CLINICAL STUDY PROTOCOL

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

Protocol Number: AT1001-020

Version 5: Amendment 4

Protocol Date: 13 June 2019

Original Protocol: 20 February 2018
Amendment 1 Protocol: 10 September 2018
Amendment 2 Protocol: 31 October 2018
Amendment 3 Protocol: 22 April 2019 (UK-specific)

EudraCT No.: 2017-000146-21

US IND Number: 068456

Compound: Migalastat

Sponsor
Amicus Therapeutics UK Limited
One Globeside,
Fieldhouse Lane, Marlow
Buckinghamshire SL7 1HZ
United Kingdom

Table 1: Serious Adverse Event Reporting and Medical Monitor Contact Information

Role	Name/Address	Contact Information
Safety Physician (Questions Regarding SAE Reporting)	Amicus Amicus Therapeutics, Inc. 1 Cedar Brook Drive Cranbury, NJ 08512 USA	Tel: +1 609-366-1164 Email: Amicus
SAE Reporting		**Primary method:** **Safety FAX number:** +1 866-422-1278 **If the primary method fails, please use:** **Safety Email address:** safetyreporting@amicusrx.com
Contract Medical Monitor	Amicus Syneos Health 3201 Beechleaf Court, Suite 600 Raleigh, NC 27604 USA	Tel: +1 919-745-2723 Email: Amicus
Sponsor Medical Monitor	Amicus Amicus Therapeutics, Inc. 1 Cedar Brook Drive Cranbury, NJ 08512 USA	Tel: +1 609-662-2033 Email: Amicus

Abbreviation: SAE = serious adverse event

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: _____

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

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)

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

Investigational Product, Dosage and Mode of Administration:

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

Administration

One migalastat 150 mg capsule will be administered with water every other day for 12 months. Subjects should take study drug at the same time of day during 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.

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. 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.

Duration of Treatment:

There will be 2 stages of treatment administration totaling approximately 12 months.

Reference Therapy, Dosage and Mode of Administration:

There is no reference therapy for this study.

Criteria for Evaluation:

Safety

Safety assessments include monitoring of adverse events (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.

Safety endpoints are as follows:

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

Stage 1 Pharmacokinetic Assessments

The schedule for sparse PK sampling is presented in the table below. All samples must be collected within a 24-hour period following the same dose of migalastat, between Day 15 and Day 30 following initiation of migalastat treatment.

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

Abbreviations: h = hour(s); min = minutes; PK = pharmacokinetic

Note: The timing of PK samples was determined using optimal sampling theory using PopED and mrgsolve software packages in R using a D-optimality algorithm.

[a] Subjects will be randomly assigned 1:1:1 to 1 of 3 PK sampling groups. In one 24-hour period between Day 15 and Day 30 following initiation of study drug administration, each subject will have 4 PK samples collected at the times specified in the table above (relative to the last dose of study drug) according to their randomized PK sampling group assignment.

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

In the event that follow-up PK assessments are required, at each follow-up visit additional sparse PK samples will be drawn at 4 time intervals according to the sampling group to which the subject was initially assigned.

Stage 2 Pharmacokinetic Assessments

Single blood samples for analysis of plasma migalastat concentration will be collected at the Month 6 and Month 12/ET study visits, at the same time that samples are collected for clinical laboratory tests, ie, trough sample taken prior to migalastat administration.

Pharmacokinetic endpoints are as follows:

- population PK model that describes the relationship between weight and age and migalastat pharmacokinetics in pediatric subjects (with primary PK parameter outputs listed in the following text)
- PK parameters based on simulated plasma-concentration data for migalastat after multiple-dose administration at steady-state concentration
  - C_{max}: maximum observed plasma concentration
  - C_{min}: minimum observed plasma concentration
  - t_{max}: time to reach C_{max}
  - $AUC_{0-\tau}$: area under the plasma concentration-time curve from time 0 over the dosing interval (ie, 48 hours)
  - $t_{½}$: terminal elimination half-life
  - CL_{ss}/F: apparent oral clearance at steady-state concentration
  - V_{ss}/F: apparent oral volume of distribution at steady-state concentration

Pharmacodynamic Assessments

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.

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

Efficacy Assessments

Efficacy assessments include eGFR, urine protein and albumin levels, LVMi and other cardiac parameters 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™]).

Efficacy endpoints are as follows:

- change in eGFR from baseline to Months 1, 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

Statistical Methods:

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

The Stage 1PK population will include all subjects who have a complete set of sparse PK samples from the single day of collection at steady-state during Days 15 to 30 of Stage 1. There will be 2 interim PK analyses. One will be performed using the entire Stage 1 PK population of adolescents aged 12 to < 18 years. A second interim analysis will include a subpopulation of at least 7 to 10 subjects age 12 to less than 16 years.

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.

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.

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 subjects and for the subgroup aged 12 to < 16 years at the end of Stage 1.

Sample Size:

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

First, assuming the final plasma clearance estimates and inter-individual variability of 28.5% (Migalastat Abbreviated Report of the Simulations of Migalastat in Pediatric Patients with Fabry Disease, 16 October 2016), 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 SELCL 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, SELCL 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).

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
α-Gal A	α-galactosidase A
AE	adverse event
AT1001	migalastat
AUC	area under the plasma concentration-time curve
$AUC_{0-\tau}$	area under the plasma concentration-time curve over the dosing interval (ie, 48 hours)
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
CFR	Code of Federal Regulations
CL/F	plasma clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CRO	contract research organization
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
eGFR	estimated glomerular filtration rate
ERT	enzyme replacement therapy
ET	early termination
EU	European Union
FABPRO-GI	Fabry Disease Patient-Reported Outcome – Gastrointestinal Signs and Symptoms
FPHPQ	Fabry-Specific Pediatric Health and Pain Questionnaire
GCP	Good Clinical Practice
GL-3	globotriaosylceramide
GLA	gene encoding α-galactosidase A
HCl	hydrochloride
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
lyso-Gb_3	globotriaosylsphingosine
LVMi	left ventricular mass index

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

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.

