# 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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| **Unique Protocol ID:** | A**T1001-042** |
| **NCT Number:** | NCT02194985 |
| **Date of Protocol:** | 21 October 2015 |

# CLINICAL STUDY PROTOCOL

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

**Protocol Number:** AT1001-042

**Original Protocol**: 10 June 2014

**Amendment 1:** 30 September 2015

**Amendment 1.1:** 21 October 2015

**Compound: AT1001 (migalastat hydrochloride)**

**Sponsor**

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US IND Number: 68,456

EudraCT Number: 2014-002701-38

Sponsor Information Page

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# 1. DECLARATIONS OF SPONSOR AND INVESTIGATOR

## 1.1. DECLARATION OF SPONSOR

This clinical study protocol was subject to critical review and has been approved by the sponsor.

The information it contains is consistent with:

- The current benefit-risk evaluation of migalastat HCl
- The moral, ethical, and scientific principles governing clinical research, as set out in the Declaration of Helsinki, the principles of Good Clinical Practice described in the United States Code of Federal Regulations (CFR; Parts 50, 54, 56, and 312), and in the ICH Guidelines for Good Clinical Practice (E6)

The investigator will be supplied with details of any significant or new findings relating to treatment with migalastat HCl.

Amicus

Date: 21 OCT 2015 Signature: _____

Amicus

Amicus Therapeutics, Inc.

## 1.2. DECLARATION OF INVESTIGATOR

I confirm that I have read this clinical study protocol. I understand it, and I will work according to the moral, ethical, and scientific principles governing clinical research, as set out in the Declaration of Helsinki and the principles of Good Clinical Practice described in the United States Code of Federal Regulations (CFR; Parts 50, 54, 56, and 312) and in the ICH Guidelines for Good Clinical Practice (E6). I will also work in accordance with applicable local requirements.

**Investigator**

Date: _____ Signature: _____

PRINTED NAME: _____

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# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| α-Gal A | α-galactosidase A |
| ACEIs | Angiotensin-converting enzyme inhibitors |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ARBs | Angiotensin II receptor antagonists |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CD | Compact disc |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration equation |
| CPK | Creatine phosphokinase |
| CRF | Case report form |
| CS | Clinically significant |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| eGFR | Estimated glomerular filtration rate |
| ER | Endoplasmic reticulum |
| ERT | Enzyme replacement therapy |
| FDA | Food and Drug Administration |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| GGT | Gamma –glutamyltransferase |
| GL-3 | Globotriaosylceramide |
| HCl | Hydrochloride |
| HDL | High density lipoprotein |
| HR | Heart rate |

| | |
|---|---|
| ICH | International Conference on Harmonization |
| IEC | Independent ethics committee |
| IgM | Immunoglobulin M |
| IND | Investigational new drug |
| INR | International normalized ratio |
| IP | Investigational product |
| IRB | Institutional Review Board |
| ISFN | Investigator Site File Notebook |
| ITT | Intent to treat |
| ITTE | Intent to treat efficacy |
| IV | Intravenous |
| LDH | Lactate dehydrogenase |
| LDL | Low density lipoprotein |
| LSLV | Last subject's last visit |
| LVID | Left ventricular internal dimension |
| LVM | Left ventricular mass |
| LVMi | Left ventricular mass index |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minute |
| mL | Milliliter |
| MSDS | Material Safety Data Sheet |
| MWFS | Midwall fractional shortening |
| NCS | Not clinically significant |
| QOD | Once every other day |
| PD | Pharmacodynamic(s) |
| PHI | Personal Health Information |
| PK | Pharmacokinetic(s) |
| PSRAEs | Possible suicidality related adverse events |
| RBC | Red blood cell |
| RNA | Ribonucleic acid |
| RR | Respiration rate |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |

| | |
|---|---|
| SD | Standard deviation |
| SF-36 | Short Form-36 survey |
| SOC | System Organ Class |
| SPM | Study Procedures Manual |
| ULN | Upper limit of normal |
| WBC | White blood cell |

# PROTOCOL SUMMARY

## Rationale

Fabry disease is a rare X-linked lysosomal storage disease caused by mutations of the *GLA* gene, resulting in reduced or absent levels of the lysosomal enzyme α-galactosidase A (α-Gal A). Reduced enzyme activity results in accumulation of the natural substrate globotriaosylceramide (GL-3) in tissues, giving rise to the disease symptoms and ultimately premature death due to renal failure, cardiac disease, and stroke. Current treatment for Fabry disease is enzyme replacement therapy (ERT) which is administered by intravenous infusion every two weeks.

Migalastat hydrochloride (HCl) is an orally administered small molecule that has widespread tissue distribution and is being developed for the treatment of patients with Fabry disease. Migalastat HCl is a pharmacological chaperone and as such stabilizes endogenous α-Gal A allowing it to be properly trafficked to the lysosome where it can degrade GL-3.

The purpose of this study is to investigate the long-term safety and explore the efficacy/pharmacodynamics of migalastat HCl administered 150 mg (equivalent to 123 mg migalastat) every other day (QOD). Subjects enrolled in this clinical protocol will have completed treatment in a previous study of migalastat HCl. **In Japan, subjects enrolled in this clinical protocol will have completed AT1001-012.**

## Objective(s)

**Primary Objective:**

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

**Secondary Objective:**

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

## Study Design

This is an open-label, non-comparative, long-term extension study for subjects with Fabry disease who have completed treatment in a previous trial of migalastat HCl given as monotherapy. Subjects will enter this extension study immediately upon completion of their final treatment visit in a previous migalastat HCl study. The planned 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). There will be continuous monitoring of safety data and use of specific stopping criteria for discontinuation of individual subjects who show evidence of clinical deterioration.

