Methodology:

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

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

Number of Subjects (planned):

Approximately 20 subjects are planned globally for enrollment in this study. An attempt will be made to enroll subjects of each sex. At least 7 to 10 of these subjects will be aged 12 to < 16 years for a subgroup analysis to be conducted at the end of Stage 1.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Subjects must meet all of the following criteria to be considered for enrollment in the study:

1. have a parent or legally-authorized representative who is willing and able to provide written informed consent and authorization for use and disclosure of personal health information or research-related health information, and subject provides assent, if applicable
2. male or female, diagnosed with Fabry disease aged between 12 and < 18 years at baseline, and who might benefit from specific treatment for their condition, in the opinion of the investigator
3. confirmed amenable *GLA* variant determined using the migalastat amenability assay

   Note: For subjects without a known amenable *GLA* variant, *GLA* genotyping must be performed prior to Visit 2.

   Note: For subjects with a *GLA* variant that has not yet been tested in the Migalastat Amenability Assay, amenability testing must be completed before Visit 2.
4. weight of ≥ 45 kg (99 pounds) at screening
5. treatment-naïve or discontinued ERT treatment at least 14 days prior to screening
6. have at least one complication (ie, historical or current laboratory abnormality and/or sign/symptom) of Fabry disease, for example:
   a. corneal whorls
   b. neuropathic pain and/or acroparesthesia and/or acute crises persisting or recurring at least twice over the previous 3 months or longer, or; requiring management with analgesia
   c. Fabry disease-related gastrointestinal signs and symptoms (eg, diarrhea, abdominal pain) persisting or recurring at least twice over the previous 3 months or longer
   d. hypohidrosis (present for at least 3 months)

1. DECLARATIONS OF SPONSOR AND INVESTIGATOR

1.1. Declaration of Sponsor

This clinical study protocol is subject to critical review and has been approved by the sponsor, Amicus Therapeutics.

The information it contains is consistent with the following:

- the current benefit-risk evaluation of migalastat
- the moral, ethical, and scientific principles governing clinical research, as set out in the current version of the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) described in the United States (US) Code of Federal Regulations (CFR) Title 21 Parts 50, 54, 56, and 312, and in the International Conference on Harmonisation (ICH) GCP E6 guidelines

Sponsor

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

Date: 13JUN2019 Signature: Amicus

Amicus

Amicus Therapeutics

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 current version of the Declaration of Helsinki and the principles of Good Clinical Practice described in the United States CFR Title 21 Parts 50, 54, 56, and 312, and in the ICH GCP E6 guidelines. I will also work in accordance with applicable local requirements.

Investigator

Date: _____ Signature: _____

Printed Name: _____

Table 3: Schedule of Assessments (Continued)

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

Subjects for whom *GLA* genotyping must be performed may require additional time for screening (see Section 7.1). Genotyping must be completed prior to any other screening procedures. Screening for subjects without a known variant will resume following receipt of the genotyping result and confirmation of amenability.

9.1.2. Baseline Visit

Baseline assessments will be performed pre-dose on Day 1, which should be scheduled as soon as possible after a subject is determined to be eligible for participation in the study.

All inclusion/exclusion criteria must be reviewed and verified at this visit to ensure that there have been no changes to a subject's health that would affect that subject's eligibility to participate in the study. If a subject is not well at the time the Baseline Visit is scheduled, the Baseline Visit should be postponed.

9.1.3. Treatment Period Visits/Telephone Contacts

Periodic visits are scheduled between Days 15 and Day 30 and at Month 1 (end of Stage 1), and at Months 3, 6, 9, and 12 (Stage 2). Telephone contacts are scheduled for interim months, Months 2, 4, 5, 7, 8, 10, and 11 (Stage 2). A month will be defined as 30 days.

Telephone contacts will include questions regarding any AEs or pregnancies (ie, including delay in menstrual period for female subjects with regular menses) that may have occurred and any changes in concomitant medications.

Visits during which sparse PK samples will be collected may be conducted at the subject's residence by a visiting nurse.

9.1.4. Unscheduled Visits

Unscheduled visits for medical reasons such as evaluation of AEs and/or repeat laboratory tests can be performed at any time at the investigator's discretion. The date and reason for the visit, in addition to all information collected during the visit, should be captured in source documents and on the appropriate eCRFs.

Follow-up visits triggered by subjects' weight monitoring also are considered unscheduled visits for data management purposes.

9.1.5. Early Termination Visit

Subjects who are withdrawn from the study should complete Month 12/ET procedures as soon as possible. If early termination coincides with a scheduled visit (ie, Visit 4, 6, or 10), all procedures outlined for the ET visit should be performed.

9.1.6. 30-day Safety Follow-up Visit

All subjects who do not enroll in a long-term extension study, including subjects who discontinue study drug or withdraw from the study, should complete a 30-day safety follow-up visit, to be scheduled at least 30 days after the last dose of study drug.

samples for determination of plasma migalastat concentrations and PK analysis will be collected. The pharmacodynamic biomarker to be evaluated in this study is lyso-Gb_3 levels in plasma. Blood samples will also be collected for exploratory biomarkers. Efficacy assessments include eGFR, urine protein and albumin levels, left ventricular mass index (LVMi) using echocardiograms, and subject questionnaires (electronic diary [e-diary] for gastrointestinal signs and symptoms and pain [Short Fabry Disease Patient-Reported Outcome – Gastrointestinal Signs and Symptoms {FABPRO-GI and Pain Questionnaire for Clinical Trials (24-hour version)}], Patient Global Impression of Change [PGI-C], Fabry-Specific Pediatric Health and Pain Questionnaire [FPHPQ], and Pediatric Quality of Life Inventory™ [PedsQL™]).

