An Open-Label Extension Study to Evaluate the Long-term Safety and Efficacy of Migalastat Hydrochloride Monotherapy in Subjects With Fabry Disease

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STATISTICAL ANALYSIS PLAN

AT1001-042

AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG TERM SAFETY AND EFFICACY OF MIGALASTAT HYDROCHLORIDE MONOTHERAPY IN SUBJECTS WITH FABRY DISEASE

AUTHOR: Amicus

VERSION NUMBER AND DATE: FINAL V1.0**, 21AUG2019**

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 21Aug2019) for Protocol AT1001-042

	Name	Signature	Date
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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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1.0	21Aug2019	Amicus	Not Applicable – First Version

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1. LIST OF ABBREVIATIONS

ACEi	Angiotensin-converting Enzyme Inhibitors
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
APOINT	Peak Mitral Inflow Velocity A
ARB	Angiotensin II Receptor Blockers
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quatification
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
CS	Clinically Significant
CTMS	Clinical Trial Management System
DSMB	Data Safety Monitoring Board
EARATIO	Mitral Valve E/A Ratio
ECG	Electrocardiogram
ECHO	Echocardiography
eGFR	Estimated Glomerular Filtration Rate
ENR	All Enrolled Population
EOS	End of Study
EPOINT	Peak Mitral Inflow Velocity E
ERT	Enzyme Replacement Therapy
FS	Fractional Shortening
GGT	Gamma – Glutamyltransferase
GH	General Health
HDL	High Density Lipoprotein
HR	Heart Rate
IA	Interim Analysis
IP	Investigational Product
ITT	Intent-to-Treat
IVSTD	Intraventricular Septum Thickness Diastolic
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
LVIDd	Left Ventricular Internal Dimension at End Diastole
LVIDs	Left Ventricular Internal Dimension at End Systole
LVMi	Left Ventricular Mass Index
LVPWTD	Left Ventricular Posterior Wall Thickness Diastole

MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
MWFS	Midwall Fractional Shortening
NCS	Not clinically Significant
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PF	Physical Functioning
PK	Pharmacokinetic
PSRAE	Possible Suicidality Related Adverse Event
PT	Preferred Term
Q4D	Every Fourth Day
QOD	Every Other Day
RBC	Red Blood Cell
RE	Role Emotional
RI	Renin Inhibitors
RP	Role Physical
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF	Social Functioning
SF-36	Short Form 36
SOC	System Organ Class
ULQ	Upper Limit of Quantification
VI	Vitality
WBC	White Blood Cell
WHO-DDE	World Health Organization Drug Dictionary Enhanced

2. INTRODUCTION

This statistical analysis plan (SAP) is based on protocol amendment 1.1 with site-specific addendum 1.1.2, dated 22Jan2018, and it describes the rules and conventions to be used in the presentation and analysis of long-term safety, tolerability, pharmacodynamic (PD), and efficacy data for Protocol AT1001-042, and additionally pharmacokinetic (PK) data for addendum 1.1.2. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

A Data Safety Monitoring Board (DSMB) has been chartered to evaluate accumulating safety data in this clinical trial and a DSMB SAP final version 1.1 was effective on 25Oct2015.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

To assess the long-term safety of migalastat HCl in the treatment of subjects with Fabry disease who completed treatment in a previous study of migalastat HCl.

3.2. SECONDARY OBJECTIVES

To explore the long-term efficacy/pharmacodynamics of migalastat HCl in subjects with Fabry disease who completed treatment in a previous study of migalastat HCl.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This study is a multi-center, non-comparative, open-label, long-term extension study of migalastat HCl in subjects with Fabry disease who have completed treatment in a previous trial of migalastat HCl given as monotherapy. All subjects who were eligible for enrollment and completed migalastat HCl monotherapy treatment in a previous study, and who in the opinion of the investigator could benefit from remaining on migalastat HCl treatment were given the option to enroll into this trial. An alternative dosing regimen will be established per the addendum 1.1.2 for those

subjects with renal impairment (glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2), confirmed during the enrollment of the original protocol and amendment 1 and 1.1. The number of subjects to be enrolled in this study is expected to be up to 100, but is dependent on the number of eligible subjects completing migalastat HCl treatment in previous studies and who consent to enter this open-label extension study. Therefore, no sample size will be calculated.

The study will consist of a Baseline Visit (Visit 1) which will be performed at the time of the final visit of the previous study, followed by clinic visits every 6 months during the study. For the Addendum 1.1.2 subjects with renal impairment, clinical visits are performed approximately every 3 months. The duration of the treatment will vary among subjects and will continue until the date of regulatory approval or marketing authorization and/or commercialization in the participating subject's country, or study termination by the Sponsor, Amicus Therapeutics (Amicus).

Migalastat HCl will be administered 150 mg every other day (QOD) for subjects enrolled under standard protocol [AT1001-042], or 150 mg every 4th day (Q4D) or every 7th day (Q7D) for Addendum 1.1.2 subjects as a starting point and is subjected to change depending on baseline and follow-up PK and PD assessments for the addendum subjects. Within each participating country, subjects will continue to receive treatment with migalastat HCl within the protocol until one of the study conclusion conditions is met as specified in the protocol section 5.1, or until one of the withdrawal criteria is met as specified in standard protocol section 6.4 or Addendum 1.1.2 section 4.4.

4.2. SCHEDULE OF EVENTS

All study visits should be scheduled from the Baseline Visit (Visit 1), and subsequent visits are planned at approximately 6-month intervals for Amendment 1.1. Follow-up visits will be scheduled one month later with similar window allowances (one week prior and 2 weeks following the designated visit) and will be undertaken only if needed based on PK and PD results from the prior visit. As a comparison, study visits will be planned at approximately 3-month intervals for Addendum 1.1.2 and similarly, follow-up visits will follow one month later. The time and events can be found in Table 1, whereas the time and events of Addendum is described in Table 2.