5.2. Migalastat

Migalastat (also known as AT1001), a low molecular weight iminosugar, is an analogue of the terminal galactose of GL-3/lyso-Gb_3. Nonclinical in vitro and in vivo pharmacologic studies have demonstrated that migalastat acts as a pharmacological chaperone, selectively and reversibly binding with high affinity to the active site of wild-type α-Gal A and specific mutant forms of α-Gal A (Ishii, Chang et al. 2007), the genotypes of which are referred to as amenable variants. Migalastat is a precision medicine targeted specifically to patients with Fabry disease who express specific mutant variants of the *GLA* gene that can be functionally restored by migalastat. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum, facilitating their proper trafficking to lysosomes where dissociation of migalastat allows the now active α-Gal A to reduce the level of GL-3 and other substrates (Yam, Zuber et al. 2005; Yam, Bosshard et al. 2006; Benjamin, Flanagan et al. 2009).

The Migalastat Amenability Assay, which is compliant with Good Laboratory Practices and has been clinically validated, was developed to identify patients with variants amenable to treatment with migalastat. Amenable variants are those that translate to mutant forms of the enzyme and that show a relative increase in enzyme activity that is ≥ 1.20-fold above the baseline value and an absolute increase of ≥ 3.0% of wild-type at a threshold of 10 μM migalastat in the Migalastat Amenability Assay (Benjamin, Della Valle et al. 2017). Approximately 35% to 50% of patients with Fabry disease are currently estimated to have amenable variants, the majority of which are associated with the classic phenotype of the disease (Benjamin, Flanagan et al. 2009; Filoni, Caciotti et al. 2010; Germain, Shabbeer et al. 2002; Shabbeer, Yasuda et al. 2006).

5.3. Summary of Nonclinical and Clinical Safety Data

5.3.1. Nonclinical Data

Available results from single-dose and repeat-dose nonclinical studies with migalastat having a wide margin of safety (ie, with doses that were ≥ 25-fold higher than those used in clinical studies) suggest no specific hazard regarding chronic toxicity to humans, based on values for area under the plasma concentration-time curve (AUC), with the exception of possible transient, fully reversible male infertility. In addition, a 39-week toxicity study in juvenile monkeys did not demonstrate a concern for toxicity, suggesting that migalastat does not induce adverse effects in the developing organ systems evaluated in that study.

In nonclinical studies using hR301Q α-Gal A Tg/knockout mice, a 30-mg/kg dose of migalastat was found to be optimal (AUC, 18400 ng•hr/mL; Study RR1001-08); at this dose, significant increases in α-Gal A activity and GL-3 substrate reduction were demonstrated across all tissues. At higher doses, no further improvements were observed.

Nonclinical studies also demonstrated that greater GL-3 reductions were observed with a regimen less frequent than daily administration, including every-other-day administration.

In regard to safety, the pivotal chronic dosing studies utilized rats and monkeys of approximately 6 weeks and 21 to 27 months of age, respectively, at the initiation of dosing. Developmentally, this corresponds to a human of approximately 12 years of age with respect to the rat, and less than 12 years of age with respect to the monkey (Beck 2006).

The main finding identified with migalastat in nonclinical studies was reversible infertility in male rats. Full fertility returned to the previously migalastat-treated animals after a 4 week washout period, a period of less than a full spermatogenic cycle (> 2 months). No effects on sperm count, morphology, or motility were detected to account for the reduction in male fertility.

These observations with migalastat, and the published information on other iminosugars including miglustat, strongly suggest that the infertility is due to effects on sperm maturation or function (Zavesca Prescribing Information 2017). Numerous studies indicate that these effects are related to sexual maturation processes that only occur after puberty, and not an adverse effect on testicular spermatogenesis. There is no indication of adverse effects on the germinal epithelium or testicular spermatogenesis that would be of particular concern for the proposed pediatric use of migalastat. There were also no effects on sperm motility, count or morphology in rats, and no changes in organ weights or pathology in the testes or accessory sex organs reported in rats, mice or monkeys. In addition, there were also no observations suggesting that the reproductive effects may be mediated by endocrine disruption which also would be of importance in developing animals and relevant for the proposed use in young people. Based on these findings, the fertility effects are not considered to pose any increased risk to pediatric patients compared to adults. In addition, a 39-week toxicity study in juvenile monkeys did not demonstrate adverse effects in the developing organ systems evaluated in that study.

5.3.2. Clinical Data

Clinical data for migalastat are available for healthy adults, and adolescents (16 to < 18 years of age) and adult patients with Fabry disease.

5.3.2.1. Pharmacology

In adult subjects with Fabry disease and amenable variants, the dose and regimen of migalastat were selected to obtain the optimal balance between migalastat concentration and its subsequent clearance, in order to maximize in situ α-Gal A activity and GL-3 substrate reduction. Dose selection was based on findings from nonclinical and clinical studies. Exposure observed following a single oral dose of migalastat hydrochloride (HCl) 150 mg in humans (AUC, 13521 ng•hr/mL) was similar to that observed after a 30-mg/kg dose in mice (see Section 5.3.1).