7.2. Details of Study Treatment

Migalastat will be supplied as capsules that are generally referred to as "migalastat"; the term "migalastat HCl" refers to the salt form and is used only when referring to a specific dosage of migalastat for administration.

Migalastat capsules contain 123 mg migalastat free base, which is equivalent to 150 mg migalastat HCl.

7.2.1. Administration of Study Treatment

One migalastat 150 mg capsule will be administered with water every other day continuously for 12 months during Stages 1 and 2 of the study. Subjects should take study drug at the same time of day during the every other day dosing schedule. Subjects are to record the date and time of each migalastat administration in the Dosing Diary provided in the dosing wallet containing their study drug.

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

Subjects will be instructed not to eat for at least 2 hours before and for 2 hours after administration of study drug. Water can be consumed during this period.

Pharmacokinetic simulations suggest that if a subject's weight decreases to 43 kg, their exposure following a 150 mg QOD dose is not substantially higher than exposure in subjects weighing ≥ 45 kg. Therefore, in the event of weight loss down to 43 kg during Stage 2, subjects may continue on study drug with close monitoring. During Stage 2, if a subject's weight decreases to below 43 kg, an unscheduled visit will be arranged 2 to 4 weeks later in order to monitor the subject's weight. If the subject's weight remains below 43 kg at the follow-up visit, additional blood samples will be drawn for PK and PD (plasma lyso-Gb_3) assessments. Follow-up PK assessments will be drawn at 4 time intervals according to the sampling group the subject was initially assigned to. Based on the PK results and other parameters, at the discretion of the investigator and the Amicus medical monitor, the subject may remain on study drug with additional monthly follow-up visits until his/her weight returns to at least 43 kg.

Term	Definition
PedsQL™	Pediatric Quality of Life Inventory™
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic
QOD	*quaque altera die* (once every other day)
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time to reach the maximum observed plasma concentration
WBC	white blood cell

7. INVESTIGATIONAL PLAN

7.1. Study Design

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

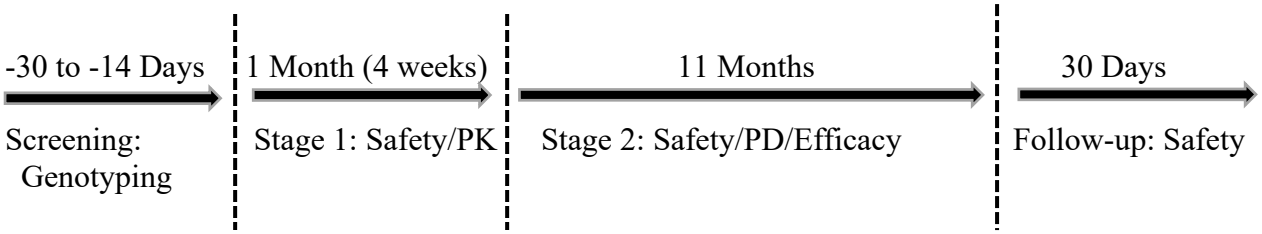
The study will consist of 2 stages. Stage 1 will be a treatment period of approximately 1 month (4 weeks); Stage 2 will be a treatment period of 11 months and a 30-day (untreated) safety follow-up period. There will be no break in treatment between Stages 1 and 2. Prior to Stage 1, there will be a screening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

At screening, all subjects first must have a blood test to confirm their *GLA* variant prior to completing any additional screening assessments. Subjects with a documented variant (ie, those who have a full genotype report) that is known to be amenable to migalastat may continue to be screened according to the procedures outlined for Visit 1.

For subjects without a known *GLA* variant, screening will resume after receipt of the variant result, if amenability is confirmed. For subjects with a *GLA* variant that has not yet been tested in the Migalastat Amenability Assay, amenability testing also will be performed. If variants are determined to be amenable according to the Migalastat Amenability Assay, screening procedures will resume at that time. If the variant is non-amenable, the subject will be considered a screen failure. (Note: the Migalastat Amenability Assay may take up to 8 weeks.)

The study design is displayed in Figure 1.

Figure 1: Study Design



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

Safety assessments include monitoring of AEs, clinical laboratory tests, vital signs, physical examinations, body weight and height, 12-lead electrocardiograms (ECGs), echocardiograms, Tanner staging of sexual development, and use of concomitant medications. Sparse blood

Table 3: Schedule of Assessments

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

9.2. Description of Study Assessments

All assessments will be conducted according to the schedule presented in Table 3. Assessments may be repeated if requested by the Medical Monitor.

9.2.1. Screening Assessments

Informed consent/assent will be obtained before any study-specific procedures are performed. Screening assessments will include review of inclusion and exclusion criteria, collection of demography information (date of birth, sex, and race; ethnicity in the US only), collection of medical history (including menarcheal status), review of prior/current medications, confirmatory *GLA* genotyping, confirmation of documented amenable *GLA* variant, a complete physical examination, vital signs, body weight, a 12-lead ECG, chemistry (including calculation of eGFR), measurement of plasma lyso-Gb_3 levels, urinalysis, urine pregnancy test (if applicable), and echocardiogram.

For subjects whose *GLA* variant amenability status in regard to migalastat treatment is not known at screening, the migalastat amenability assay must be performed and results must be received before other screening procedures are performed. If a subject's *GLA* variant is amenable to treatment with migalastat, the 30-day screening period will begin when the first of the remaining screening procedures is performed. If a subject's *GLA* variant is not amenable to treatment with migalastat, that subject will be considered a screen failure.