Table 1 Time and Events Table of Amendment 1.1

Study Month #	Baseline (Month 0)[1]	6 Months (±30 days)	12 Months (±30 days)	Repeat 6 & 12 Month visits in the subsequent years	End of Study (Approximately 30 days after last treatment)
Visit Number	**V1**	**V2**	**V3**	**V4, V5, etc**	
Assessments					
Review Informed Consent	X				
Review Inclusion/Exclusion Criteria	X	X	X		
Physical Examination	X	X	X		X
Concomitant Medications	X	X	X		X
Vital Signs (BP, HR, RR, Temp)	X	X	X		X
Weight	X	X	X		X
Height	X				X
12 Lead ECG	X	X	X		X
Echocardiography[2]	X		X		X[3]
Chemistry[4,5]	X	X	X		X
Hematology[5]	X	X	X		X
Urinalysis[5]	X	X	X		X
24-Hour Urine[5]	X	X	X		X
eGFR calculation[5]	X	X	X		X
WBC α-Gal A Activity[5]	X	X	X		X
Pregnancy Test[6]	X	X	X		X
Plasma Lyso-GB3	X	X	X		X
Adverse Events	X	X	X		X
SF-36 Survey	X	X	X		X
Study Treatment Supply/Resupply/Return[7]	X	X	X		X
Intermediate Subject Contact[8]	X	X	X		X

1. Assessments collected for the end of study visit in the previous study (which are also required at Baseline for the current study) will serve as Baseline Visit 1 assessments for this study. The visit window for the last treatment visit will apply for the completion of such assessments. Assessments required at Baseline (Visit 1) that are not performed as part of the last treatment visit in the previous study will have a visit window of +30 days.
2. ECHOs will be read centrally.

3. ECHO is to be performed for subjects who withdraw from the study and did not have an ECHO performed within the previous 6 months.
4. Subjects must fast for approximately 8 or more hours before serum chemistry is performed.
5. In the event of an abnormal lab result, at the investigator's discretion, the test can be repeated in an unscheduled visit and sent to the central laboratory for analysis.
6. Urine pregnancy test to be performed at Baseline Visit 1 according to previous protocol; thereafter the urine pregnancy test will be performed locally using dipstick.
7. Study Treatment Supply for Study AT1001-042 is intended to occur on Baseline (Visit 1) or in subsequent days within the allowable window for this visit.
8. Subjects will receive a telephone contact, or contact using another acceptable method, approximately midway between visits to assess Adverse Events and dosing compliance. It is better to have the phone contact performed earlier or later than scheduled, rather than not at all.

Table 2 Time and Events of Site Addendum 1.1.2

Study Month (Visit)	Baseline (Month 0)[1] (V1A)	Months 3 (V2A) 15 (V6A) 27 (V10A)	Months 4, 16, & 28 (Follow-up)[2]	Months 6 (V3A) 18 (V7A) 30 (V11A)	Months 7, 19, & 31 (Follow-up)[2]	Months 9 (V4A) 21 (V8A) 33 (V12A)	Months 10, 22, & 34 (Follow-up)[2]	Months 12 (V5A) 24 (V9A) 36 (V13A)	Months 13, 25, & 37 (Follow-up)[2]	End of Study (Approximately 30 days after last treatment)
Visit Window		-7 to +14 days	Phone	-7 to +14 days	Phone	-7 to +14 days	Phone	-7 to +14 days	Phone	
Assessments										
Review Informed Consent	X									
Review Inclusion/Exclusion Criteria	X	X	X	X	X	X	X	X	X	
Physical Examination	X			X				X		X
Concomitant Medications	X	X		X		X		X		X
Vital Signs (BP, HR, RR, Temp)	X	X		X		X		X		X
Weight	X	X		X		X		X		X
Height	X									X
12-Lead ECG	X			X				X		X
Echocardiography[3]	X							X		X[4]
Chemistry[5]	X	X	X	X	X	X	X	X	X	X
Hematology[5]	X	X	X	X	X	X	X	X	X	X
Urinalysis[5]	X	X	X	X	X	X	X	X	X	X
eGFR Calculation[5]	X	X	X	X	X	X	X	X	X	X
WBC α-Gal A Activity	X			X				X		X

Table 2 Time and Events of Site Addendum 1.1.2 (Continued)

Study Month (Visit)	Baseline (Month 0)[1] (V1A)	Months 3 (V2A) 15 (V6A) 27 (V10A)	Months 4, 16, & 28 (Follow-up)[2]	Months 6 (V3A) 18 (V7A) 30 (V11A)	Months 7, 19, & 31 (Follow-up)[2]	Months 9 (V4A) 21 (V8A) 33 (V12A)	Months 10, 22, & 34 (Follow-up)[2]	Months 12 (V5A) 24 (V9A) 36 (V13A)	Months 13, 25, & 37 (Follow-up)[2]	End of Study (Approximately 30 days after last treatment)
Plasma Lyso-Gb_3	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Subject Diary[6]		X	X	X	X	X	X	X	X	
Study Treatment Supply/Resupply/Return[7]	X	X		X		X		X	X	X
Urine Collections for Migalastat Assessments[8]	X	(X)[9]	(X)[9]	(X)[9]	(X)[9]	(X)[9]	(X)[9]	(X)[9]	(X)[9]	
Blood Sampling for PK Assessments[10]	X	X	X	X	X	X	X	X	X	

α-Gal A = α-galalactosidase A; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; Lyso-Gb_3 = globotriaosylsphingosine; HR = heart rate; PK = pharmacokinetics; RR = respiratory rate; Temp = temperature; WBC = white blood cell.

NOTE: Following Month 12 (or 13, if needed), visits will repeat for the duration of the study, occurring every 3 mos with follow-up visits one month later, if needed.