A data safety monitoring board (DSMB) will be chartered to monitor and evaluate the safety of all subjects in this trial by periodically reviewing summaries of safety data, evaluating risk/benefit where possible, identifying any clinically relevant trends through the study, and assessing whether it is safe for the study to continue. Predefined stopping

criteria will be observed for discontinuation of individual subjects who show evidence of clinical deterioration.

## Study Assessments

The safety assessments are:

- Adverse events (AEs), possible suicidality related AEs (PSRAEs) and serious adverse events (SAEs)
- Withdrawal due to AEs
- Vital signs (blood pressure, body temperature, respiratory rate, and heart rate) and body weight
- Hematology, chemistry, and urinalysis parameters
- Electrocardiograms (ECGs)
- Stopping criteria

The efficacy/pharmacodynamic assessments are:

- Estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
- Plasma lyso-$Gb_3$
- Evaluation of left ventricular mass index (LVMi), as measured by echocardiography
- Ejection fraction, as measured by echocardiography
- Fractional shortening, as assessed by echocardiography
- Measurement of LV internal dimension (LVIDd and LVIDs), midwall fractional shortening (MWFS), and wall thickness, as assessed by echocardiography
- Evaluation of white blood cell (WBC) α-Gal A activity
- Evaluation of subject reported Quality of Life as assessed by the Short Form-36 Survey (SF-36)

# 3. INTRODUCTION

## 3.1. Background

Fabry disease is a rare X-linked lysosomal storage disorder caused by mutations in the gene (*GLA*) that encodes the lysosomal enzyme α-galactosidase A (α-Gal A). Mutations in *GLA* lead to reduced enzyme activity as a result of lowered catalytic activity, improper folding, decreased enzyme stability and/or inefficient trafficking into the lysosome (Bishop and Desnick 1981; Lemansky 1987; von Scheidt, Eng et al. 1991; Aerts, Groener et al. 2008).

The primary biological role of α-Gal A is to catalyze the first step in the degradation of neutral glycosphingolipids, in particular globotriaosylceramide (GL-3, also known as Gb3). Reduced enzyme activity results in the accumulation of GL-3 in cells and organs throughout the body (Desnick, Ioannou et al. 2001) leading to the life-threatening manifestations of Fabry disease, which include kidney failure, heart disease and stroke.

Migalastat hydrochloride (HCl) is an orally administered, low molecular weight iminosugar, and an analog of the terminal galactose group that is cleaved from the substrate GL-3. Migalastat HCl, which binds at the active site of α-Gal A, is a potent, reversible, competitive inhibitor of the enzyme. The binding of migalastat to both mutant and wild-type forms of α-Gal A stabilizes the enzyme. As a result, the mutant enzyme quaternary structure is sufficiently improved for it to pass the endoplasmic reticulum (ER) quality control systems and can be properly trafficked to the lysosomes. At this site, the low pH and high concentration of accumulated GL-3 in the lysosomes favor dissociation of migalastat from α-Gal A, freeing the enzyme to bind and break down GL-3. As such, migalastat acts as a "pharmacological chaperone" to α-Gal A.

The only specific treatment for Fabry disease is intravenously (IV) administered enzyme replacement therapy (ERT). No oral therapies are currently approved for treating Fabry disease.

## 3.2. Rationale

Migalastat HCl has been studied in 27 patients with Fabry disease in four completed Phase 2 studies [migalastat HCl Investigator's Brochure]. In these studies, as judged by improvements in both α-Gal A activity in different tissues and reduction in the pathological substrate (GL-3), treatment with migalastat HCI was associated with pharmacodynamic evidence of efficacy. Migalastat HCl therapy resulted in increases in endogenous α-Gal A activity in WBCs, skin, and kidney tissue in the majority of subjects. In those subjects with responsive *GLA* mutations as determined by *in vitro* assay, GL-3 concentrations tended to decrease in urine and in kidney interstitial capillaries. The decrease in urine GL-3 concentration was greater after administration of 150 mg migalastat HCl once every other day (QOD) than after either once daily or twice daily administration. Migalastat HCl was well tolerated and there were no treatment related serious adverse events SAEs and no treatment limiting toxicities identified.

After completing one of the four Phase 2 studies subjects were eligible to participate in a long-term extension study, FAB-CL-205. In this study, increasing doses up to 500 mg

QOD did not show additional treatment effect relative to 150 mg QOD. To further investigate the efficacy and safety of migalastat HCl treatment, two pivotal Phase 3 studies were initiated.

The pivotal Phase 3 studies include AT1001-011, a 24-month randomized double-blind placebo-controlled (through month 6) study to evaluate the efficacy and safety of migalastat HCl in ERT-naïve male and female patients with amenable mutations, and AT1001-012 an 18-month, randomized open-label active comparator trial to evaluate the efficacy and safety of migalastat HCl compared to ERT in ERT-experienced male and female patients with amenable mutations.

These pivotal studies have demonstrated efficacy of migalastat in Fabry patients with amenable mutations. Based on the adverse event profile, laboratory evaluations, physical examinations, vital signs, and ECGs, these studies have demonstrated that migalastat HCl 150 mg QOD is a generally safe and well-tolerated treatment for Fabry disease. Long term extension studies AT1001-041 and AT1001-042 (the current study) are ongoing at this time.

Since Fabry disease is a chronic condition, typically resulting in declining renal function, and usually requiring life-time treatment, the current study (AT1001-042) was designed to provide continued migalastat HCl treatment to those subjects who have completed treatment in a previous migalastat study, as well as to enable collection of longer term safety and efficacy data. However, previous Phase 1 studies with migalastat HCl have shown migalastat HCl to be primarily excreted (77% of the dose) via the kidneys. Therefore, it is not unexpected that migalastat HCl would demonstrate increased systemic exposure with declining renal function. A Phase 1 renal impairment study, AT1001-015, conducted in non-Fabry patients with varying stages of renal impairment and normal renal function demonstrated significant accumulation of plasma migalastat in subjects with eGFR < 30 mL/min/1.73m$^2$.