9.2.2. Safety Assessments

9.2.2.1. Adverse Events and/or Serious Adverse Events

Throughout the study, subjects will be given an opportunity to report AEs. The definitions, reporting, and monitoring of AEs and SAEs are described in Section 10.

9.2.2.2. Clinical Laboratory Tests

9.2.2.2.1. Safety Laboratory Tests

Samples for chemistry, hematology, and urinalysis are outlined in Table 6. Laboratory samples collected on a dose administration day will be collected predose.

Table 6: Clinical Laboratory Parameters

Chemistry	Hematology	Urinalysis
ALT	Platelet count	Color
Alkaline phosphatase	RBC count	Appearance
AST	WBC count (absolute)	Specific gravity
Albumin	Hematocrit	pH
Bilirubin, total	Hemoglobin	Protein
BUN	Automated WBC differential	Albumin or microalbumin
Calcium, total	Neutrophils	Glucose
Carbon dioxide, total (bicarbonate)	Lymphocytes	Ketones

Table 6: Clinical Laboratory Parameters (Continued)

Chemistry	Hematology	Urinalysis
Chloride	Monocytes	Blood
CPK	Eosinophils	WBCs
Creatinine, serum	Basophils	Nitrite
GGT		Bilirubin
Glucose		Microscopy of sediment
Lactate dehydrogenase		
Magnesium		
Phosphorous		
Potassium		
Protein, total		
Sodium		
Uric acid		

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; GGT = gamma-glutamyltransferase; RBC = red blood cell; WBC = white blood cell

Safety laboratory tests will be performed at a central laboratory. Instructions for the collection, processing, and shipment of clinical laboratory samples will be provided in the Laboratory Manual.

The investigator or a designee will review laboratory results and assess any out-of-range laboratory results as "not clinically significant" or "clinically significant." Any results that are considered clinically significant may 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 levels or until an etiology is determined. The investigator or a designee will sign and date all laboratory reports.

Clinically significant laboratory abnormalities must be captured as AEs or SAEs, as appropriate.

9.2.2.2.2. Other Laboratory Tests

GLA genotyping will be performed at screening for all subjects.

Urine pregnancy tests will be performed for all female subjects of childbearing potential (as defined in Section 8.5); date of last menstrual period, as applicable, will be recorded during telephone contacts.

Any subject who has a positive urine pregnancy test result should have a serum pregnancy test performed as soon as possible for confirmation. Any subject who becomes pregnant must discontinue study drug. Procedures for pregnancy reporting are described in Section 10.5.1.

9.2.2.3. Vital Signs

Vital signs include blood pressure (systolic and diastolic), respiration rate, heart rate, and body temperature. Measurements are to be taken with the subject in a sitting or supine position after

9.2.5.2. Urine Protein and Albumin Levels

Protein and albumin (or microalbumin) levels in urine (as part of urinalysis) will be measured.

9.2.5.3. Echocardiogram

The key echocardiogram parameter considered for efficacy is LVMi. In addition, ejection fraction, fractional shortening, left ventricular internal diameter end diastole and end systole, midwall fractional shortening, and wall thickness will be assessed.

Echocardiograms will be read centrally.

9.2.5.4. Subject Questionnaires

All Questionnaires will be provided in a separate Patient Outcomes Manual.

9.2.5.4.1. Electronic Diary

Subjects will be asked to complete daily diary entries at approximately the same time of day (preferably in the evening before bed time) beginning on Day 1 and for the duration of the study. Diary entries will include completion of the FABPRO-GI and Pain Questionnaire for Clinical Trials (24-hour version).

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

9.2.5.4.2. Patient Global Impression of Change

The PGI-C consists of 4 questions regarding diarrhea, abdominal pain, overall pain, and daily living to be answered using a 7-point scale. Subjects will complete the questions by themselves without assistance from their parents or legal guardians.

9.2.5.4.3. Fabry-Specific Pediatric Health and Pain Questionnaire

The FPHPQ includes questions about Fabry disease-specific symptoms (eg, sweating, pain, dizziness and tiredness, heat and cold intolerance, swollen eyelids, gastrointestinal symptoms, feeling thirsty, difficulty hearing, ringing or buzzing noise in the ears, and ability and enjoyment to participate in sports). The frequency of these symptoms will be rated using a 5-point Likert scale (always, often, sometimes, seldom, never). Pain intensity is measured on a 10-point scale, numeric responses are given for onset of pain and school days missed, and yes/no questions are posed about difficulty hearing and other problems not specifically mentioned. There are 2 age-specific self-report versions for children 8 to 12 years and 13 to 18 years, respectively.

9.2.5.4.4. Pediatric Quality of Life Inventory

The PedsQL™ is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. It consists of 23 items and includes questions about physical functioning, emotional functioning, social functioning, and school functioning relative to the prior 7 days, using a 5-point scale. Both parents or legally-authorized representatives and subjects complete the appropriate version of the PedsQL independently of one another. Parents or legally-authorized representatives and subjects may self-administer the questions after introductory instructions are given by study site personnel.