In a Phase 1 repeat-dose study in healthy subjects, greater increases in wild-type α-Gal A activity levels were observed in white blood cells (WBCs) after oral administration of migalastat HCl 150 mg twice daily (BID) for 7 days as compared to that seen after 50 mg BID. In five Phase 2 studies, ranges of regimens and doses were explored in 27 subjects (18 males and 9 females): BID (25, 100, 250 mg), once daily (50 mg), every other day (50, 150, 250 mg), and 3 days on/4 days off (250, 500 mg). In these studies, migalastat HCl 150 mg every other day (QOD) resulted in the best balance of substrate (ie, urine GL-3) reduction and safety in subjects with amenable variants compared with other doses and regimens. Treatment with 150 mg QOD also resulted in decreases in kidney interstitial capillary GL-3 levels and was associated with long-term stability of renal function. In Study FAB-CL-205, when subjects were switched from 150 mg QOD to higher, less frequent doses (250/500 mg 3 days on/4 days off), no further increases in WBC α-Gal A activity or reductions in urine GL-3 levels were observed. Additionally, a higher incidence of treatment-related adverse events (AEs) was observed at the 250- and 500-mg dose levels. On the basis of these collective data, 150 mg every other day was

selected as the dose and regimen for Phase 3 studies of migalastat in adults (ie, ≥ 16 years of age).

Migalastat is to be taken 2 hours before and 2 hours after a meal based on 2 food-effect studies (Study FAB-CL-103 and AT1001-016), which demonstrated that food reduces the bioavailability of migalastat as assessed using area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), and time to reach maximum observed plasma concentration (t_{max}) (Johnson, Mudd et al. 2015). Details of these studies are provided in the Investigator's Brochure.

5.3.2.2. Safety

Migalastat has a favorable safety profile in adults based on results from a comprehensive development program. A total of 386 adult and adolescent (≥ 16 years of age) subjects have been exposed to migalastat in Phase 1, Phase 2, and Phase 3 clinical studies conducted globally. The extent of exposure to migalastat among subjects with Fabry disease in Phase 2 and Phase 3 studies is approximately 595.2 patient-years, with the longest subject exposure being 11.2 years as of 17 March 2017.

No treatment-related deaths have been reported in clinical studies, and most serious adverse events (SAEs) were not considered treatment-related. In Phase 1 studies, the most frequently reported adverse event (AE) was headache. In completed Phase 2 studies in subjects with Fabry disease (Study FAB-CL-201 through Study FAB-CL-204), the most frequently reported AEs were headache, arthralgia, diarrhea, and nausea. In completed Phase 3 studies in subjects with Fabry disease (Study AT1001-011, Study AT1001-012, and Study AT1001-041), the most frequently reported AEs were diarrhea, headache, arthralgia, pain in extremity, nausea, fatigue, nasopharyngitis, dizziness, and influenza, though the order by frequency was not necessarily the same in all 3 studies.

5.3.2.3. Pharmacokinetics

Pharmacokinetic parameters for migalastat from single-dose studies are summarized in Table 2. Migalastat had a moderate rate of absorption reaching C_{max} in approximately 3 hours (t_{max}) after oral administration over the dose range of 25 to 2000 mg. Mean C_{max} and $AUC_{0-\infty}$ values increased in a dose-proportional manner following oral doses from 75 to 1250 mg migalastat. The mean elimination half-lives ($t_{½}$) ranged from 3.0 to 4.8 hours.

Table 2: Single Dose Plasma Pharmacokinetic Summary

Dose Group (mg)	N	C_{max} (ng/mL)[a]	t_{max} (hours)[b]	$AUC_{0-\infty}$ (ng•h/mL)[a]	$t_{½}$ (hours)[a]	CL/F (L/h)[a]
25	6	211 (70)	3.0 (2-4)	1178 (353)	3.0 (0.48)	19.0 (6.5)
75	6	693 (113)	3.0 (1.5-5)	4677 (429)	4.0 (0.67)	13.0 (1.1)
150	51	1700 (464)	3.0 (1-6)	10,654 (2612)	3.8 (0.39)	NR
225	6	2200 (921)	3.0 (2-4)	12,462 (5521)	4.6 (0.71)	18.6 (12.1)
500	6	5330 (2009)	3.0 (1.5-5)	29,045 (12,586)	4.3 (0.28)	15.8 (5.4)
675	6	6645 (1527)	2.5 (2-4)	36,419 (8228)	4.2 (0.30)	15.8 (3.6)
1250	58	13,374 (3959)	3.0 (2-4)	75,522 (20,146)	4.0 (0.45)	13.9 (4.4)
2000	6	17,752 (5370)	2.5 (2.5-3.5)	75,855 (17,765)	4.8 (0.52)	22.9 (6.8)

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL/F = plasma clearance; C_{max} = maximum observed plasma concentration; NR = not reported; $t_{½}$ = elimination half-life; t_{max} = time to reach the maximum observed plasma concentration
[a] Arithmetic mean (standard deviation)
[b] Median (range)
Source: Johnson, Mudd et al. 2013

5.4. Study Rationale

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 with Fabry disease and amenable *GLA* variants. The youngest pediatric subjects included in previous studies with migalastat were 16 years of age.

Early signs and symptoms of Fabry disease tend to manifest during childhood and adolescent years (ie, < 18 years), particularly in males with the classic phenotype, and are followed later in life by the development of overt kidney, cardiovascular, and central nervous system complications. In the 2 largest disease registries, the Fabry Outcome Survey and the Fabry Registry (Ramaswami, Whybra et al. 2006; Hopkin, Bissler et al. 2008), the median age of symptom onset is reported to be approximately 6 years in boys and 8 to 9 years in girls. Diagnosis is often delayed due to the different manifestations of the disease, its relative rarity, and the lack of clinical awareness of the condition, making the median age of diagnosis approximately 9 years in boys and 9 to 13 years in girls.