Eleven subjects had > 2-fold increase in AUC relative to the mean (12400 ng·hr/mL) of normal renal function (> 90 mL/min/1.73m$^2$) in study AT1001-015. Eight of the 11 subjects had severe renal impairment (< 30 mL/min/1.73m$^2$) with 2.9- to 6.7-fold increased area under the concentration-time curve (AUC), and all 8 had elevated (> 100 ng/mL) trough concentrations of plasma migalastat from 238 to 582 ng/mL. Based on AT1001-015 results, an eGFR of < 30 mL/min/1.73 m$^2$ in non-Fabry subjects is associated with plasma migalastat accumulation.

# 4. OBJECTIVE(S)

## 4.1. 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.

## 4.2. Secondary Objective:

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.

# 5. INVESTIGATIONAL PLAN

## 5.1. Study Design

This will be a multi-centre open-label extension study of migalastat HCl in subjects with Fabry disease. All subjects who 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, may be considered for enrollment in this study.

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 for each year of the study. The duration of the treatment will vary among subjects.

Within each participating country, subjects will continue to receive treatment with migalastat HCl within this protocol until one of the following study conclusion conditions apply:

1. Regulatory approval and/or commercialization of migalastat HCl in the local country **or**
2. Migalastat HCl is rejected by the regulatory authority in the local country **or**
3. The study is terminated by the sponsor for reasons including, but not limited to safety issues **or**
    - If the sponsor decides to continue to provide AT1001, it may occur via a separate open-label extension protocol, early access, or other program depending on local regulations.
4. The subject is withdrawn or withdraws consent.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual/Investigator Site File Notebook (SPM/ISFN). The SPM/ISFN will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

## 5.2. Discussion of Design

This is an open-label extension study intended to provide continued treatment with migalastat HCl for subjects with Fabry disease who completed treatment of a previous migalastat HCl monotherapy study as outlined in Section 5.1.

The study will be used to assess the long-term safety and explore the efficacy/pharmacodynamics of migalastat HCl in subjects with Fabry disease who completed migalastat HCl treatment in a previous study.

# 6. SUBJECT SELECTION AND WITHDRAWAL CRITERIA.

## 6.1. Number of Subjects

The number of subjects to be enrolled will be dependent on the number of eligible subjects completing migalastat HCl treatment in previous studies and who consent to enter this open-label extension study. It is expected that up to 100 subjects will be eligible to enter into this study based on current enrollment in existing studies and potential enrollment in future studies.

## 6.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the Amicus investigational product (IP) or other study treatment that may impact subject eligibility is provided in the Investigator Brochure.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Subject with Fabry disease who completed treatment in a previous study of migalastat HCl given as monotherapy.
2. Male or female subjects 18 years of age or older.
   Note: Subjects under the age of 18 will be enrolled only at sites with all required regulatory and ethics approvals to do so.
3. A female subject is eligible to participate if she is:
   a. Of non-childbearing potential, or
   b. Of childbearing potential and NOT pregnant or nursing, has a negative urine pregnancy test at the Baseline Visit (Visit 1), and agrees to one of the methods of avoiding pregnancy listed in Appendix 1 from the time of first dose of study medication until 30 days after study completion.

   A female is considered “Non-childbearing potential” if she is status-post hysterectomy, status-post surgical removal of both ovaries, has current, documented tubal ligation, or is postmenopausal and >2 years without menses. Female subjects who are post-menopausal <2 years must be confirmed menopausal by Follicle Stimulating Hormone (FSH) and estradiol levels.

   A female is considered “childbearing potential” if she has functional ovaries, ducts, and uterus with no impairment that would cause sterility. This includes women with oligomenorrhea (even severe), and women who are perimenopausal or who have just begun to menstruate.
4. Male subjects must agree to use one of the contraception methods listed in Appendix 1. This criterion must be followed from the time of the first dose of study medication until 30 days after study completion.

5. Subject is willing and able to provide written informed consent and authorization for use and disclosure of Personal Health Information (PHI) or research related health information or has a legally authorized representative who has given written informed consent.

**Note: In Japan, subjects under 20 years of age will provide written informed assent, and written informed consent will be provided by their parent or legal guardian.**

## 6.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. The last available estimated glomerular filtration rate (eGFR) in the previous study was <30 mL/min/1.73m$^2$; unless there is measured GFR available within 3 months of Baseline Visit (Visit 1), which is >30 mL/min/1.73m$^2$.
2. The subject has undergone, or is scheduled to undergo kidney transplantation or is currently on dialysis.
3. The subject is treated or has been treated with another investigational drug (except migalastat HCl) within 30 days of study start.
4. Subject is unable to comply with study requirements, or deemed otherwise unsuitable for study entry, in the opinion of the investigator.
5. Had a documented transient ischemic attack, stroke, unstable angina, or myocardial infarction within the 3 months before Visit 1.
6. Has clinically significant unstable cardiac disease in the opinion of the investigator (e.g., cardiac disease requiring active management, such as symptomatic arrhythmia, unstable angina, or NYHA class III or IV congestive heart failure).
7. Has a history of allergy or sensitivity to AT1001 (including excipients) or other iminosugars (e.g., miglustat, miglitol).
8. Requires treatment with Glyset® (miglitol) or Zavesca® (miglustat).
9. Has any intercurrent illness or condition that may preclude the subject from fulfilling the protocol requirements or suggests to the investigator that the potential subject may have an unacceptable risk by participating in this study.
10. Patients with severe or unsuitable concomitant medical condition (cardiovascular, neurological, hepatic, renal, metabolic, hematological, immunological, pulmonary, or gastrointestinal disorder). The medical monitor or designee must be contacted to discuss the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.
11. Patients with clinically significant abnormal laboratory value(s) and clinically significant electrocardiogram (ECG) findings. The medical monitor or designee

must be contacted to discuss the subject's medical condition(s) and the potential impact of the condition(s) on continued trial participation.