1. All Baseline safety assessments will be repeated prior to first administration of migalastat at re-entry into the study.
2. Follow-up visits will occur only if needed, based on PK/PD assessments performed at the prior visit. If needed, the subject may be contacted by phone and have assessments done at the study site or drawn by a home healthcare professional. All samples will be sent to the central Laboratory.
3. Echocardiograms will be read centrally.
4. Echocardiogram is to be performed upon withdrawal from the study only if one was not performed within the previous 6 months.
5. In the event of an abnormal lab result, at the investigator's discretion, the test can be repeated in an unscheduled visit and sent to the central laboratory for analysis.
6. A diary will be maintained throughout the study to record study drug administration and the occurrence of any adverse events.
7. Study Treatment Supply for Study AT1001-042 is intended to occur on Baseline (Visit 1) or on subsequent days within the allowable window visits.
8. See Appendix 1 for urine collection intervals.
9. Additional urine collections for migalastat assessment will be done prior to any change in dose regimen.

10. See Appendix 1 for PK assessment times.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for DSMB (described elsewhere in the DSMB Charter)
- Final Analysis

5.1. DATA SAFETY MONITORING BOARD (DSMB)

A DSMB SAP describing the methodology and presentation of results and access to results is provided by IQVIA as a separate document. The final version (Final V1.1) of DSMB SAP was effective on 25Oct2015.

5.2. INTERIM ANALYSIS

There will be no interim analysis (IA) for this study.

5.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan and Database Lock.

6. ANALYSIS SETS

6.1. ALL ENROLLED (ENR)

The all subjects enrolled (ENR) set will contain all subjects who provide informed consent for this study.

6.2. INTENT-TO-TREAT [ITT]

The Intent-to-Treat (ITT) Population will include subjects who take at least one dose of Investigational Product (IP) after they have enrolled into this open-label extension study (excluding addendum 1.1.2 subject), and is the primary population of interest. All safety, efficacy and demography summaries will be based on the ITT population. Protocol

deviations will be reported in a listing.

6.3. ADDENDUM 1.1.2

The Addendum 1.1.2 Population will include the only subject whose treatment with migalastat HCl was terminated after a confirmed estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2, which met the withdrawal criteria, but re-initiated into this ongoing study with the attempt to establish an alternate dosing regimen. This subject (original subject ID 20045027) is re-enrolled under the site-specific Addendum 1.1.2 with a different subject ID 20045029, and the data about this subject ID will be handled separately and reported in listings only under Addendum 1.1.2 Population. All the safety and efficacy assessments planned in Table A-1 of Protocol Addendum 1.1.2 will be presented in data listings for this population. Demographics, baseline characteristics, drug compliance and other historical information will be presented under the ITT population data listings based on subject ID 20045027 and flagged in a footnote.

7. GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE AND STUDY DAY

Study Day (or Start and End Study Day) will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.
Reference start date is defined as the day of the first dose of study medication in this study, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- Study Day = (date of event – reference date) +1, (if event date >= reference date)
- Study Day = date of event – reference date, (if event date is < Day 1)

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

7.2. BASELINE

During the subjects transition from their previous study into AT1001-042, the intent is for treatment with migalastat HCl to continue without a drug holiday. Assessments collected in the last treatment visit of their previous study

(previous studies include AT1001-012 and AT1001-041), are also required for the Baseline Visit in the current study, which will serve as the assessment for the Baseline Visit. The visit window for the last treatment visit in the previous study will also apply to those Baseline assessments. However, to provide flexibility to investigators and subjects, any Baseline Visit assessment that are required for the current study and not a required assessment for the last treatment visit in the previous study, may be performed up to 30 days after entry into the current study. The baseline will then be determined as the last non-missing measurement taken prior to the first migalastat dose date (including unscheduled assessments) during this study. Should there be no observations prior to the first dose, the baseline will then be assigned to the observation at the nominal baseline visit.

Blood and urine sampling for plasma migalastat determination will be taken just prior to dosing and at selected time points post-dose.

Use of ACEi/ARB/RI at baseline is defined as having either ACE inhibitor, ARB or RENIN inhibitor within the past five years (with start date on or before the baseline visit) and is ongoing through, or the stop day is on or after the baseline visit date (informed consent date).

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will be included in tables presenting the clinically significant (CS) evaluations at any time of the study. All visits, including nominal, unscheduled, retest, and early termination visits will be sorted and presented chronologically. The visit wording to be presented in all outputs can be referred in Appendix 1.

In the case of a retest (same visit number assigned but tested on different dates), the first available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

7.5. STATISTICAL TESTS

There will be no formal inferential statistics performed in this study and only descriptive statistics will be presented.

7.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Change from Baseline = Test value at Visit X – Baseline Value
- Continuous variables (e.g., age) are summarized using descriptive statistics (the number of subjects with available data, mean, standard deviation [SD], median, minimum, and maximum). Categorical variables (e.g., gender) are summarized using counts and percentages. Percentages are calculated using the total subjects (per population).
- For continuous variables, all mean and median values are formatted to one more decimal place than the measured value. SD values are formatted to two more decimal places than the measured value. The minimum and maximum values are presented with the same number of decimal places as the measured value.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses. In case of 0 counts, only "0" with no percentage will be presented and a percentage of 100 will not include decimals, e.g. 85 (100%).

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 and above.

8. STATISTICAL CONSIDERATIONS

8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Since there are no formal inferential statistics performed, no analysis will be adjusted for covariates or factors.

8.2. MULTICENTRE STUDIES

This study will be conducted by multiple investigators at multiple centers internationally, but no site-specific considerations will be included in the analysis, and data from all sites will be pooled in the analysis.

8.3. MISSING DATA

No missing data imputation will be carried out in this study.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment for multiplicity will be performed. All analyses will be descriptive.