Data from these Fabry disease registries indicate that the most common symptom among pediatric subjects was neuropathic pain (eg, episodic pain crises, chronic pain, and acroparesthesia), which was reported more frequently by boys than by girls (58.8% versus 40.5%), and with an earlier age of onset (7 vs 9 years). The gastrointestinal tract was the second most commonly involved organ system with 18% of children experiencing signs and symptoms (eg, abdominal pain and diarrhea); the median age at onset of symptoms was 5 years in boys and 9.5 years in girls. The next most common sign was skin findings such as angiokeratomas. As with neuropathic pain, these symptoms and signs were more prevalent in boys than girls and occurred at an earlier age of onset.

Renal involvement appears less commonly in the younger population; however, a limited number of older adolescents have been reported to have impaired glomerular filtration rate (GFR), proteinuria, and hyperfiltration, along with cardiac abnormalities, pain, and gastrointestinal symptoms.

Considering the young age of symptom onset, diagnosis, and the progressive nature of Fabry disease, early intervention and treatment for pediatric patients could be important in slowing the progression of this disease (Hopkin, Jefferies et al. 2016).

5.5. Dose Selection

The dose regimen of migalastat HCl proposed for evaluation in pediatric subjects aged 12 to < 18 years with Fabry disease is the same as the adult dose and is supported by simulation results from a population pharmacokinetic (PK) model derived using data from adults, based on body weight (Migalastat Abbreviated Report of the Simulations of Migalastat in Pediatric Patients with Fabry Disease, 20 October 2016). The proposed dose is 150 mg every other day for subjects aged 12 to < 18 years and weighing ≥ 45 kg (99 pounds).

5.6. Justification for Proposed Dose and Regimen in Pediatric Subjects with Fabry Disease

Migalastat has not been studied in pediatric subjects under 16 years of age. Although adolescent subjects with Fabry disease 16 to < 18 years of age were included in Phase 3 studies, the number of adolescent subjects included in those studies was limited. Therefore, simulations have been performed (100 subjects per age group) to select doses that match exposure in pediatric patients to exposure observed in adults receiving migalastat HCl 150 mg QOD. Area under the plasma concentration-time curve over the dosing interval ($AUC_{0-\tau}$) at steady-state concentration was selected as the target parameter for dose selection in pediatric subjects because existing safety and tolerability data in adults suggest that increased risk is not expected with increases in C_{max} and that changes in minimum observed plasma concentration (C_{min}) are not likely to affect efficacy given there is likely an indirect relationship between plasma concentrations and efficacy. The aim is to achieve AUC values in pediatric subjects that are similar to those in adults with Fabry disease and with normal renal function who were receiving migalastat HCl 150 mg every other day.

The largest biological factor affecting migalastat plasma clearance (CL/F) is renal function. While many adult patients with Fabry disease have reduced renal function (15% and 42% of subjects in Study AT1001-011 with moderate or mild renal impairment, respectively, based on estimated glomerular filtration rate [eGFR]), pediatric patients with Fabry disease have relatively high values for eGFR (mean, 147 mL/min/1.73 m^2) (Hopkin, Bissler et al. 2008).

Body weight also explains variability in the pharmacokinetics of migalastat in individuals < 70 kg, with effects on CL/F, volume of distribution in the central compartment (V2/F), volume of distribution in the peripheral compartment (V3/F), and distribution clearance (Q/F). These effects were incorporated into the dose rationale simulations for pediatric subjects by using the range of weights from the Centers for Disease Control and Prevention weight chart (data on file).

Lastly, there is a very small change in CL/F (15%) and V2/F (31%) in the presence of Fabry disease. This effect was accounted for in the simulations, even though these differences result in exposures that are similar to those reported for healthy subjects.

6. OBJECTIVES AND PURPOSE

6.1. Primary Objectives

The primary objectives of this study are as follows:

Stage 1

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

Stage 2

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

6.2. Secondary Objectives

The secondary objectives of this study are as follows:

Stage 1

Not applicable

Stage 2

- to characterize the pharmacodynamics 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

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.

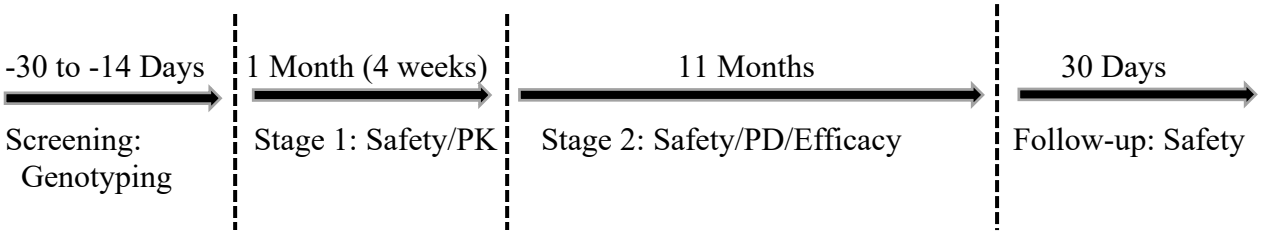
The study will consist of 2 stages. Stage 1 will be a treatment period of approximately 1 month (4 weeks); Stage 2 will be a treatment period of 11 months and a 30-day (untreated) safety follow-up period. There will be no break in treatment between Stages 1 and 2. Prior to Stage 1, there will be a screening 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

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.

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]

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

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.

8.2. Eligibility Criteria

Adherence to the eligibility criteria for participation in this study is essential to ensure scientific integrity, regulatory acceptability, and subject safety. Waivers of inclusion/exclusion criteria will not be granted.

8.2.1. 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 provides written informed consent
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)
   e. 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 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 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

8.2.2. 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

Note: "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.