## 6.4. Withdrawal Criteria

Subjects may discontinue migalastat HCl and withdraw from the study for any reason including, but not limited to, the following:

- At their own request or at the request of their parent or guardian (if the subject is a minor) or legally authorized representative*.
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
- Occurrence of an intolerable adverse event (AE) as determined by the investigator and/or the subject.
- Subject initiates or plans to initiate regular ERT for Fabry disease.
- Suspected hepatotoxicity, as defined by increase of ALT or AST ≥3X upper limit of normal (ULN) and total bilirubin >2X ULN when no other reason can be found to explain the increase in liver enzymes.
- Persistent noncompliance with study requirements, such as failure to return to the study site for scheduled visits.
- Pregnancy and/or breast feeding.
- Documented $eGFR_{MDRD}$ value meeting the criteria defined below:
  - An eGFR value (calculated centrally) that is < 30 mL/min/1.73$m^2$

In all cases, the reason for withdrawal and the date of withdrawal must be recorded in the electronic case report form (eCRF) and in the subject's medical records.

* "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

# 7. STUDY TREATMENTS

## 7.1. Investigational Product

Migalastat HCl, 150 mg (equivalent to 123 mg migalastat) per capsule, and reminder capsules are formulated with magnesium stearate (vegetable) and pregelatinized starch in a hard gelatin capsule and will be supplied in blister packs. Reminder capsules will not be identical in appearance to migalastat HCl capsules.

## 7.2. Dosage Schedule

Blister packs contain either 1) alternating 150 mg migalastat HCl capsules and inactive reminder capsules or 2) 150 mg migalastat HCl capsules only. Subjects will take one 150 mg capsule of migalastat HCl every other day (QOD) at approximately the same time of day. On alternate days when migalastat HCl is not administered, a reminder capsule will be provided which should be taken at approximately the same time of day or punch-out foil in the blister pack to keep track of QOD dosing regimen instead. Subjects are required to fast (no food or beverages, except water) 2 hours before and 2 hours after taking migalastat HCl. In order to ensure continuous treatment with migalastat HCl as subjects transition from the previous study; the first dose of study medication (either a reminder or active capsule, as appropriate to maintain the migalastat 150 QOD dosing regimen) should be taken within the window of the Baseline Visit.

## 7.3. Packaging and Labeling

Migalastat HCl will be supplied by the sponsor to the study sites as capsules packaged in blister packs. The blister pack contains migalastat HCl capsules and may include non-identical reminder capsules.

The contents of the label will be in accordance with all applicable regulatory requirements.

Each blister pack will have a label that will contain the drug name, strength, quantity, lot number, sponsor name, and applicable local law statements.

## 7.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Amicus (or designee), when applicable. Product accountability records must be maintained throughout the course of the study.

## 7.5. Supplies and Accountability

Sites will be instructed to store the study medication at room/ordinary temperature (15°C to 25°C / 59°F to 77°F) in a secure area, free from environmental extremes, and with

restricted access. The capsules must be dispensed to subjects in the original study medication container provided by the sponsor.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

The investigator, or appropriately assigned designee, will inventory and acknowledge receipt of all shipments of the study medication. The investigator agrees to keep accurate records of the quantities of study medication dispensed, used, and returned by each subject. Subjects will be instructed to return all unused, partially used, or empty study medication containers at the specified visits. The study monitor will periodically check the supplies of study medication held at the site to verify accountability of all study medication used and to verify that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file. When instructed by the monitor, the investigator agrees to return all original containers of study medication, whether empty, or containing used or unused study medication to the sponsor or their designee.

## 7.6. Treatment Compliance

Dosing compliance will be assessed at each clinic visit through subject interview and comparison of the amount of study medication the subject was scheduled to take over the number of days during the study with the amount returned.

The investigator may choose to interrupt or discontinue the study medication in case of an AE. Any interruption in dosing for this, or other reasons, must be documented.

The investigator should discontinue the study medication if continued administration of the study medication is believed to be contrary to the best interest of the subject. The reasons for discontinuation must be documented.

If the reason for the interruption or discontinuation of the study medication is an AE, an abnormal assessment (e.g., ECG finding), or a laboratory test abnormality, this information will be recorded as an AE.

If the subject is not compliant with the study medication administration, the investigator may need to evaluate whether the noncompliance should warrant subject withdrawal from the study.

## 7.7. Prohibited Medications and Non-Drug Therapies

Use of investigational/experimental therapy is not allowed at any time during the study.

Routine use of the following medications during this trial is prohibited:

- Glyset (miglitol)
- Zavesca (miglustat)
- Fabrazyme (agalsidase beta)

- Replagal (agalsidase alfa)

If the subject receives investigational therapy, or if routine use of prohibited medications is initiated, the subject must be prematurely discontinued from the trial and final assessments performed at the last treatment visit.

Drugs that affect lysosomal pH (e.g., chloroquine) and drugs that result in accumulation of phospholipids in lysosomes (e.g., gentamicin, amiodarone) should be avoided due to the theoretical potential for interactions with migalastat. If alternative therapies exist these should be used.

## 7.8. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not Amicus is providing specific post study treatment.

## 7.9. Treatment of Study Treatment Overdose

An overdose of migalastat HCl is defined as an ingestion of a dose greater than the prescribed dose of 150 mg migalastat HCl QOD. There are no known antidotes and Amicus does not recommend a specific treatment in the event of a suspected overdose. The investigators will use clinical judgment in treating the symptoms of a suspected overdose.

# 8. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table displays each study assessment and procedure along with the scheduled time of occurrence (Table 1). All study assessments should be conducted by the investigator, and/or a suitably qualified designee. Information will be recorded in the source documents and, where appropriate, the eCRF.