10.1.2. Serious Adverse Event

An SAE is any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening event
  - This includes any AE that in the view of either the investigator or sponsor places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more serious form, might have caused death.
- requires inpatient hospitalization or prolongs existing hospitalization
  - Hospitalization signifies the subject has been admitted, regardless of duration, for observation and/or treatment that would not have been appropriate in a physician's office or outpatient setting.
  - Hospitalizations for elective or pre-planned treatment of a pre-existing condition do not have to be reported as SAEs if the following criteria are met:
    - the condition is documented in the subject's medical history and has not worsened since the informed consent form was first signed; and
    - the condition and planned procedure are documented in the subject's source records at screening.
  - Emergency room/department or outpatient treatments that do not result in admission do not have to be reported as an SAE, unless another SAE criterion is met. Events assessed and treated in these circumstances should be captured as AEs in the eCRF and documented in the subject's source records.
  - Hospitalizations solely based on subject logistics (eg, subject is admitted due to limited hospital accessibility for what would otherwise be an out-subject procedure) do not have to be reported as SAEs provided that the hospitalizations are clearly defined as such in the subject's source record.
- persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- congenital anomaly/birth defect

An important medical event that does not result in one of the above serious outcomes may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the listed serious outcomes. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

If the following 4 elements are known, the event must be reported as described in Section 10.4.2:

- identifiable subject
- event term
- study drug
- identifiable reporter

Additionally, the investigator's assessment of an event's relationship to study drug (see Section 10.2) is essential for the sponsor to appropriately process the report and must be included.

Subjects and parents or legally-authorized representatives must be informed and understand that they should report events meeting the definition for SAE to study site personnel as soon as possible (and not wait until their next study visit).

If a non-serious event becomes serious, the change in status must be appropriately entered in the eCRF and the subject's source record, and reported to the sponsor as described in Section 10.4.2.

If the investigator becomes aware of an SAE that occurs more than 30 days after the last dose of study drug, and considers the event possibly, probably, or definitely related to study drug, the investigator should contact the Medical Monitor (see Table 1)/Clinical Operations Lead to determine how the SAE should be documented and reported.

10.2. Relationship to Study Drug

The investigator or a medically qualified sub-investigator will review each event and assess its relationship to study drug based on available information and according to the following guidelines:

- Definite: a reaction that follows a distinct temporal relationship from administration of study drug; that follows a known reaction to the agent or chemical group of the study drug; and that cannot be explained by the subject's clinical state or other factors
- Probable: a reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the suspected study drug; and that could not be reasonably explained by the known characteristics of the subject's clinical state
- Possible: a reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the suspected study drug; but that could readily have been produced by a number of other factors
- Unlikely: a reaction that does not follow a reasonable temporal sequence from administration of study drug; however, causality from the study drug cannot be ruled out
- Unrelated: a reaction for which sufficient data exist to indicate that the etiology is unrelated to study drug

de-identified in accordance with local data privacy regulations prior to sending to the sponsor. The subject's study number must be included on each page included in the faxed report or in the subject line of the email. Reporting timelines (as described above) must not be delayed while obtaining or preparing supporting information.

If more than 1 SAE is identified in 1 subject simultaneously, separate SAE reports should be generated for each event.

Information not available at the time of the initial report (eg, event end date and outcome, supporting documents (eg, discharge summary, etc) must be reported to the sponsor within **24 hours of any knowledge/receipt by study site personnel of the information**. Information must be faxed (or emailed, if necessary) to the designated safety fax number (or email address) (Table 1) to ensure appropriate dissemination and processing. All supporting documents must be thoroughly reviewed and de-identified in accordance with local data privacy regulations prior to sending to the sponsor. The subject's study number must be included on each page included in the fax or in the subject line of the email.

Medical history, concomitant medication, and AE information obtained through SAE reporting must also be consistently recorded in the eCRF.

10.4.3. Additional Reporting Requirements for Suspected Unexpected Serious Adverse Reaction

The sponsor is responsible for processing suspected unexpected serious adverse reactions (SUSARs). SUSARs are also referred to as alert reports, expedited safety reports, and investigational new drug application (IND) safety reports.

A SUSAR is defined as any SAE that is determined to be associated with the use of study drug and is unexpected (not currently listed in the safety reference information or is not listed at the specificity or severity that been observed). The sponsor will notify all investigators currently conducting migalastat clinical studies of all SUSARs in accordance with applicable regulations. SUSARs will be reported to the relevant regulatory authorities and IRBs/IECs according to the rules in effect in each country where study sites are located:

- If the SUSAR is fatal or life-threatening, regulatory authorities and ethics committees will be notified within 7 calendar days after the sponsor learns of the event.
- If the SUSAR is not fatal or life-threatening, regulatory authorities and ethics committees will be notified within 15 calendar days after the sponsor learns of the event.

These notifications will need to be filed in each site's Study File Notebook and submitted to each site's IRB/IEC in accordance with policy.

Safety updates will be provided periodically to the regulatory authorities and IRBs/IECs responsible for the study according to the rules in effect in each country where study sites are located. These updates will include information on SUSARs and other relevant safety findings.

11.1.3. Pharmacodynamic Endpoints

The pharmacodynamic endpoint is the change in plasma levels of lyso-Gb_3 from baseline to Months 3, 6, and 12/ET.