8.3. Withdrawal Criteria

Subjects may discontinue study drug, withdraw from the study, or be withdrawn from the study for any reason including, but not limited to, the following reasons:

- at their own request or at the request of their parent 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 AE as determined by the investigator, subject, and/or parent or legally-authorized representative
- inability to tolerate or comply with PK blood sampling procedures
- failure of the subject to comply with the study visit schedule
- persistent noncompliance, at the discretion of the investigator
- pregnancy
- inability to contact subject (ie, subject is lost to follow-up)
- sponsor request

The reason for and date of discontinuation or withdrawal must be recorded in the eCRF and in source documents. All subjects who discontinue study treatment will be encouraged to complete an early termination (ET) visit and follow-up safety assessments.

The investigator must make every effort to contact subjects who are lost to follow-up to schedule end-of-study assessments. Attempts to contact subjects who are lost to follow-up (eg, times and dates of attempted telephone contact, documentation of a registered letter) must be recorded in the subject's source document.

If a subject wishes to discontinue treatment, the investigator must determine the extent that a subject may be willing to continue participation in the study, as follows:

- the parent or legally-authorized representative and/or subject wants to discontinue study drug, but agrees to the follow-up procedures
- the parent or legally-authorized representative and/or subject wants to discontinue study drug and all follow-up procedures
- the parent or legally-authorized representative and/or subject wants to revoke consent/assent to collect and use further data

  Note: In the United States, the authorization to use and disclose data for research can only be revoked in writing by the subject, or parent or legally-authorized representative of minor subjects.

8.4. Replacement of Subjects

Subjects who withdraw from the study may be replaced. Replacement of a subject may only occur after consultation with and written approval of the Amicus Medical Monitor.

8.5. Subjects of Childbearing Potential

Female subjects of reproductive potential, and all male subjects must use a medically accepted contraceptive regimen during their participation in the study and for 30 days after the last dose of migalastat. A medically acceptable birth control method is defined as one which results in a low failure rate (ie, < 1% per year) when used consistently and correctly.

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

A female is considered of non-reproductive potential if she is at least 26 weeks status-post documented surgical sterilization (includes hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or salpingectomy).

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

Medically acceptable methods of contraception for female subjects enrolled in the study include the following:

- total abstinence, which refers to refraining from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle
- hormonal contraception (ie, combination oral contraceptive pills, implant, injection, ring, or patch) for at least 12 weeks before screening
- intrauterine device that meets the < 1% failure per year rate, as stated in the product label, for at least 12 weeks before screening
- double-barrier method, defined as condom and occlusive cap (eg, diaphragm or cervical/vault caps) used in combination with spermicide (eg, foam, gel, film, cream, suppository)
  - Note: the double-barrier method does not satisfy the requirements for an effective method of birth control in all countries and may not be utilized as a contraceptive method by subjects participating at sites in those countries.

Medically acceptable methods of contraception for male subjects enrolled in the study include the following:

- total abstinence, which refers to refraining from penile-vaginal intercourse, when this is the male's preferred and usual lifestyle
- surgical sterilization (eg, vasectomy with documentation of azoospermia) prior to the subject's entry into the study

Note: For this definition, "documented" refers to the outcome of the investigator's or 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, defined as condom and occlusive cap (eg, diaphragm or cervical/vault caps) used in combination with spermicide (eg, foam, gel, film, cream, suppository)
  - Note: the double-barrier method does not satisfy the requirements for an effective method of birth control in all countries and may not be utilized as a contraceptive method by subjects participating at sites in those countries.

Any pregnancy (in a female subject or the female partner of a male subject) occurring during the study must be reported as described in Section 10.5.1.

In the event of pregnancy in a female subject, migalastat must be discontinued immediately upon becoming aware of the pregnancy. Female subjects or a female partner of a male subject who becomes pregnant during the study must be monitored by the investigator until the outcome of the pregnancy is known. Both the detection and the outcome of the pregnancy must be reported to the sponsor.

Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

9. STUDY ASSESSMENTS AND PROCEDURES

The schedule of study assessments and procedures is presented in Table 3. The schedule for sparse PK sampling (all samples must be collected within a 24-hour period following the same dose of migalastat between Day 15 and Day 30 following initiation of migalastat treatment) is presented in Table 4; additional PK sampling time points are included in Table 3. Total blood volume to be drawn per subject is presented in Table 5.

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 assessments that occur during the study, where applicable and to the extent possible, should be completed during the designated visit, preferably in the order specified below. Once established, every effort should be made to maintain the order of procedures at each study visit throughout the study.

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	

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	

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

Table 4: Sparse Pharmacokinetic Sampling

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

Abbreviations: h = hour(s); min = minutes; PK = pharmacokinetic
Note: The timing of PK samples was determined using optimal sampling theory using PopED and mrgsolve software packages in R using a D-optimality algorithm.
[a] Subjects will be randomly assigned 1:1:1 to 1 of 3 PK sampling groups. In one 24-hour period between Day 15 and Day 30 following initiation of study drug administration, each subject will have 4 PK samples collected at the times specified in the table above (relative to the last dose of study drug) according to their randomized PK sampling group assignment.
[b] Sample should NOT be taken at the same time as the previous sample. Samples should be taken approximately 15 minutes apart at a minimum.

Table 5: Total Blood Volume to be Collected (as Scheduled) per Subject

	Blood Volume per Test (mL)							
Assessments	**Screening**	**Baseline**	**Day 15 to 30**	**Month 1**	**Month 3**	**Month 6**	**Month 12/ET**	**Total**
GLA Genotyping	4							4
Chemistry	4	4			4	4	4	20
Hematology		2				2	2	6
Plasma lyso-Gb_3		2			2	2	2	8
PK blood sample			1 × 4[a]			1	1	6
PD blood sample		2				2	2	6
							Total:	**50 mL**

Abbreviations: ET = early termination; *GLA* = gene encoding α-galactosidase A; lyso-Gb_3 = globotriaosylsphingosine; PD = pharmacodynamic; PK = pharmacokinetic
Note: Total collection volume does not take into account additional blood samples drawn during potential follow-up visits.
[a] Four serial samples (Table 4) will be collected.