All study visits should be scheduled from the Baseline Visit (Visit 1) as specified. Further information can be found in the SPM/ISFN.

**Table 1: Time and Events Table**

| **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 last treatment 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.

**Baseline**

During transition from the previous study into the current study, the intent is for treatment with migalastat HCl to continue without a break.

Assessments collected as a part of the last treatment visit in the previous study, that are also required for the Baseline Visit in the current study, will serve as the assessment for the Baseline Visit. The visit window for the last treatment visit in the previous study will apply to those Baseline Visit assessments. However, to provide flexibility to investigators and subjects, any Baseline Visit assessment that is 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.

**Unscheduled visits**

Unscheduled visits can be performed at any time point at the investigator's discretion for medical reasons, such as evaluation of AEs and/or repeat laboratory tests.

**Early Withdrawal**

Subjects who meet any of the withdrawal criteria in Section 6.4 and withdraw from the study will be asked to return for a visit approximately 30 days after last treatment and have end of study assessments performed as shown in Table 1. An echocardiogram (ECHO) will be performed for subjects who have not had an ECHO within the previous 6 months.

**End of Study**

An End of Study visit will occur within approximately 30 days of the subject's last treatment dose.

## 8.1. Critical Baseline Assessments

Fabry disease may result in end stage cardiovascular and renal disease and organ damage. Cardiovascular and other medical history and risk factors will be assessed at the Baseline Visit (Visit 1). The medical monitor or designee must be contacted to discuss the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.

## 8.2. Safety

### 8.2.1. Safety Assessments

Safety assessments include the following:

- Adverse events (AEs), possible suicidality related adverse events (PSRAEs), and serious adverse events (SAEs)
- Withdrawal due to AEs
- Vital signs (blood pressure, body temperature, respiration rate, and heart rate) and weight
- Hematology, chemistry, and urinalysis parameters
- Echocardiography (ECHO)
- Electrocardiograms (ECGs)
- Stopping criteria

### 8.2.2. Stopping Criteria

Subjects must discontinue study medication and be withdrawn from the study if they meet any of the following stopping criteria:

- 30% increase in serum creatinine from Baseline (Visit 1) confirmed by repeat analysis in fully hydrated subject
- 25% decrease from Baseline in cardiac ejection fraction as determined by echocardiogram
- Cerebrovascular event with significant sequelae, including stroke
- An eGFR value of < 30 mL/min/1.73m$^2$

### 8.2.3. Liver chemistry stopping and follow up criteria

**Liver chemistry stopping and follow up criteria** have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). Phase 3 criteria will be used for this study.

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and in Appendix 2.

1. ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN and INR>1.5, if INR measured)

   NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug if ALT ≥3xULN and bilirubin ≥2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥8xULN.
3. ALT ≥5xULN but <8xULN persists for ≥2 weeks.

4. ALT ≥3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
5. ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks.

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product.
- Report the event to Amicus **within 24 hours** of learning its occurrence.
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct) (or ALT ≥3xULN **and** INR >1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug if ALT ≥3xULN **and** bilirubin ≥2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the **study** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to the clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below).

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the Quintiles and Amicus medical monitor within 24 hours of learning of the abnormality to discuss subject safety.
- Can continue investigational product.
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline.
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above.
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C ribonucleic acid (RNA);
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody
- Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated or a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM/ISFN.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.

- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash, or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use)(James, Letzig et al. 2009).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

### 8.2.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### 8.2.4.1. Definition of an AE

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, biologic (at any dose), or medical device, which does not necessarily have a causal relationship with the treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medical product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions.

The routine evolution of the disease condition under treatment according to the protocol will be evaluated as part of the disease symptoms assessments. Changes in the disease condition may not qualify as AEs. However, if there is a clinically relevant worsening of a sign or symptom of the condition under treatment and the outcome fulfills the definition of an AE, it must be reported as directed in the protocol.

#### 8.2.4.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.
f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 8.2.5. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

### 8.2.6. Possible Suicidality Related Adverse Event(s) (PSRAE)

The PSRAE eCRF form should be completed (in addition to the AE or SAE pages, as appropriate) if there is an occurrence of an adverse event which, in the investigator's opinion, is possibly related to suicidality. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly related to suicidality. The investigator will record this information in the source document and the PSRAE eCRF. The PSRAE form should be completed in its entirety as soon as the information is available and updated with any additional follow-up information received.

If the adverse event meets the definition of an SAE, the investigator must ensure that there are no discrepancies between the PSRAE and SAE forms. Both forms (PSRAE and SAE) should be updated with any follow-up information.

### 8.2.7. Pregnancy

Any pregnancy that occurs during study participation must be reported using a notification of pregnancy form. To ensure subject safety, each pregnancy must be reported to Amicus within 5 days of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to Amicus.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Amicus as described above.

### 8.2.8. Reporting of Overdose

Any event associated with or observed in conjunction with a product overdose (whether accidental or intentional) is considered by the sponsor to be an AE and must be reported as such. If a subject experiences an overdose (defined as higher than the dose of study medication prescribed in the protocol) during the course of the study (whether symptomatic or not), the sponsor must be informed within 5 working days of the investigator or study staff first becoming aware of the overdose. Follow-up information must be forwarded on the outcome as applicable. If an SAE occurs in conjunction with the overdose, then the reporting time frame for an SAE as described below must be met.

### 8.2.9. Reporting of Possible Study Drug Product Quality Complaints

Any defect or possible defect associated with the study medication provided by the sponsor must be reported by the investigator or study staff to the sponsor within 1 working day of first becoming aware of the possible defect. The study medication and packaging components in question, if available, must be stored in a secure area under the specified storage conditions until it is determined whether the study medication and/or

packaging is required for investigation of the possible defect. If the possible defect is associated with an SAE, the SAE must be reported as described below. The SAE report form must mention the possible study medication defect complaint.