11.1.4. Efficacy Endpoints

Efficacy endpoints are as follows:

- change in eGFR from baseline to Months 3, 6, and 12/ET
- change in urine protein and albumin levels from baseline to Months 3, 6, and 12/ET
- change in LVMi and other echocardiogram parameters from baseline to Month 12/ET
- change in gastrointestinal signs and symptoms and pain from baseline to Month 12/ET, as measured by e-diary responses (FABPRO-GI and Pain Questionnaire for Clinical Trials [24-hour version])
- mean PGI-C values at Months 3, 6, and 12/ET
- change in FPHPQ scores from baseline to Month 12/ET
- change in PedsQL scores from baseline to Month 12/ET

11.2. Sample Size Considerations

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

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

Second, according to the sample size calculation for a study with sparse/rich PK sampling intended for population PK analysis, $(e^{-t(0.975,df)\times SE_{LCL}}, e^{t(0.975,df)\times SE_{LCL}})$ should be within the pre-defined criteria of (0.6, 1.4), where SE_{LCL} is the standard error for log-transformed pediatric clearance that relates to weight, and t (0.975, df) is the 97.5% upper quantile values from t distribution corresponding to the sample size. Mathematically, SE_{LCL} was approximately equal to the relative standard error of untransformed clearance, 0.16. Therefore, a sample size of approximately 10 subjects is adequate to achieve the pre-defined boundary of (0.6, 1.4).

11.3. Data Analysis Considerations

11.3.1. Analysis Populations

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

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

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

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

11.3.2. Statistical Methods

Data will be summarized using descriptive statistics. Continuous variables will be summarized by number of subjects, mean, standard deviation, median, minimum, and maximum values. Discrete variables will be summarized by counts and percentages.

In general, data will be summarized by sex and combined across all subjects.

A month will be defined as 30 days.

No missing data imputation method is planned to handle missing data. Data will be summarized as observed. All data will be listed.

11.3.2.1. Interim Analysis

The interim PK endpoint is a graphical presentation of plasma-concentration time data (observed versus predicted).

Interim analysis of the plasma concentration-time data collected during Stage 1 will be conducted when these results are available. There will be 2 interim PK analyses. One analysis will be performed using the entire Stage 1 PK population of adolescents aged 12 to < 18 years. A second analysis will include a subpopulation of at least 7 to 10 subjects age 12 to < 16 years.

11.3.2.2. Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. Summaries will be provided for TEAEs, TEAEs by severity, and TEAEs by relationship to study drug as well as deaths, SAEs, and TEAEs leading to discontinuation of study treatment. Listings will also be provided for SAEs and TEAEs leading to discontinuation of study treatment.

Actual values and changes from baseline for clinical laboratory test results, vital signs, body weight and height, ECG parameters, echocardiogram parameters (other than LVMi) and Tanner stages will be summarized using descriptive statistics. Shift tables will also be provided for clinical laboratory tests and ECG results. Physical examination findings will be summarized by body system.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and will be summarized by Anatomical-Therapeutic-Chemical classification.

11.3.2.3. Pharmacokinetic Analyses

For the population PK analysis, predicted median (2.5^{th} and 97.5^{th} percentile) concentration-time data based on a previously established population PK model will be visually compared with observed concentration-time data for all patients and for the subgroup aged 12 to < 16 years at the end of Stage 1.

e. left ventricular mass index (LVMi) above the normal range for age and sex

f. rhythm and/or conduction disturbances, for example:

- episode of tachycardia or bradycardia,
- arrhythmia, or;
- abnormal PR, QRS, or QT interval

g. reduced estimated glomerular filtration rate (eGFR) (using the Schwartz formula) for age and sex, or hyperfiltration (> 135 ml/min/1.73 m^2)

h. proteinuria or albuminuria in spot urine (early morning preferable) or as determined by the investigator (based on local laboratory results documented in the patient's medical record)

i. plasma globotriaosylsphingosine (lyso-Gb_3) levels above normal (based on local laboratory results documented in the patient's medical record)

j. hearing impairment and/or tinnitus

7. able to swallow capsules
8. if of reproductive potential, agree to use medically accepted methods of contraception throughout the duration of the study and for up to 30 days after last dose of study medication

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. moderate or severe renal impairment (eGFR < 60 mL/min/1.73 m^2 at screening)
2. advanced kidney disease requiring dialysis or kidney transplantation
3. history of allergy or sensitivity to migalastat (including excipients) or other iminosugars (eg, miglustat, miglitol)
4. subject has received any gene therapy at any time or anticipates starting gene therapy during the study period
5. requires treatment with Glyset® (miglitol) or Zavesca® (miglustat), within 6 months before screening or throughout the study
6. requires treatment with Replagal® (agalsidase alfa) or Fabrazyme® (agalsidase beta) within 14 days before screening or throughout the study
7. received any investigational/experimental drug, biologic or device within 30 days before screening
8. any intercurrent illness or condition at screening or baseline 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
9. is pregnant or breast-feeding, or is planning to become pregnant during the study period
10. in the opinion of the investigator, the subject and/or parent or legally-authorized representative is unlikely or unable to comply with the study requirements

2. SYNOPSIS

Name of Sponsor/Company:
Amicus Therapeutics (Amicus)

Name of Investigational Product:
Migalastat hydrochloride (HCl)

Name of Active Ingredient:
Migalastat

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

Study Centers: Global, multicenter

Protocol Number: AT1001-020

Studied Period:	**Phase of Development:**
Estimated date first subject enrolled: Third quarter 2018 Estimated date last subject completed: First quarter 2021	Phase 3b

Objectives:

Stage 1

Primary Objectives

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

Secondary Objectives

Not applicable

Stage 2

Primary Objective

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

Secondary Objectives

- to characterize the pharmacodynamics (PD) of migalastat in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat
- to evaluate the efficacy of migalastat in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat
- to evaluate the relationship between exposure to migalastat and response

Table 3: Schedule of Assessments (Continued)