8.5. EXAMINATION OF SUBGROUPS

Descriptive analyses of the efficacy endpoints (annualized change in MDRD eGFR and CKD-EPI eGFR) will be performed on the following subgroups:

- Males, 24-hr urine protein < 100 mg/24h
- Males, 24-hr urine protein ≥100, <1000 mg/24h
- Males, 24-hr urine protein ≥ 1000 mg/24h
- Females, 24-hr urine protein < 100 mg/24h
- Females, 24-hr urine protein ≥100, <1000 mg/24h
- Females, 24-hr urine protein ≥ 1000 mg/24h

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describes the presentations for this study as well as format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. Number of subjects, subject discontinuation, and primary reason for discontinuation will be presented for the ITT and Addendum 1.1.2 population.

The list of primary reasons for discontinuation (as per CRF) can be referred to as below:

- Screen Failure
- Adverse Event
- Subject Met Protocol Defined Stopping Criteria
- Physician Decision
- Lost to Follow-up
- Non-Compliance with Study Requirements
- Pregnancy and/or Breast feeding
- Protocol Violation
- Withdrawal by Subject
- Study Terminated by Sponsor
- Death
- Other

11. PROTOCOL DEVIATIONS

Protocol Deviations as classified in the clinical trial management system (CTMS) will be summarized in a table according to the following categories and presented overall based on the ITT population:

- Administrative Criteria
- Concomitant Medications Criteria
- Efficacy Criteria
- Eligibility and Entry Criteria
- Investigational Product Compliance
- Informed Consent Criteria
- Laboratory Assessment Criteria
- Randomization Criteria
- Regulatory or Ethics Approvals Criteria

- Serious adverse event (SAE) Criteria
- Source Document Criteria
- Study Procedures Criteria
- Visit Scheduled Criteria
- Other Criteria

All protocol deviations will be listed.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT population. The following demographic and other baseline characteristics will be summarized using descriptive statistics under AT1001 (Migalastat HC1) column:

- Age (years) (calculated relative to date of consent)
- Sex
- Race
- Ethnicity (USA and Japan Sites only)
- Country
- Protocol Version
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Use of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB)/renin inhibitors (RI)
- 24-hour urine protein (mg/24h)
- Estimated Glomerular Filtration Rate based on Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD-EPI}$) ($mL/min/1.73m^2$)
- Estimated Glomerular Filtration Rate based on Modification of Diet in Renal Disease ($eGFR_{MDRD}$) ($mL/min/1.73m^2$)
- Previous Studies (subjects can be in more than one previous study)

It will be considered use of ACEi/ARB/RI if the reported medication is taken on the date of consent, regardless of the start or end date.

$eGFR_{MDRD}$ data will be calculated by the central lab and included in the data transfer, whereas $eGFR_{CKD-EPI}$ data will be derived from serum creatinine based on the formula in Section 17.1.2.

Some of the baseline characteristics will not be collected directly in the eCRF and will be derived as follows:

- Age = (date of consent – date of birth) / 365.25. If date of birth contains only partial date, use the first day of the month in the calculation if day part is missing, or first day of the year if both day and month parts are missing.
- BMI (kg/m^2) = weight (kg)/ height $(m)^2$ at the baseline visit

Demographic and baseline characteristics will be provided in two separate data listings.

13. MEDICAL HISTORY

Medical History information including the concomitant illness (Ongoing at Study Entry, or start on or after the Study Entry) for this study is not complete entry for most subjects and is collected only for a small portion of the subjects whose information is collected from the eCR. This information will be presented in a set of summary tables and listing. Medical History for other subjects whose information are not collected in this study will be integrated from their feeder study (AT1001-041 and AT1001-012) as Medical History, and this information will not be included in SDTM or ADaM dataset, and will only be presented in a separate set of summary table and listing. All Medical History will be coded using version 16.1 of MedDRA and presented by SOC and PT for the ITT population.

14. MEDICATIONS

Medications will be coded using September 2013 version of the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and presented for the ITT population, and a table will be provided to summarize the medications by ATC Level 3 and PT. Medications will similarly be summarized for subjects taking ACEi/ARB/RI. A listing of all medications will be provided for ATC Level 3 and PT. In addition, a listing presenting the enzyme replacement therapy (ERT) history will be provided.

15. STUDY MEDICATION EXPOSURE AND ACCOUNTABILITY

Migalastat HCl, 150 mg per capsule, and reminder capsules in blister packs will be administered at the baseline visit and subsequent visits in 6-month intervals. Subjects are expected to take one 150 mg capsule every other day (QOD)

except for the Addendum 1.1.2 subjects, who are expected to take one 150 mg capsule on every 4th (Q4D) or 7th day (Q7D)..

Exposure to study medication will be presented for the ITT population by descriptive statistics. The date of first and last study medication administration will be taken from the eCRF Study Drug Administration form for duration of exposure as follows, and interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.

Duration of exposure (months) = Duration of exposure (days) / (365.25/12) rounded to one decimal place.

Duration of exposure [months] categorized by 6-month interval up to 48 months will also be included in the table. Listings presenting the study drug administration information including duration of exposure and drug accountability will be provided. In addition, a listing is provided to present dosing regimen for Addendum 1.1.2.

16. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be presented for the ITT population. Since no patient diary will be filled for ITT population and only a study drug administration eCRF page will be completed to capture the first and last dose date, an estimate of the compliance will be calculated as follows:

$$\text{Compliance} = \frac{[(\text{Last dose date} - \text{first dose date}) + 1]/2 - \text{missed doses} + \text{extra doses}}{[(\text{Last dose date} - \text{first dose date}) + 1]/2} \times 100\%$$

Descriptive statistics for the compliance (n, mean, median, standard deviation, minimum, maximum values) will be presented and a frequency distribution will be computed for the following categories: < 80%, >= 80 - <120%, and >= 120%.

A listing presenting the overall study medication compliance will be provided.

17. EFFICACY OUTCOMES

17.1. EFFICACY OUTCOMES AND VARIABLES

All efficacy outcomes will include all subjects (excluding the renal impairment subject) and will be summarized using nominal visits (not including unscheduled visit or early termination) and descriptive statistics. Efficacy assessments will be performed at the Baseline Visit, followed by subsequent clinic visits in every 6 months until the

End of Study visit. All efficacy outcomes will follow the same visit pattern unless otherwise specified. Descriptive statistics will be calculated for baseline and each post-baseline visit (as well as time point if applicable), followed by change from baseline at that visit. Baseline is defined in section 7.2, whereas change from baseline is defined in section 7.6.

