2 age-specific self-report versions for children 8 to 12 years and 13 to 18 years, respectively.

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 experienced), and overall if feasible. Unscheduled visits will not be included.

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

8.3.4. 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 PedsQL™ 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.

A by-subject listing of PedsQL™ scores for each single question as well as psychosocial, physical and total scores will be provided.

9. Analysis of Pharmacokinetics

Analysis of PK will be described in a separate PKAP.

10. Analysis of Pharmacodynamics

10.1. Primary PD Endpoint and Analysis

The PD endpoint is change in plasma levels of lyso-Gb_3. Descriptive summaries will be provided for the change from baseline to Month 3, Month 6, and Month 12/ET by sex (male and female) , ERT status (ERT naïve, ERT experienced), and overall based on the safety population.

A by-subject listing will also be provided.

10.2. Other PD Analogs Analysis

Other PD endpoints are change in plasma levels of lyso-Gb_3 analogs. Descriptive summaries will be provided for the change from baseline to Month 3, Month 6, and Month 12/ET by sex (male and female), ERT status (ERT naïve, ERT experienced), and overall based on the safety population.

A by-subject listing will also be provided.

11. Safety

The analysis population used for safety analyses will be the safety 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, ECHO, ECG parameters, physical examinations, and tanner stage.

11.1. Extent of Exposure and Drug Compliance

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

Average Dose Every Other Day is defined as:

Average Dose Every Other Day = [Total dose received/ (Duration of exposure + 1)] * 2

Drug Compliance is defined as:

Drug Compliance (%) = Average Dose Every Other Day/Planned Dose Every Other Day (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.

11.2. Adverse Events

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

- 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 intensity, by SOC and PT
- Serious TEAEs by SOC and PT
- Any non-serious TEAE by PT

The number and percentage of subjects reporting TEAEs will be tabulated by SOC and PT. Subjects are counted only once within each SOC and PT. TEAEs will be presented alphabetically by SOC and PT.

The number and percentage of subjects reporting TEAEs will also be tabulated by PT. Subjects are counted only once in each PT. TEAEs will be presented in the order of descending frequency in the overall group.

The number and percentage of subjects reporting TEAEs will be tabulated by SOC, PT and maximum 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 preferred term, but one was moderate and the other severe, the severe TEAE will be included in the tabulation.

The number and percentage of subjects reporting treatment-related serious TEAEs will be tabulated by SOC and PT. Subjects are counted only once within each SOC and PT. Subject listings will also be provided for subjects with SAEs.

11.3. 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 safety population. In addition, the following clinical summaries will be presented:

- The frequencies and percentages of potential clinically significant (PCS) abnormalities at any time;
- Tables displaying shifts from baseline to each assessment time-point in laboratory test values from normal to high or low using normal range including eGFR, urine protein, and albumin.

Potential clinically significant abnormalities will be determined both by investigator assessment or derivation from lab alert ranges provided by Amicus.

Clinically significant abnormal assessments for eGFR, urine protein and albumin will be summarized with frequency tables by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible. Unscheduled visits will be included. Clinically significant abnormal values will be collected from investigator assessment on the CRF page.

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).

11.4. Vital Signs, Body Weight, and Height

Vital signs (blood pressure, pulse rate, respiratory rate, and oral 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 safety population, from baseline at Day 1-15, Month 1, Month 3, Month 6, Month 9 and Month 12/ET. Clinically significant abnormal results, in which unscheduled visits will be included, will be summarized with the frequency tables by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible.

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

11.5. Echocardiography

For categorical echocardiography results, an observed summary table will be provided by each parameter and visit in safety population. Scheduled visits will be included for by-visit summary tables.

Clinically significant abnormal assessments for each parameter will be summarized with frequency tables by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible. Unscheduled visits will be included. Clinically significant abnormal values will be collected from investigator assessment on the CRF page.

11.6. ECG

A summary table of observed and change from baseline values in ECG results will be provided at each scheduled visit for the safety population. A summary table displaying shifts from baseline to worst post-baseline interpretation assessment (including unscheduled assessments as applicable) will be provided by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible.

A by-subject listing will be provided, including each ECG parameter: heart rate (beats per minute [bpm]), RR interval [msec], 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.

12. Reference List

Wang Y, Jadhav P, Lala M, Gobburu J. (2012). Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. The Journal of Clinical Pharmacology. 52:1601-1606.

Online source for PedsQL™ scoring:

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

12.1. 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 Month 3, 6, and 12/ET visits. A categorical summary table will be provided of the physical examination findings at each scheduled visit for the safety population by sex (male, female), ERT status (ERT naïve, ERT experienced), and overall if feasible. A by-subject listing will be presented for each body system.

Brief physical examination will be summarized at Day 15-30, Month 1 and 9 visits. A by-subject listing will also be presented.

12.2. Tanner Stage

A summary table of assessment results in Tanner stage will include Baseline, Month 6 and12/ET visits for the safety population by sex (male, female), ERT status (ERT naïve, ERT experienced). A by-subject listing will be presented for each Tanner stage parameter, including pubic hair development, breast development, and genital development.

13. Interim Analyses

An interim analysis was conducted on Stage 1 data for PK and safety assessments. The details are provided in a separate Interim SAP.

14. Changes from Analysis Planned in Protocol

No changes are planned from the analyses described in the protocol, amendment 1 (10Sep2018), amendment 2 (31Oct2018), Protocol Amendment 3 (22Apr2019), and Protocol Amendment 4 (13Jun2019).

15. 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.

15.1. 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

15.2. Table, Listing, and Figure Format

15.2.1. 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 (eg, μ). Certain subscripts and superscripts (eg, 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.

15.2.2. 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 (ie, 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.

15.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (ie, 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
(ITT population)

15.2.4. 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.

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

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

- Alphanumeric values are left-justified;

- Whole numbers (eg, counts) are right-justified; and

- Numbers containing fractional portions are decimal aligned.

15.2.5.2. 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 (eg, 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 (eg, 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 adverse event 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 are 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.

15.2.5.3. 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 (eg, 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

15.2.5.4. Figure Conventions

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

15.2.6. 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').

16. 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.