Assessments	Screening[a]	Treatment Period														Treatment Period
		Stage 1			Stage 2											
	Day -30 to -14	Baseline[b] Day 1	Day 15-30	Month 1	Month 2 (TC)	Month 3	Month 4 (TC)	Month 5 (TC)	Month 6	Month 7 (TC)	Month 8 (TC)	Month 9	Month 10 (TC)	Month 11 (TC)	Month 12/ET	30-Day Safety[c]
Window (days)	—	—		±3	±3	±3	±3	±3	±6	±6	±6	±6	±6	±6	±6	+6
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Urinalysis (urine protein and albumin or microalbumin levels)	X	X		X		X			X						X	
Urine pregnancy test or date of LMP (as applicable)[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Echocardiogram (LVMi and additional parameters)	X	X							X						X	
Study treatment supply/ Resupply/Return		X		X		X			X			X			X	

Abbreviations: BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FABPRO-GI = Fabry Disease Patient-Reported Outcome-Gastrointestinal; FPHPQ = Fabry-Specific Pediatric Health and Pain Questionnaire; *GLA* = gene encoding α-galactosidase A; HR = heart rate; LMP = last menstrual period; LVMi = left ventricular mass index; lyso-Gb_3 = globotriaosylsphingosine; PD = pharmacodynamic; PedsQL = Pediatric Quality of Life Inventory; PGI-C = Patient Global Impression of Change; PK = pharmacokinetic; RR = respiration rate; TC = telephone call; Temp = body temperature

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

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

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

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

[e] Female subjects only

7.2.2. Study Drug Interruptions

The investigator may choose to interrupt administration of study drug in case of an AE (eg, abnormal result of an assessment or laboratory test) or for administrative reasons.

Any interruption in dosing must be documented in the subject's electronic case report forms (eCRFs) and source medical record. The Medical Monitor/Clinical Project Manager should be informed as soon as possible after the decision is made to interrupt study drug for a subject.

7.2.3. Treatment Compliance

Treatment compliance will be assessed at each clinic visit through subject interview, and by comparing the amount of study drug that should have been taken since the last study visit with the amount of study drug returned. If a subject is not compliant with study drug administration, the investigator (in consultation with the Medical Monitor) will consider whether the noncompliance should warrant withdrawal of the subject from the study.

7.3. Concomitant Medications

Concomitant medications, including vaccinations, taken within 1 month before screening or at any time throughout the study must be recorded in the eCRFs, along with the reason for use, dates of administration, dosage, frequency, and route of administration.

7.4. Prohibited Medications

Use of the following medications or treatments during this study is prohibited and will result in withdrawal from the study:

- investigational/experimental therapy
- ERT (eg, Replagal® [agalsidase alfa], Fabrazyme® [agalsidase beta])
- Glyset® [miglitol]
- Zavesca® [miglustat]

5. INTRODUCTION AND STUDY RATIONALE

5.1. Fabry Disease

Fabry disease is a rare, progressive and devastating X-linked lysosomal storage disorder affecting males and females, with an estimated prevalence of 1:117,000 up to 1:40,000 (Desnick and Schindler 2001; Germain 2010; Meikle, Hopwood et al. 1999; Eurordis 2005). Newborn screening studies have identified a higher incidence of variants in *GLA*, the gene encoding the lysosomal enzyme, α-galactosidase A (α-Gal A) (Spada, Pagliardini et al. 2006; Mechtler, Stary et al. 2012), although the impact of these findings on disease prevalence has not been established. Disease-causing variants in the *GLA* gene result in a deficiency of α-Gal A, which is required for glycosphingolipid metabolism (Brady, Gal et al. 1967). Beginning early in life, the reduction in α-Gal A activity results in an accumulation of glycosphingolipids, including globotriaosylceramide (GL-3) and plasma globotriaosylsphingosine (lyso-Gb_3), and leads to the symptoms and life-limiting sequelae of Fabry disease, which include pain, gastrointestinal symptoms, renal failure, cardiomyopathy, cerebrovascular events, and early mortality (Germain 2010). Early initiation of therapy and lifelong treatment may provide an opportunity to slow disease progression and prolong life expectancy.

Fabry disease encompasses a spectrum of disease severity and age of onset, although it has traditionally been divided into 2 main phenotypes, “classic” and “late-onset” (Desnick, Ioannou et al. 2001; Filoni, Caciotti et al. 2010; Topaloglu, Ashley et al. 1999; Shabbeer, Yasuda et al. 2002; Shabbeer, Yasuda et al. 2006; Ishii, Chang et al. 2007). The classic phenotype has been ascribed primarily to males with undetectable to low α-Gal A activity and is associated with earlier onset of renal, cardiac, and/or cerebrovascular manifestations. The late-onset phenotype has been ascribed primarily to males and females with higher residual α-Gal A activity and is associated with later onset of disease. Heterozygous female carriers typically express the late-onset phenotype, but may also display the classic phenotype depending on the pattern of X-chromosome inactivation.

More than 1000 Fabry disease-causing *GLA* variants have been identified (data on file). Approximately 67% are missense variants, resulting in single amino acid substitutions in the α-Gal A enzyme (Germain 2010; Gal, Schäfer et al. 2006). Missense *GLA* variants often result in the production of abnormally folded and unstable forms of α-Gal A (Fan, Ishii et al. 1999; Ishii, Chang et al. 2007) and the majority are associated with the classic phenotype (Filoni, Caciotti et al. 2010; Topaloglu, Ashley et al. 1999; Shabbeer, Yasuda et al. 2002; Shabbeer, Yasuda et al. 2006; Ishii, Chang et al. 2007). Normal cellular quality control mechanisms in the endoplasmic reticulum block the transit of these abnormal proteins to lysosomes and target them for premature degradation and elimination. Many missense mutant forms are targets for migalastat, an α-Gal A-specific pharmacological chaperone (Yam, Zuber et al. 2005; Yam, Bosshard et al. 2006; Benjamin, Flanagan et al. 2009).