The efficacy endpoints to be presented are

- $eGFR_{MDRD}$ and $eGFR_{CKD-EPI}$
- Plasma lyso-Gb_3 (Plasma globotriaosylsphingosine)
- Measurement of white blood cell (WBC) α-Gal A activity
- Measurement of 24-hour urine protein
- Measurement of left ventricular mass (LVM) and LVM index (LVMi), as assessed by echocardiography
- Measurement in ejection fraction, as assessed by echocardiography
- Measurement of fractional shortening, as assessed by echocardiography
- Measurement of left ventricular internal dimension (LVIDd and LVIDs), midwall fractional shortening (MWFS), and wall thicknesses, as assessed by echocardiography
- Measurement of patient reported Quality of Life as assessed by the Short Form 36 (SF-36)

Each endpoint (consisting of one or more variables) will be summarized in a table. Listings will be provided by domain or sub-domain categories, e.g. Laboratory categories - Chemistry, Hematology, Urinalysis, Echocardiography, and Questionnaire.

17.1.1. ANNUALIZED CHANGE IN MDRD EGFR

The MDRD eGFR values at every visit will be provided by the central laboratory.

The annualized change (the slope) in MDRD eGFR will be computed over the available visits of each patient between baseline and End of Study (EOS). A simple linear regression between the observed values and the assessment times (study day of the visits as the dependent variable) will be applied to estimate the annualized change.

The duration between baseline and the last post-baseline visit in years (study days of the visit/365.25 days per year) will be presented along with the annualized rate of change for MDRD eGFR.

17.1.2. ANNUALIZED CHANGE IN CKD-EPI EGFR

The CKD-EPI values will be computed for every visit using the following equation: (Levey et.al.,2009):

CKD-EPI eGFR = 141 x $\min(SCR/k, 1)^{\alpha}$ x $\max(SCR/k, 1)^{-1.209}$ x 0.993^{Age} x 1.018(if female) x 1.159(if black) where

k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCR/k or 1, and max indicates the maximum of SCR/k or 1, SCR is the serum creatinine (mg/dL).
The annualized change (the slope) in CKD-EPI eGFR will be computed over the available visits of each patient between baseline and EOS. A simple linear regression between the observed values and the assessment times (study day of the visits as the dependent variable) will be applied to estimate the annualized change.
The duration between baseline and the last post-baseline visit in years (study days of the visit/365.25 days per year) will be presented along with the annualized rate of change for CKD-EPI eGFR.

17.1.3. PLASMA LYSO-GB_3

A blood draw will be collected for testing of plasma lyso-GB_3, a biomarker that has been shown to be elevated in Fabry subjects and appears to be related to the clinical condition and disease progression in Fabry disease. Concentrations of lyso-GB_3 will be measured in plasma using a qualified assay in triplicates. The mean of each time point within the same visit is calculated (regardless of possible missing data for one or two of the triplicates). The derived parameter based on the average of the triplicates is summarized in a table. However, all the originally collected data as well as the derived lyso-GB_3 parameter will be included in a listing.

17.1.4. WBC α-GAL A ACTIVITY

The α-Gal A enzyme activity in leukocytes data will be collected after repeated oral doses at each visit, and will be analyzed for PD analyses by descriptive statistics. The WBC α-Gal A activity will also be reported in a listing.

17.1.5. 24-HOUR URINE PROTEIN

A 24-hour urine sample will be collected per the eCRF at every study visit in a 6-month interval until the End of Study visit with information of starting date and time, and stopping date and time. The urine volume will also be collected. These samples will be used to measure 24-hour urine protein, albumin and creatinine levels, and in case of duration of collection not being compliant with the exact 24 hours, the corrected values with respects to 24 hours will be used in the summary tables.
The 24-hour urine protein samples will be summarized in a table. A shift table and another table presenting clinically significant (CS) result are included. Similarly, other 24-hour urine parameters will be presented in a summary table as well as a shift table and a CS table. All 24-hour urine sample related parameters including the 24-hour urine protein will be presented in a listing.

17.1.6. ECHOCARDIOGRAPHY (ECHO)

An ECHO will be performed at baseline, and every 12 months subsequently until the end of study visit, and the ECHO data will be collected in the EC domain. The following parameters will be summarized separately in tables

- LVM and LVMi
- Ejection Fraction
- Fractional Shortening
- LVIDd, LVIDs, MWFS, Wall Thickness.

These parameters will be presented to summarize the data by each visit for baseline, post-baseline and change from baseline. Supportive listings to these parameters will also be provided. ECHO parameters for safety evaluation is provided in the Safety Outcomes section.

17.1.7. SF-36 QUESTIONNAIRE

SF-36 is an indicator of overall health status which consists of eight sub-scaled scores. The scores are weighted sums of the questions in each sub-scale. The SF-36 will be collected at Baseline, and every 6 months subsequently until the End of Study visit. The SF-36 consists of the following subscales:

- Physical Functioning (PF)
- Role Physical (RP)
- Bodily Pain (BP)
- General Health (GH)
- Vitality (VI)
- Social Functioning (SF)
- Role Emotional (RE)
- Mental Health (MH)

And can be further summarized into physical and mental components:

- Physical Component Summary
- Mental Component Summary

Norm based scoring of the SF-36v2 will be performed by OPTUM Insight Life Sciences and the above mentioned sub-scales and component summaries will be provided. Each sub-scale and component summary scores will be summarized at baseline and every post-baseline visit, as well as change from baseline, in a summary table.

Three listings presenting SF-36 individual questions, norm based scores, and physical and mental component summary scores will be provided.