9.1. Description of Study Visits

9.1.1. Screening Period

With the exception of determination of amenable *GLA* variant status for subjects whose *GLA* variant status is unknown at screening, screening assessments must be performed within 14 to 30 days before Day 1. At least 14 days must be allowed between screening and baseline in order to allow time for return of screening assessment results.

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.

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

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.

9.2.3. Pharmacokinetic Assessments

The timing of PK samples was determined using optimal sampling theory using PopED and mrgsolve software packages in R using a D-optimality algorithm. The exact times for dosing and sample collection will be recorded. Migalastat concentrations in plasma will be determined using a validated LCMS assay and will be used for pharmacokinetic analyses.

Stage 1

Subjects will be randomly assigned 1:1:1 to 1 of 3 PK sampling groups using interactive response technology (IRT). Four blood samples for determination of migalastat concentrations in plasma will be collected in one 24-hour period between Day 15 and Day 30 following initiation of study drug administration. If they are to be done at the site, the PK collection visit should be scheduled on a migalastat administration day and subjects are to be instructed to bring their study drug with them. Blood sampling for PK is relative to migalastat administration and ***collection times must be recorded on the appropriate eCRF page.*** Each subject will have 4 PK samples collected at the times specified in Table 4 according to their randomized PK sampling group assignment.

Alternately, PK blood collections may be done by a home healthcare professional. In either case, the collections must follow migalastat administration at the times specified in Table 4 and the ***time of migalastat administration prior to the collections and the times of each collection must be recorded***.

Stage 2

In addition, blood samples for analysis of plasma migalastat concentration will be collected at the Month 6 and Month 12/ET study visits, at the same time that samples are collected for clinical laboratory tests.

In the event that follow-up PK assessments are required, at each follow-up visit additional sparse PK samples will be drawn at the 4 time intervals according to the sampling group to which the subject was initially assigned.

Details regarding processing, storage, and shipping procedures will be provided in the Laboratory Manual. The actual date and time of the last dose before sampling and each blood sample collection will be recorded.

9.2.4. Pharmacodynamic Assessments

Blood samples will be collected for measurement of lyso-Gb_3 levels in plasma. In addition, to get a better understanding of early PD biomarkers for Fabry disease, blood will be collected for exploratory cardiac biomarkers such as high sensitivity tropin and NT-proBRN. Plasma levels of lyso-Gb_3 will be measured using a validated LCMS assay.

9.2.5. Efficacy Assessments

9.2.5.1. Estimated Glomerular Filtration Rate

Estimated GFR will be calculated using the Schwartz formula according to the standards of the central laboratory.

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. 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).

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

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

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.

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.

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Details of the data handling rules and statistical calculations will be provided in the statistical analysis plan.

11.1. Endpoints

11.1.1. Safety Endpoints

Safety endpoints are as follows:

- incidence of TEAEs, SAEs, and AEs leading to discontinuation of study drug
- changes in clinical laboratory test results from baseline over time
- changes in vital signs from baseline over time
- changes in physical examination findings from baseline over time
- change in body weight and height from baseline over time
- changes in ECG results from baseline over time
- changes in echocardiogram parameters from baseline to Month 12/ET
- change in Tanner stage from baseline to Month 12/ET
- use of concomitant medications

11.1.2. Pharmacokinetic Endpoints

Pharmacokinetic endpoints are as follows:

- population PK model that describes the relationship between weight and age and migalastat pharmacokinetics in pediatric subjects (with primary PK parameter outputs listed in the following text)
- PK parameters based on simulated plasma-concentration data for migalastat after multiple-dose administration at steady-state concentration
  - C_{max}: maximum observed plasma concentration
  - C_{min}: minimum observed plasma concentration
  - t_{max}: time to reach C_{max}
  - $AUC_{0-\tau}$: area under the plasma concentration-time curve from time 0 over the dosing interval (ie, 48 hours)
  - $t_{½}$: terminal elimination half-life
  - CL_{ss}/F: apparent oral clearance at steady-state concentration
  - V_{ss}/F: apparent oral volume of distribution at steady-state concentration

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.

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.

Pharmacodynamic endpoints (ie, changes from baseline in plasma lyso-Gb_3 at 3, 6, and 12 months) and simulated PK exposures (ie, $AUC_{0-\tau}$ and C_{max}) will be plotted and graphically examined for potential exposure-response relationships.

11.3.2.5. Efficacy Analyses

Actual values and changes from baseline (as applicable) in eGFR, urine levels of protein and albumin, LVMi, e-diary responses, FPHPQ scores, and PedsQL scores, and actual values for PGI-C responses will be summarized using descriptive statistics.

Efficacy endpoints (ie, changes from baseline in eGFR, urine levels of protein and albumin, LVMi, e-diary responses, FPHPQ scores, and PedsQL scores and actual values for PGI-C responses) and simulated PK exposures (ie, $AUC_{0-\tau}$ and C_{max}) will be plotted and graphically examined for potential exposure-response relationships. If data permit, mathematical modeling approach will be used; if conducted, this analysis will be reported separately.

11.3.2.6. Other Summaries

A summary of subject disposition will include number of subjects enrolled, number of subjects in each analysis population, number of subjects who completed the study, and number of subjects who did not complete the study by reason for discontinuation.