> Note: In the Migalastat Clinical Development Program, all subjects were previously, and continue to be, required to have a *GLA* variant that is amenable to migalastat treatment. Historically in Amicus Therapeutics (Amicus) documents, these variants were referred to as “mutations”. Mutation will be referred to as “variant” in all new or revised Amicus-sponsored protocols, consistent with the guidelines of the American Medical College of Genetics and Genomics.

having rested for 5 minutes, and the same position should be used at all visits. Blood pressure should be obtained using the same arm for all measurements.

9.2.2.4. Physical Examination

Complete physical examinations will include assessment of head/eyes/ears/nose/throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. Brief physical examinations will include assessment of the skin, lungs, cardiovascular system, abdomen (liver and spleen), and any other systems, as clinically indicated.

9.2.2.5. Body Weight and Height

Body weight (kg) must be measured with the subject's shoes and clothes (except underwear) removed and will be rounded to the nearest whole number. The same scale should be used for individual subjects throughout the study and scales should be calibrated periodically throughout the study to ensure accuracy of measurement.

Height (cm) must be measured with the subject's shoes removed.

9.2.2.6. Electrocardiograms

A standard 12-lead ECG will be performed.

Subjects will rest for approximately 5 minutes before the ECG recording begins and will be in the supine position throughout the ECG evaluation. Electrocardiograms will be read centrally. Clinically significant findings not present before the start of treatment, which meet the definition of an AE, must be recorded in the eCRF.

9.2.2.7. Echocardiogram

Echocardiogram parameters considered for safety include LVMi, ejection fraction, fractional shortening, left ventricular internal diameter end diastole and end systole, midwall fractional shortening, and wall thickness.

Echocardiograms will be read centrally.

9.2.2.8. Tanner Staging

Tanner Staging will be performed for all subjects.

Because reversible infertility was noted in nonclinical studies with male rats, Tanner Staging will be used to assess sexual development, ie, breast development (B1 to B5) and pubic hair development (Ph-1 to Ph-5) in females and pubic hair and genital development (G-1 to G-5) in males (see Appendix A).

9.2.2.9. Concomitant Medications and Procedures

Subjects will be asked to report any new or changes in previously reported prescription and non-prescription medications, including dosage, frequency, and administration dates. Information will be entered in the eCRF and source records. Information regarding any procedures performed since the last visit will also be collected.

10. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Investigators and study site personnel are responsible for detecting, documenting, and reporting AEs and SAEs. For each subject, reporting of AEs and SAEs begins after written informed consent is provided.

10.1. Definitions

10.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore, AEs include the following:

- the onset of new signs, symptoms, conditions, and illnesses
- exacerbation of pre-existing conditions or illnesses
- abnormal laboratory findings deemed clinically significant by the investigator
- physical examination changes deemed clinically significant by the investigator
- abnormal medical evaluation findings (eg, ECG) that are not documented at screening and/or, in the investigator's opinion, represent a clinically significant change in the subject's health during study participation

  Note: Screening medical evaluation findings (eg, ECG) that were not previously provided as medical history and can be determined as starting before screening, are not considered AEs and will be recorded as medical history.

Adverse events will be recorded in the eCRF and subject's source record beginning from the time written consent (assent) is provided through the follow-up visit (at least 30 days after the last dose of study drug).

A single diagnosis should be entered when known. If a clear diagnosis cannot be determined at the time of eCRF completion and the subject's source record entry, each sign and symptom must be recorded individually, until a final diagnosis is established. Conditions, signs, symptoms, etc that are present in the subjects' medical history at screening should only be reported as AEs if they worsen (ie, increase in severity) since screening.

Adverse events that begin after the first dose of study drug will be considered treatment-emergent adverse events (TEAEs).

For the purpose of expedited SAE regulatory reporting obligations (ie, to regulatory authorities and Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]), events assessed by the investigator as definitely, probably, or possibly related to study drug will be considered "related" to study drug (ie, associated with the use of study drug). Events assessed as unlikely or unrelated will be considered "not related" to study drug (ie, not associated with the use of study drug).

10.3. Severity Assessment

The investigator or a qualified sub-investigator will review each event and use the following definitions for rating intensity:

- Mild: awareness of sign, symptom or event, but the AE is easily tolerated and does not interfere with daily activity
- Moderate: discomfort enough to cause interference with usual activity and may warrant intervention, but the subject is still able to function
- Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and requires medical intervention

It is important to distinguish the difference between events that meet the definition of serious and events that are deemed as severe in intensity. Adverse events assessed as severe in intensity are not SAEs unless at least 1 of the definitions in Section 10.1.2 is met. Adverse events of any intensity must be reported as SAEs if at least 1 definition in Section 10.1.2 is met.

10.4. Reporting Events

10.4.1. Reporting Adverse Events

Information regarding AEs is to be obtained by questioning or examining the subject and/or parents or legally-authorized representatives.

As noted in Section 10.1.1, AEs will be recorded in the eCRF and subject source record beginning from the time written consent (assent) is provided through the follow-up visit (at least 30 days after the last dose of study drug). Required information will be detailed in the eCRF Completion Guidelines.