18. SAFETY OUTCOMES

The safety parameters include Adverse Events, Physical Examination, Vital Signs, Laboratory Tests, 12 Lead ECG, use of Concomitant Medications. All outputs for safety outcomes will be based on the ITT population using nominal visits (not including unscheduled visits and early termination) except tables presenting clinically significant results. These tables presenting clinically significant results will include unscheduled visits and early termination alongside the scheduled visits. Each continuous variable will be summarized for quantitative analysis using descriptive statistics by each visit including baseline, and change from baseline for that visit. Categorical variables will be summarized for qualitative analysis using incidence counts and percentages. The summary will be performed by each visit including baseline for each categorical parameter (e.g. Urinalysis parameters except pH and specific gravity).

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 16.1 and will be summarized. The AE will be presented in summary tables for each of the following items, by the counts and percentages of subjects and events:

- The counts and percentages of subjects and events with each adverse event by SOC and preferred term
- The counts and percentages of subjects and events with each (investigator determined) treatment related adverse event by SOC and preferred term
- The counts and percentages of subjects and events with each adverse event leading to discontinuation of study medication by SOC and preferred term
- The counts and percentage of subjects and events with each serious adverse event by SOC and preferred term
- The counts and percentage of subjects and events with each adverse event leading to death
- Possible Suicidality Related Adverse Event (PSRAE)

Adverse events will also be summarized by the following categories:

- Severity
- Relationship to Study Drug

An overall summary of number of subjects and the events within each of the categories described in the sub-section

below, will be provided as specified in the templates.
A listing including all AEs will be provided. Separate listings for AEs Leading to Discontinuation of Study Medication, Serious AEs, AEs Leading to Death, and PSRAE will also be provided.

18.1.1. ALL AEs

Incidence of AEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication. The following summary tables will be provided using counts and percentages of subjects and events:

- Overall summary of AEs
- Summary of AEs by SOC and PT
- Summary of AEs by PT
- Summary of AEs by SOC, PT and Severity
- Summary of AEs by SOC, PT and Relationship
- Summary of Serious AEs (SAE) by SOC and PT
- Summary of Non-serious AEs by SOC and PT
- Summary of Non-serious AEs by PT
- Summary of Non-serious AEs occurred in 5% or more of Subjects by SOC and PT
- Summary of AEs occurred in 5% or more of Subjects by SOC and PT

18.1.1.1. Severity

Severity is classified as mild/ moderate/ severe (increasing severity). AEs with a missing severity will be classified as severe. If a subject reports an AE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

18.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classified as *"Unrelated", "Unlikely", "Possible", "Probable", and "Definite"* (increasing level of relationship). A "Potentially Related" AE is defined as an AE with a relationship to study medication as *"Possible", "Probable" or "Definite"* to study medication. AEs with a missing relationship to study medication will be regarded as *"Potentially related"* to study medication. If a subject reports the same AE more than once within that SOC/PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

18.1.2. AEs Leading to Discontinuation of Study Medication

AEs leading to permanent discontinuation of study medication will be identified by using the eCRF AE form with "Stopped Permanently" recorded for question "Action Taken with Study Drug". For AEs leading to discontinuation of study medication, a summary on the number of subjects and events by SOC and PT will be prepared.

18.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Yes" to the question "Serious" on the Adverse Events page of the eCRF. A summary of serious AEs on the number of subjects and events by SOC and PT will be prepared.

18.1.4. Non-Serious Adverse Events

A summary of non-serious AEs (excluding SAEs) by SOC and PT will be prepared. A supporting listing will also be provided for non-serious AEs.

18.1.5. Adverse Events Leading to Death

AEs leading to Death are those events which are recorded as having "Fatal Outcomes" on the Adverse Events page of the eCRF.

18.1.6. Possible Suicidality Related Adverse Event (PSRAE)

If an occurrence of an adverse event which, in the investigator's opinion, is possibly related to suicidality, it will be recorded on the PSRAE eCRF form and reported under this category. The AE number of PSRAE will be collected in the PSRAE eCRF, which will be linked to the particular AEs in the AE eCRF pages in EDC. A summary of PSRAE by SOC and PT will be prepared.
A listing with SOC and PT for PSRAE will be presented. In addition, all other information captured in the PSRAE eCRF will be presented in another listing.

18.2. Physical Exams

A data listing will be provided to present physical examination findings.

18.3. VITAL SIGNS

Vital Signs will be assessed at each study visit and results will be summarized descriptively by study visit for baseline, post-baseline visit and change from baseline.
The following Vital Signs measurements will be reported for this study:

- Sitting / Supine Systolic Blood Pressure (mmHg)
- Sitting / Supine Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{0}C)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Body Mass Index (BMI) will be calculated using the same formula as baseline: BMI (kg/m^2) = weight (kg)/ height (m)^2 of the same visit. It will be reported only for Baseline and Study Completion Visits.
Each measurement of the following parameters will be evaluated against the criteria of abnormality detailed below for potentially clinically significant vital signs. Potentially clinically significant vital signs are derived and categorized into PCS Low and PCS High, as well as Normal. In addition, a table summarizing the counts and percentages of each PCS category at any time including unscheduled visits will be presented.

Vital Signs	Criteria	Abnormality Categories
Pulse	≥ 120 bpm at any post-baseline time point and ≥ 15 bpm increase from baseline at any post-baseline time point	PCS High
	≤ 50 bpm at any post-baseline time point and ≥ 15 bpm decrease from baseline at any post-baseline time point	PCS Low
Systolic blood pressure	≥ 180 mm Hg at any post-baseline time point and ≥ 20 mm Hg increase from baseline at any post-baseline time point	PCS High
	≤ 90 mm Hg at any post-baseline time point and ≥ 20	PCS Low

Vital Signs	Criteria	Abnormality Categories
	mm Hg decrease from baseline at any post-baseline time point	
Diastolic blood pressure	≥ 105 mm Hg at any post-baseline time point and ≥ 15 mm Hg increase from baseline at any post-baseline time point	PCS High
	< 40 mm Hg at any post-baseline time point and ≥ 15 mm Hg decrease from baseline at any post-baseline time point	PCS Low
Weight	≥ 7% change from baseline at any post-baseline time point	PCS High

A listing presenting all available vital signs assessments for subjects with potentially clinically significant vital signs any time during the study will be provided.