### 8.2.10. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of the subject's first dose of study medication in the current study and until the follow up contact or 30 days after last dose, whichever comes first.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy), will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to Amicus within 24 hours, as indicated in Section 8.2.11.

### 8.2.11. Prompt Reporting of Serious Adverse Events and Other Events to Amicus

SAEs, pregnancies, medical device incidents and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to Amicus as described in the following table once the investigator determines that the event meets the protocol definition for that event.

**Table 2: SAE and Pregnancy Reporting Time Frames**

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs | 24 hours | "SAE" data collection tool | 24 hours | Updated "SAE" data collection tool |
| Pregnancy | 5 days | "Pregnancy Notification Form" | 5 days | "Pregnancy Follow-up Form" |
| **Liver chemistry abnormalities for Phase III to IV:** | | | | |
| ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)[1] | 24 hours[2] | "SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable[3] | 24 hours | Updated "SAE" data collection tool/"Liver Event" Documents[3] |
| ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks | 24 hours[2] | "Liver Event" eCRF[3] | 24 hours | Updated "Liver Event" eCRF[3] |
| ALT≥5xULN plus bilirubin <2xULN | 24 hours[2] | "Liver Event" eCRF do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3] | 24 hours | Updated "Liver Event" eCRF if applicable[3] |
| ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks | 24 hours[2] | "Liver Event" Documents (defined above)[3] | 24 hours | Updated "Liver Event" eCRF[3] |
| ALT≥3xULN and <5x ULN and bilirubin <2xULN | 24 hours[2] | "Liver Event" eCRF do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3] | 24 hours | Updated "Liver Event" eCRF, if applicable[3] |

[1] INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.

[2] Amicus must be contacted at onset of liver chemistry elevations to discuss subject safety.
[3] Liver Event Documents should be completed as soon as possible.

ALT = alanine aminotransferase, eCRF = electronic case report form, INR = international normalized ratio, SAE = serious adverse event, ULN = upper limit of normal

The method of detecting, recording, evaluating, and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to Amicus are provided in the SPM/ISFN. Procedures for post-study AEs/SAEs are provided in the SPM/ISFN.

Procedures for documenting, transmitting, and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SPM/ISFN.

#### 8.2.11.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to Amicus is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Amicus has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Amicus will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Amicus policy, and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Amicus will file it with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.2.12. Other Safety Assessments

Planned time points for all safety assessments are listed in the Time and Events (Table 1).

#### 8.2.12.1. Physical Examination

All subjects will undergo a complete physical examination at Baseline (Visit 1) and each subsequent scheduled visit. Any clinically significant abnormal observation, newly emerged or worsened after the start of the subject's first dose of study medication in the current study, should be reported as an AE.

#### 8.2.12.2. Vital Signs, Weight, and Height

At all visits, blood pressure (systolic and diastolic) measurement should be obtained using the same arm, and the respiration and heart rate values, and body temperature will be assessed. The measurements will be taken with the subject in sitting or supine position after having rested for a 5-minute period. The same position should be used at all visits.

Body weight will be recorded at all scheduled visits. Height will be recorded at the Baseline (Visit 1) and at the Follow-up Visit.

#### 8.2.12.3. ECG

A standard 12-lead ECG will be performed at every scheduled visit. Subjects will rest for approximately 5 minutes before the ECG recording begins and will be supine throughout the ECG evaluation. Significant findings not present prior to start of treatment, which meet the definition of an AE, must be recorded in the CRF.

#### 8.2.12.4. Clinical Laboratory Tests

If any results from the Baseline Visit (Visit 1) demonstrate, in the investigator's opinion, a clinically significant abnormality that the subject has not previously experienced, then the subject should be asked to return as soon as possible but no later than 3 months of the Baseline Visit for an unscheduled visit so that repeat specimens can be obtained.

The collection, processing and shipment of clinical laboratory samples will be fully described in the study laboratory manual. The parameters measured in these samples are described below.

The investigator (or his/her designee) will review each laboratory report from the central laboratory and assess any out of range lab results as "not clinically significant" (NCS) or "clinically significant" (CS). Any results which are considered clinically significant should be confirmed in a repeat test at the investigator's discretion. The investigator should consider repeat testing of persistent clinically significant results until the analyte returns to normal, or until an etiology is determined. The investigator (or his/her designee) will sign and date all laboratory reports.

Clinically significant laboratory abnormalities must be reported as an AE or SAE as appropriate.

**Serum Chemistry**

The serum chemistry parameters in Table 3 will be assessed at every visit. Subjects are required to fast for approximately 8 or more hours prior to the serum chemistry being performed.

**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 |

**Hematology**

The hematology parameters in Table 4 will be assessed at every visit.

**Table 4: Hematology Parameters**

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

**Urinalysis**

Safety urinalysis parameters in Table 5 will be assessed at every visit, using the urine sample collected during the visit (not the 24-hour urine sample).

**Table 5: Urinalysis Parameters**

| | |
|---|---|
| Color | Ketones |
| Appearance | Blood |
| Specific gravity | WBC |
| pH | Nitrite |
| Protein | Bilirubin |
| Glucose | Microscopy of sediment |

**24-hour Urine Collection**

A 24-hour urine sample will be collected at every study visit. These samples will be used to measure 24-hour urine protein, albumin, and creatinine levels.

Investigators are asked to minimize factors that may affect variability of results from 24-hour urine samples, which could confound interpretation of the efficacy of treatment with migalastat HCl. Refer to the SPM/ISFN for guidance on educating subjects and reminding them of proper methods for collection of 24-hour urine. Refer to the laboratory manual for following correct techniques for measuring and processing 24-hour urine samples.