10.4.2. Reporting Serious Adverse Events

Serious adverse events must be documented and reported to the sponsor immediately, but no later than within **24 hours of any knowledge by study site personnel of events**. Serious adverse event reports must be faxed to the designated safety fax number (Table 1) to ensure appropriate dissemination and processing of the information. An alternate email address is provided as a backup, if the fax transmission is unsuccessful.

Serious adverse event forms, which will be provided by the sponsor, should be as complete as possible, with all information known at the time included. All relevant supporting documentation (eg, admission and progress notes, results of diagnostic evaluations/procedures/examinations, etc) available at the time of reporting, should be included in the fax (or email, if necessary) along with the SAE report form. All supporting documents must be thoroughly reviewed and

10.5. Other Reporting Situations

10.5.1. Pregnancy

Pregnancy information for female subjects and female partners of male subjects participating in the study is collected by the sponsor. Pregnancy, in and of itself, is not regarded as an AE (unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication).

If a female subject becomes pregnant during the course of the study, or if the female partner of a male subject becomes pregnant during the subject's participation in the study, the sponsor must be informed within 5 working days of any knowledge of the pregnancy by study site personnel. If an SAE occurs in conjunction with the pregnancy, the SAE must be reported as described in Section 10.4.2. The sponsor will provide pregnancy report forms (initial and follow-up) and instructions to study site personnel regarding collection of pregnancy and outcome information (subject to receipt of data privacy release approvals where required under local privacy laws). Pregnancy report forms must be faxed (or emailed, if necessary) to the designated safety fax number (or email) (Table 1) to ensure appropriate dissemination and processing of the information.

10.5.2. Medication Errors, Including Overdose and Under Dose

Medication error refers to any unintended error in the dispensing or administration of a study drug.

If a subject experiences an overdose (defined as ≥ 20% higher than the assigned dose of study drug for that period in the protocol) or an under dose (defined as ≥ 20% lower than the assigned dose of study drug for that period in the protocol) during the course of the study (whether symptomatic or not), the Amicus' medical monitor must be notified within 5 working days of the investigator or study staff first becoming aware of the overdose.

Medication errors, including overdose and under dose, should be captured in subjects' source records and recorded in the eCRFs. Any AE or SAE that occurs as a result of a medication error should be reported according to AE/SAE reporting requirements (see Section 10.4).

10.5.3. Reporting of Possible Study Drug Product Quality Defects

Any defect or possible defect associated with study drug must be reported to the sponsor (clinicalcomplaints@amicusrx.com) within 1 working day of any study site personnel knowledge of the possible defect. The study drug and packaging components in question, if available, must be segregated and stored in a secure area at the site under the specified storage conditions (see Section 12.4) until it is determined whether or not the study drug 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 in Section 10.4.2. The SAE report must include the possible study drug defect complaint.

The PK analyses for the current study will be performed according to the following steps:

- Step 1: After combining previous concentration-time data from adults with pediatric data from the current study, the population PK model established previously (Migalastat Amended Population Pharmacokinetic Analysis of Migalastat, Amendment 02; Migalastat Abbreviated Report of the Simulations of Migalastat in Pediatric Patients with Fabry Disease, 20 October 2016) will be updated. Most importantly, the allometric scaling functions for CL/F and volume parameters (ie, V2/F, V3/F) will be re-evaluated and corrected, if necessary. Other covariates that are predictive of drug disposition (eg, age, weight, body surface area) may be evaluated.
- Step 2: Using the updated population PK model, clinical trial simulations will be conducted assuming administration of migalastat to steady-state concentration for each pediatric subject and for adults (with equivalent renal function) receiving migalastat HCl 150 mg every other day. The simulations will use population PK parameter uncertainty from a nonparametric bootstrap, inter-individual variability, and residual variability. At least 1000 clinical trials will be simulated assuming at least 24 subjects per age group.
- Step 3: Pharmacokinetic endpoints (ie, C_{max}, C_{min}, and $AUC_{0-\tau}$) for migalastat will be calculated from simulated concentration-time data in pediatric groups and in adults. The $AUC_{0-\tau}$ and C_{max} in 12 to < 18 year olds will be compared to the values in adults with equivalent renal function using an analysis of variance (ANOVA). The 90% confidence intervals (CIs) for the ratio of the geometric least squares means of C_{max} and $AUC_{0-\tau}$ will be constructed for comparison of the pediatric group with adult group. These 90% CIs will be obtained by exponentiation of the 90% CIs for the difference between the least squares means based on an ln-transformed scale.
- Step 4: Exposures in the pediatric group and adults will be considered equivalent when 90% CIs of the ratio of the geometric least squares means of $AUC_{0-\tau}$ are within the range of 0.8 to 1.25 (ie, 80% to 125%). Intervals obtained from Step 3 will be evaluated according to these a priori criteria. The ratios and CIs will also be determined for C_{max}.
- Step 5: If the bioequivalence criteria cannot be met in Step 4 using the dosing regimen listed in Section 7.2.1, adjusted dosing regimens will be proposed to achieve bioequivalence considering dose proportionality, if necessary, and used for future pediatric clinical trial simulations.
- Step 6: The proposed dose for pediatric subjects (12 to < 18 years and 12 to < 16 years) will then be considered the dosage regimen producing an $AUC_{0-\tau}$ meeting the 80% to 125% rule and a C_{max} that either meets this rule or, if not possible, is as close as possible balancing the available dosage strengths with safety.

11.3.2.4. Pharmacodynamic Analyses

Actual values and changes from baseline in plasma lyso-Gb_3 levels will be summarized using descriptive statistics.