18.4. LABORATORY EVALUATIONS

Results of continuous variables from the Q^2 Solutions Clinical Lab (QLAB) will be summarized in the reporting for Hematology, Serum Chemistry, Urinalysis (excluding the 24-hour urine), and 24-hour Urine Collection (excluding 24-hour urine protein). Similar to 24-hour urine protein, any other 24-hour parameters including 24-hour urine albumin and creatinine with a collection duration not equal to 24 hours will be adjusted to 24-hour. A list of laboratory parameters to be included in the outputs can be found below in Tables 3, 4, and 5. The lab results will be converted to SI units prior to any analysis and all presentations will be based on SI units.

Table 3 Serum Chemistry Parameters

Alanine aminotransferase (ALT)	Creatinine, serum
Alkaline phosphatase	Gamma – glutamyltransferase (GGT)
Aspartate aminotransferase (AST)	Glucose
Albumin	Lactate dehydrogenase (LDH)
Bilirubin, total	Magnesium

Blood urea nitrogen (BUN)	Phosphorous
Calcium, total	Potassium
Carbon dioxide, total (bicarbonate)	Protein, total
Chloride	Sodium
Alanine aminotransferase (ALT)	Creatinine, serum
Creatine phosphokinase	Low density lipoprotein (LDL) cholesterol
Uric acid	High density lipoprotein (HDL) cholesterol
Cystatin C	triglycerides

Table 4 Hematology Parameters

Platelet count	*Automated WBC Differential:*
RBC count	Neutrophils
WBC count (absolute)	Lymphocytes
Hematocrit	Monocytes
Hemoglobin	Eosinophils
	Basophils

Table 5 Urinalysis Parameters

Color	Ketones
Appearance	Blood
Specific gravity	WBC
pH	Nitrite

Protein	Bilirubin
Glucose	Microscopy of sediment

For parameters not having Baseline assessments, the data of last visit is imported from the previous study AT1001-012 and will serve as the baseline for this study.
Quantitative laboratory measurements reported as "< X", e.g. below the lower limit of quantification (BLQ), or "> X", e.g. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, e.g. as "< X" or "> X" in the listings.
Listings presenting lab results in each subcategory (e.g. Hematology, Serum Chemistry, Urinalysis, 24-hour Urine, Serum Pregnancy, and Urine Pregnancy) will be provided.
A listing of subjects with at least one assessment falling outside of the normal range will also be provided and clinical significance will be included in this listing.
A listing including all historical laboratory data will be provided.

18.4.1. LABORATORY REFERENCE RANGES AND CLINICAL SIGNIFICANCE

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

For reference range with a single boundary, there will be only two of the three categories presented for the parameter (either Low/Normal, or Normal/High), e.g. Magnesium concentration is deemed High if result > 1.25 mmol/L, and Normal if at or below 1.25 mmol/L.
For categorical results in Urinalysis, they will be categorized into two categories, i.e. Normal/Abnormal if the result is different from that of the normal reference value. Shifts from baseline to any post-baseline visit summary tables based on the Low/Normal/High categories (and the variants) described above will be provided.
In addition to the high and low quantitative laboratory assignments, any result deemed clinically significant by the PI will be captured in the eCRF, and will be presented in the summary tables.

18.5. 12 LEAD ECG (ECG) EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study. The following ECG parameters will be reported in summary tables using descriptive statistics for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- HR (bpm)
- RR (msec)

All findings, including clinically significant findings, will be captured by the eCRF for the overall ECG evaluation, and categorized into Normal; Abnormal, NCS; and Abnormal, CS.
In addition to the change from baseline descriptive statistics summary, the number and percentage of subjects will be presented in a table for the overall ECG evaluation of clinical significance at any time of the study including unscheduled visits. A shift table by visits will also be constructed for change from baseline to post-baseline visits with regards to the three categories of the overall ECG evaluation.
A listing presenting all available ECG assessments will be provided. In addition, a listing of subjects with at least one clinically significant finding will be provided.

18.6. ECHOCARDIOGRAPHY (ECHO)

ECHO parameters are categorized into Normal, Mildly Abnormal, Moderately Abnormal, Severely Abnormal (or Low, Normal, High) by gender (or age) based on the criteria below for safety purpose, and a table presenting counts and percentages of each category by parameter and visit will be provided. A table presenting Severely Abnormal incidence at any visits through the study including unscheduled visits will be included.

ECHO Parameters	Criteria for Female	Criteria for Male	Abnormality Category
Left Ventricular Posterior Wall Thickness Diastole (cm) (LVPWTD)	0.6 - 0.9	0.6 - 1.0	Normal
	1.0 - 1.2	1.1 - 1.3	Mildly Abnormal

ECHO Parameters	Criteria for Female	Criteria for Male	Abnormality Category
	1.3 - 1.5	1.4 - 1.6	Moderately Abnormal
	>= 1.6	>= 1.7	Severely Abnormal
Intraventricular Septum Thickness Diastolic (cm) (IVSTD)	0.6 - 0.9	0.6 - 1.0	Normal
	1.0 - 1.2	1.1 - 1.3	Mildly Abnormal
	1.3 - 1.5	1.4 - 1.6	Moderately Abnormal
	>= 1.6	>= 1.7	Severely Abnormal
Left Ventricular Ejection Fraction (%) (LVEF)	>= 55	Same as female	Normal
	45 - 54	Same as female	Mildly Abnormal
	30 - 44	Same as female	Moderately Abnormal
	< 30	Same as female	Severely Abnormal
Fractional Shortening (%) (FS)	27 - 45	25 - 43	Normal
	22 - 26	20 - 24	Mildly Abnormal
	17 - 21	15 - 19	Moderately Abnormal
	<= 16	<= 14	Severely Abnormal
Left Ventricular Mass (g) (LVM)	67 - 162	88 - 224	Normal
	163 - 186	225 - 258	Mildly Abnormal
	187 - 210	259 - 292	Moderately Abnormal
	>= 211	>= 293	Severely Abnormal
Left Ventricular Mass Index (g/m2) (LVMi)	43 - 95	49 - 115	Normal