Demographics and baseline characteristics will be summarized using descriptive statistics.

Baseline characteristics will include height, body weight, body mass index, number of years since diagnosis of Fabry disease, previous use of ERT, and previous and current use of angiotensin-converting enzyme inhibitors, renin inhibitors, and angiotensin receptor blockers.

Protocol deviations will be listed.

12. STUDY TREATMENTS

12.1. Description of Study Drug

Migalastat (also known as AT1001) is an iminosugar that functions as a selective and reversible pharmacological chaperone of agalsidase beta. Migalastat will be supplied as a gelatin capsule (Table 7). Migalastat capsules must be swallowed whole and must not be cut, crushed, or chewed.

Table 7: Investigational Product (Capsule)

	Investigational Product
Product Name	Migalastat
Dosage Form	Capsule
Unit Dose	123 mg (equivalent to 150 mg migalastat HCl)
Excipients	Pregelatinized starch, magnesium stearate
Route of Administration	Oral
Physical Description	White opaque/blue opaque, hard gelatin capsules (size “2”), printed with an identifying code "SGXXX" or “A1001” and supplied in blister packs
Manufacturer	Almac Pharma Services Limited Seagoe Industrial Estate Portadown Craigavon County Armagh BT63 5UA United Kingdom

Abbreviation: HCl = hydrochloride

12.2. Packaging and Labeling

Migalastat HCl 150-mg oral capsules will be supplied by the sponsor as hard gelatin capsules in blister packs.

Each container will be labeled in conformance with regulatory requirements and where applicable, local laws. All labels will be printed with the following information at a minimum: study identifier, identity of drug and dosage, sponsor name and contact details (and/or details of a local designee contact), dosing instructions, storage information, and other applicable local law statements.

12.3. Study Drug Accountability

In accordance with local regulatory requirements, the investigator or designee 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 the sponsor (or designee). Product accountability records must be maintained throughout the study.

The study monitor will periodically check the supplies of study drugs held at the site to verify accountability of all study drugs used and to verify that the drug accountability logs are completed and maintained in the investigator study file. When instructed by the study monitor, the investigator will return all original containers of study drugs, whether empty, or containing used or unused study drugs to the sponsor or designee for destruction. Sites may not destroy study drugs on site unless the sponsor has provided prior written approval.

12.4. Handling, Storage, Return, and Disposal of Study Drugs

Sites will be instructed to store migalastat capsules at room temperature (15°C to 25°C/59°F to 77°F) with excursions permitted to 30°C/86°F in a secure area with temperature monitoring, free from environmental extremes, and with restricted access.

The study drug is to be stored only at the site listed on the United States Food and Drug Administration (FDA) Form 1572. Study drug is to be dispensed only to subjects from/for whom written informed consent/assent has been obtained, have met all entry criteria, and are assigned subject numbers.

13. STUDY MANAGEMENT

13.1. Documentation of Protocol-required Information and Study Findings

For this study, eCRFs with remote electronic data capture (EDC) provided through a qualified third party vendor will be used. The data will be entered on the eCRFs in a timely manner on an ongoing basis as defined in the Data Management Plan. The investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that the subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. All data must be documented separately in source records. An explanation should be given for all missing data.

Details of eCRF completion and correction will be explained to the investigator. The investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. If the investigator authorizes other persons to make entries onto the eCRFs, the names, positions, signatures, and initials of these persons must be documented in writing and supplied to the sponsor.

The completed eCRFs must be reviewed and electronically signed by the investigator who signed the study protocol signature page to ensure that the observations and findings are recorded on the eCRFs correctly and completely

13.2. Data Management

Only data specified in the protocol will be collected as part of this study. All eCRF data will be entered into the EDC system and managed by a contract research organization (CRO). Additional protocol-specified data, such as laboratory and ECG data, may be collected through third party vendors and integrated with eCRF data by the CRO to create complete datasets for analysis. All protocol-specified data will be transmitted electronically to the sponsor (or the CRO).

Management of clinical data will be performed in accordance with applicable standards and data cleaning procedures as defined in the Data Management Plan to ensure the integrity of the data (eg, determining errors and inconsistencies in the data, and ensuring data are corrected by study site personnel or designees).

After database lock, each site will receive an electronic copy containing all of their site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, an electronic copy of all data from the study collected at that study center will be retained by the sponsor or designee for storage.

13.3. Study Monitoring, Source Data Verification, and Onsite Audits

Monitoring and auditing procedures developed or endorsed by the sponsor will be followed, in compliance with Good Clinical Practice (GCP). Direct access to the onsite study documentation and source documents must be ensured by the investigator.

Monitoring will be performed by personal visits from a sponsor representative (ie, study monitor) who will check the eCRFs for completeness and clarity, and crosscheck them with source documents (see essential documents, Section 13.4). In addition to the monitoring visits, frequent communications (eg, letter, e-mail, telephone, and fax) by the study monitor will ensure that the study is conducted according to the protocol design and regulatory requirements.

Domestic and foreign regulatory authorities, the IRB/IEC, and/or an auditor authorized by the sponsor may request access to all source documents, eCRFs, and other study-related documentations for onsite audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names, family member names, telephone numbers, and addresses are obliterated on the copies to ensure confidentiality.

The investigator should contact the sponsor immediately if contacted by a regulatory authority regarding an inspection or audit.

13.4. Records Retention

The investigator must obtain approval in writing from the sponsor before destruction of any records.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of migalastat. However, because of international regulatory requirements or country-specific requirements, the sponsor may request retention for a longer period.

Prior to any decision regarding the disposal or destruction of study documents, the investigator should contact the sponsor. The sponsor may request that the site take alternative actions other than disposal or destruction of study documents.