Since angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) can reduce proteinuria, please ensure that clinically indicated initiation

of treatment with, or dose modification of, any of these medications is correctly recorded in the eCRF.

**Retained Biological Samples**

Any biological specimens remaining at the end of the study may be used for future exploratory analyses to improve the understanding of Fabry disease and its management. The retention of samples is optional; subjects will have the option to agree or refuse to have their samples retained. **In Japan, no genetic testing will be done on retained biological samples.**

**Plasma Lyso-GB3 (Plasma globotriaosylsphingosine)**

A blood draw will be collected for testing of plasma lyso-$GB_3$. Plasma lyso-$GB_3$, a biomarker, 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.

**Pregnancy Tests**

All female subjects of childbearing potential, as defined in Section 6.2, will have a urine pregnancy test performed at every study visit.

For any positive urine pregnancy test, a serum pregnancy test should be completed as soon as possible. The procedures for pregnancy reporting are described in Section 8.2.7.

## 8.3. Efficacy

### 8.3.1. Efficacy/Pharmacodynamic Assessments

- Estimated GFR (eGFR) based on the MDRD equation and CKD-EPI equation
- Plasma lyso-$Gb_3$
- Measurement of 24-hour urine protein
- Measurement of left ventricular mass (LVM) and LVM index (LVMi), as measured by echocardiography
- Measurement in ejection fraction, as measured by echocardiography
- Measurement of fractional shortening, as assessed by echocardiography
- Measurement of LV internal dimension (LVIDd and LVIDs), MWFS, and wall thicknesses, as assessed by echocardiography
- Measurement of WBC α-Gal A activity
- Measurement of patient reported Quality of Life as assessed by the SF-36.

Change from baseline will be evaluated for each efficacy endpoint, where baseline is defined (as in Table 1) as the value from the last treatment visit of the previous migalastat HCl study.

# 9. DATA MANAGEMENT

For this study, subject data will be entered into InForm Remote Data Capture system managed by Amicus therapeutics (or designee). The data will be transmitted electronically to the sponsor and combined with data from other sources in a validated data system (e.g. laboratory and ECHO data).

Management of clinical data will be performed in accordance with applicable Amicus standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events, and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA and WHOMD).

After database lock, each study center will receive a compact disc (CD) containing all of their site-specific eCRF data as entered into the InForm Remote Data Capture for the study, including full discrepancy and audit history. Additionally, a CD copy of all of the study center's data from the study will be retained by the Amicus Therapeutics and designee for storage.

# 10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 10.1. Hypotheses

No formal hypothesis testing will be performed for this study since the primary goal is to evaluate long-term safety and tolerability and the study population consists of (non-randomized) subjects taking the same open-label active treatment.

## 10.2. Sample Size Considerations

Since any subject with Fabry disease completing a treatment in a preceding migalastat HCl trial, or participating in a preceding open-label extension of migalastat HCl, can be enrolled into the this extension study, no sample size calculation will be performed for this study.

## 10.3. Data Analysis Considerations

Full details of the analysis plan will be provided in the Statistical Analysis Plan (SAP).

Continuous variables will be summarized by n, mean, standard deviation (SD), median, minimum, and maximum values. Discrete variables will be summarized by counts and percentages.

### 10.3.1. Analysis Populations

The Intent-to-Treat (ITT) Population is the primary population of interest and will include subjects who take at least one dose of IP after they have enrolled into this open-label extension study.

### 10.3.2. Analysis Data Sets

All safety and demography summaries will be based on the ITT population.

### 10.3.3. Interim Analysis

Full details of the analysis plan will be provided in the Statistical Analysis Plan (SAP).

### 10.3.4. Key Elements of Analysis Plan

#### 10.3.4.1. Safety Analyses

**Exposure**

The number of subjects exposed to IP will be summarized. Duration of exposure will also be summarized. Subject exposure will be categorized and the number and percentage of subjects in each category will be presented.

**Adverse events**

Adverse events will be coded using the MedDRA coding dictionary to collapse similar investigator terms for the adverse events. The various coded (preferred) terms will then be grouped into system organ class (SOC) categories.

The following will be summarized separately for the Treatment Phase and Follow-up Phase, as well as across all study phases combined:

- The percentage of subjects with each adverse event by SOC and preferred term.
- The percentage of subjects with each (investigator determined) treatment-related adverse event by SOC and preferred term.
- The percentage of subjects with each adverse event leading to study withdrawal by SOC and preferred term.
- The percentage of subjects with each serious adverse event by SOC and preferred term.

**Other Safety Assessments**

For all other safety variables (as listed below), continuous variables will be summarized with descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) and categorical variables will be summarized with frequency distributions.

**Vital Signs and Weight**

Vital signs (blood pressure and heart rate) and weight data will be summarized by visit. This will include a summary of changes from the Baseline Visit (Visit 1) of this study.

Baseline refers to values from the last treatment visit of the previous migalastat HCl study.

**Labs**

Laboratory data will be summarized by visit. This will include a summary of changes from the Baseline Visit (Visit1).

**ECG**

Electrocardiogram results will be assessed at each study visit and will be summarized descriptively over time in box-plots, where relevant, and in tables summarizing the distributions in each group, by study visit.

Further details will be provided in the Statistical Analysis Plan (SAP).

**Protocol Deviations**

A table will summarize the number and percent of subjects who experienced any protocol deviation. A by-subject listing will also be presented.

#### 10.3.4.2. Efficacy Analyses

Since no hypothesis testing is planned for this study, all efficacy parameters will be summarized using descriptive statistics for subjects in the ITT population. Summaries of the efficacy variables will be provided for the value at baseline and at each post-baseline time point and the change from baseline at each post-baseline time point.