ECHO Parameters	Criteria for Female	Criteria for Male	Abnormality Category
	96 - 108	116 - 131	Mildly Abnormal
	109 - 121	132 - 148	Moderately Abnormal
	>= 122	>= 149	Severely Abnormal
Peak Mitral Inflow Velocity E (cm/s) (EPOINT)	For age < 50	Same as female	
	< 58	Same as female	Low
	58 - 86	Same as female	Normal
	> 86	Same as female	High
	For age >= 50	Same as female	
	< 48	Same as female	Low
	48 - 76	Same as female	Normal
	> 76	Same as female	High
Peak Mitral Inflow Velocity A (cm/s) (APOINT)	For age < 50	Same as female	
	< 30	Same as female	Low
	30 - 50	Same as female	Normal
	> 50	Same as female	High
	For age >= 50	Same as female	
	< 45	Same as female	Low
	45 - 73	Same as female	Normal
	> 73	Same as female	High

ECHO Parameters	Criteria for Female	Criteria for Male	Abnormality Category
Mitral Valve E/A Ratio (EARATIO)	For age < 50	Same as female	
	< 1.3	Same as female	Low
	1.3 - 2.5	Same as female	Normal
	> 2.5	Same as female	High
	For age >= 50	Same as female	
	< 0.8	Same as female	Low
	0.8 - 1.4	Same as female	Normal
	> 1.4	Same as female	High
Left Ventricular Internal Dimension at End Diastole (cm) (LVIDd)	3.5 - 5.3	4.2 - 5.9	Normal
	5.4 - 5.7	6.0 - 6.3	Mildly Abnormal
	5.8 - 6.1	6.4 - 6.8	Moderately Abnormal
	>= 6.2	>= 6.9	Severely Abnormal
Left Ventricular Internal Dimension at End Systole (cm) (LVIDs)	2.49 - 3.15	2.87 - 3.61	Normal
Midwall Fractional Shortening (%) (MWFS)	15 - 23	14 - 22	Normal
	13 - 14	12 - 13	Mildly Abnormal
	11 - 12	11	Moderately Abnormal
	<= 10	<= 10	Severely Abnormal

Systolic and diastolic function grading with respect to the abnormality categories are available in the data and will

be presented in the same table as parameters listed above.

ECHO comments and other information (parameters other than those listed above) will be presented in two other listings.

18.7. OTHER SAFETY ASSESSMENTS

Use of Medications will also be presented. Refer to Section 14 for how the Use of Medications will be presented.

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the ISO8601 form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

In this OLE study, there will be only one treatment administered, e.g. investigational product AT1001, therefore, all summary tables and figures will present the treatment group as "AT1001".

PRESENTATION OF VISITS

For outputs of ITT population, visits will be represented as follows and in that order:

Long Name (default)
Baseline (V1)
6 Months (V2)
12 Months (V3)
…
End of Study

Unscheduled visits will be in a form of "Unscheduled Visit x.y", where x refers to the closest previous scheduled visit, and y is an increasing two-digit sequence number starting from 01 to 99 with a step of 1 chronologically.
For subjects re-enrolled under addendum 1.1.2, the visits are planned with a 3-month interval, followed by follow-up visits one month after. It can be presented as n Months (VxA) and n+1 Months FU A, where n refers to 3, 6, 9,

…, e.g. 9 Months FU Addendum, and x refers to the chronological visit number. The baseline and end of study visit are presented as "Baseline (V1A)" and "End of Study (A)", respectively.

SCHEDULE OF PHARMACOKINETIC ASSESSMENTS FOR ADDENDUM SUBJECT

Pre-dose	Hours Post Dose													
0	1	2	3	4	6	8	12	24	48	72	96	120	144	168
Baseline assessments (Q4D regimen)														
X	X	X	X	X	X	X	X	X	X		X[1]			
Sample Follow-up Assessments Based on Regimen														
Regimen														
QOD									X					
Q3D									X	X[1]				
Q5D									X			X[1]		
Q6D									X				X[1]	
Q7D									X					X[1]

QOD = every other day; Q3D = every third day; Q4D = every fourth day; Q5D = every fifth day; Q6D = every sixth day; Q7dD = every seventh day

1. Trough sample, to be collected just prior to the next scheduled migalastat administration

SCHEDULE OF BASELINE URINE COLLECTION FOR ADDENDUM SUBJECT

Pre-dose	Hours Post Dose						
0	0-4	4-8	8-12	12-24	24-48[1]	48-72[1]	72-96[1]
X	X	X	X	X	X	X	X

1. Total urine volumes will be collected on these days, if possible.

TOTAL URINE VOLUME COLLECTION FOLLOWING DOSE REGIMEN CHANGES

Day	24-hour Urine Collections – Time Interval			
1 (Previsit)[1]	0-4[2]	4-8[2]	8-12[2]	12-24[2]
2 (Previsit)[1]	24-48			
3 (Previsit)[1]	No urine collection			
4 (Previsit)[1]	72-96			
5 (Previsit)[1]	No urine collection			
6 (Previsit)[1]	144-168			
7 (Site visit)	No urine collection, subject will deliver Day 6 collection to site.			

1. Home healthcare provider will deliver collection bottles and/or pick up previous day's urine collection.
2. Four separate urine collections at time intervals shown

LISTINGS

All data will be presented in listings if not otherwise specified. All listings will be ordered by the following (unless otherwise indicated in the template):

- Subject ID
- Safety or efficacy parameters
- Date (and time where applicable)