#### 10.3.4.3. Pharmacodynamic Analyses

Pharmacodynamic (PD) assessment will include the evaluation of the effect of migalastat on WBC α-Gal A enzyme levels after repeated oral doses. Pharmacodynamic parameters will be summarized for the data from all subjects in the ITT population. The following data will be summarized for α-Gal A levels in WBCs and plasma lyso-$Gb_3$: the value at baseline and at each post-baseline time point and the change from baseline at each post-baseline time point.

#### 10.3.4.4. Health Outcomes Analyses

Subjects will receive a translated SF-36 questionnaire in their local language. Subjects will complete the questionnaires during appropriate site visits. Site personnel will collect the completed questionnaires and enter them into the electronic data capture (EDC) system.

SF-36 data will be handled in a similar fashion as the PD assessments, with the additional steps that domain scores for each completed questionnaire will be calculated so that the results at each study time point and change from baseline at each post-baseline time point can be reported for each of the SF-36 domains (Physical function, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health). Data collected on the SF-36 will not be reconciled with AE data.

# 11. STUDY CONDUCT CONSIDERATIONS

Amicus is contracting with Quintiles to perform study monitoring (Ex-US) and data management services for this study.

## 11.1. Posting of Information on Publicly Available Clinical Trial Registers

Amicus will be responsible for registering this clinical trial in a public registry that meets the requirements specified by the International Council of Medical Journal Editors (ICMJE), such as www.clinicaltrials.gov, and for publication of study results. Investigators will provide contact information to Amicus for the study listing.

## 11.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, Amicus will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Written informed consent must be obtained from each subject prior to participation in the study.

## 11.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Amicus procedures, Amicus monitors, or its designee will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Amicus, or its designees, requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

Amicus or its designee will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.

- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

### 11.3.1. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Amicus may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

### 11.3.2. Study and Site Closure

Upon completion or termination of the study, the Amicus monitor or its designee will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and Amicus or its designee Standard Operating Procedures.

Amicus reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If Amicus determines that such action is required, Amicus will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Amicus will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, Amicus will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Amicus or its designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

### 11.3.3. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Amicus audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The

investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Amicus will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Amicus standard operating procedures, and/or institutional requirements.

The investigator must notify Amicus of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

### 11.3.4. Use of Study Findings

All information concerning the product as well as any matter concerning the operation of the sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the sponsor and are unpublished, are confidential and must remain the sole property of the sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the sponsor is obtained.

The sponsor has full ownership of the data collected as part of the study.

By signing the clinical study protocol and the confidentiality agreement, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will ensure that a final report on the study is prepared. The sponsor will ensure that the study findings are reported in a manner that complies with applicable requirements for reporting clinical trial results.

As required by local regulation or by the IEC/IRB, a summary of the clinical study will be submitted by the sponsor to the regulatory authorities and by the investigator to the IEC/IRB.

All materials, documents and information supplied by the sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the sponsor. Subject to obligations of confidentiality, the investigator reserves the right to publish only the results of the work performed pursuant to this protocol, provided, however, that the investigator provides an authorized representative of the sponsor with a copy of any proposed publication for review and comment at least 45 days in advance of its submission for publication. In addition, if requested and prior to publication, the

investigator will remove any information determined by the sponsor to be confidential or proprietary information of the sponsor or its collaboration partner and will withhold publication an additional 90 days to allow for filing a patent application or taking such other measures as the sponsor deems appropriate to establish and preserve its proprietary rights.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

Authorship for publications derived from this study will be based on all of the following: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

### 11.3.5. Liability and Insurance

Liability and insurance provisions for this study are given in separate agreements.

### 11.3.6. Data Safety Monitoring Board

A data safety monitoring board (DSMB) will be chartered to monitor and evaluate the safety of all subjects in this trial by periodically reviewing summaries of safety data, evaluating risk/benefit where possible, identifying any clinically relevant trends, and assessing whether it is safe for the study to continue. A DSMB Charter will include operational and logistical procedures for the DSMB. The following stopping criteria will be observed for discontinuation of individual subjects:

- 30% increase in serum creatinine from baseline (confirmed by repeat measurement in fully hydrated subject)
- 25% decrease from baseline in cardiac ejection fraction by echocardiogram
- Cerebrovascular event with significant sequelae, including stroke
- An eGFR value of < 30 mL/min/1.73m$^2$

# 12. REFERENCES

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# 13. APPENDICES

## 13.1. Appendix 1: Contraceptive Requirements

The allowed methods of contraception described in the following sections are only effective when used consistently, correctly, and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

### 13.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and must use medically accepted methods of contraception with a failure rate of <1% per year throughout the duration of the study and for up to 30 days after last dose of protocol defined study medication.

A female subject is considered of childbearing potential if she has functional ovaries, ducts, and uterus with no impairment that would cause sterility. This includes women with oligomenorrhea (even severe), and women who are peri-menopausal or who have just begun to menstruate.

A female is considered of non-childbearing potential if she is status-post hysterectomy, status-post surgical removal of both ovaries, has current, documented tubal ligation, or is postmenopausal and >2 years without menses. Female subjects who are post-menopausal <2 years must be confirmed menopausal by Follicle Stimulating Hormone (FSH) and estradiol levels.

**For sites in Italy:** If of reproductive potential, agree to plan and document (or have their partner plan) a birth control strategy (or method) with his/her physician in order to avoid pregnancy throughout the duration of the study and for up to 30 days after last dose of protocol defined study medication.

**Contraceptive Methods with a Failure Rate of < 1% per year**

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure per year rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or

review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.

- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

### 13.1.2. Male Subjects

To prevent pregnancy in a female partner, male subjects must use one of the following contraceptive methods:

- Condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent.
- Male sterilization (e.g., vasectomy with documentation of azoospermia) prior to the subject's entry into the study. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.

## 13.2. Appendix 2: Liver Chemistry Stopping and Follow-up Criteria