Essential documents include the following:

- signed informed consent/assent documents for all subjects
- subject identification code list, screening log (if applicable), and enrollment log

  Note: European Union (EU) legislation requires this list to be maintained for a minimum of 15 years.
- composition of the IEC/IRB and record of all communications between the investigator and IEC/IRB as well as between the investigator and sponsor or CRO
- list of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- copies of eCRFs and documentation of corrections for all subjects
- investigational product accountability records

- record of any body fluids or tissue samples retained
- all other source documents (eg, subject medical records, hospital records, laboratory records, etc)
- all other documents as listed in Section 8 of the ICH GCP E6 guidelines (ie, Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the investigator's archives. If investigators are unable to meet this obligation, they must ask the sponsor for permission to make alternative arrangements. Details of these arrangements must be documented in writing.

13.5. Use of Study Findings

All information concerning migalastat as well as any matter concerning the operation of the sponsor, such as clinical indications for migalastat, its formula, methods of manufacture, and other scientific data relating to it, that has been provided by the sponsor and are unpublished, are confidential and must remain the sole property of 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.

Amicus 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. Regulatory 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 study results.

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

13.6. Study Close-out

The end of study is defined as date of database lock.

The study must be closed at each site on completion. Study close-out will be performed by the study monitor upon closure of the study.

Completion or premature termination of the study will be reported by the sponsor to regulatory authorities and by the sponsor or by the investigator to the IEC/IRB as required by local regulation or by the IEC/IRB.

Furthermore, the sponsor or the investigator has the right to close any study site at any time. The reason(s) for closure will be documented in writing. As much as possible, premature closure would occur after mutual consultation.

Study materials must be returned, disposed of, or retained as directed by the sponsor (Section 12.4).

14. STUDY CONDUCT CONSIDERATIONS

This global study will include both IND (US) and non-IND (foreign) sites. All investigators will be required to certify their compliance with both ICH E6 GCP and their respective country's applicable laws and regulations. Both IND and non-IND sites will be operating under a single protocol (ie, there will not be a separate protocol for non-IND sites). The sponsor will ensure that the conduct, monitoring, auditing, recording, analysis, and reporting of clinical trial results are in accordance with ICH GCP, providing assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

14.1. Posting of Information on Publicly Available Clinical Trial Registers

The sponsor will be responsible for registering this study in a public registry that meets the requirements specified by the International Council of Medical Journal Editors, such as www.clinicaltrials.gov.

14.2. Ethical and Legal Aspects

14.2.1. Informed Consent/Assent Information

Signed written informed consent/assent is to be obtained for each subject prior to any study-related assessments being performed. If the subject is under the legal age of consent, the consent form must be signed by the subject's parent or legally-authorized representative in accordance with the relevant country and local regulatory requirements. The document must be in a language understandable to the subject and/or the subject's parent or legally-authorized representative and must specify who informed the subject and/or the subject's parent or legally authorized representative. Where required by local law, the person who informs the subject must be a physician.

The subject and/or subject's parent or legally-authorized representative must be given the opportunity to read the informed consent/assent document and have all their questions and concerns addressed before giving consent/assent in writing. If the subject and/or subject's parent or legally-authorized representative is unable to read, oral presentation and explanation of the written informed consent/assent form and information to be supplied to the subject must take place in the presence of an impartial witness. Consent/assent must be confirmed at the time it is orally provided and by the personally dated signature of the subject and parent or legally-authorized representative by a local legally recognized alternative (eg, thumbprint or mark). Details about why oral presentation was used, how the information was presented, and how the subject provided consent must be described in the medical records.

The subject's consent/assent must be confirmed at the time of consent/assent by the personally dated signature (or thumbprint or mark) of the subject and parent or subject's legally-authorized representative and by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed informed consent/assent form will be given to the subject and the original will be retained by the site. An entry must be made in the subject's dated source documents to confirm that informed consent/assent was obtained prior to any study-related procedures and that the subject received a copy of the signed informed consent/assent.

The witness and the person conducting the informed consent/assent discussions must also sign and personally date the consent/assent document. Until a signed written consent/assent has been obtained, the investigator will not perform any measures specifically required for this study.

The investigator must inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

14.2.2. Ongoing Information for Independent Ethics Committee/Institutional Review Board

The information listed below must be submitted to IECs/IRBs according to timelines specified by individual IEC/IRB documented submission policies and procedures, or by local law. Submissions may be made by the sponsor (or designee) or by the investigator. The parties responsible for submissions will be identified and documented prior to shipment of study drugs.

- AE information
- expedited safety reports
- periodic reports on the progress of the study
- revised informed consent forms
- amendments to the protocol
- updated Investigator's Brochure

14.2.3. Compliance with Good Clinical Practice

This study is to be conducted according to globally accepted standards of GCP (as defined in the ICH GCP E6 guidelines), in agreement with the current version of Declaration of Helsinki, and in keeping with local regulations.

14.2.3.1. Quality Control

In accordance with applicable regulations, GCP, and sponsor procedures, the sponsor or its designee will contact the site prior to the start of the study to review with the study site personnel the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and the sponsor's or its designee's requirements. When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items that will be recorded in the eCRF and requirements for source documentation.

The sponsor or its designee will monitor the study to ensure the following:

- 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.

14.2.3.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance assessment and/or audit of the site records, and the regulatory authorities 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 medical 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 during the regulatory audit or inspection.

14.2.4. Confidentiality

Subject names (and the names of family members, telephone numbers, and addresses) will not be supplied to the sponsor. A unique subject number will be recorded in the eCRF, and if the subject name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws (eg, EU Directive 95/46/EC, EU Directive 94/45/EC, and the General Data Protection Regulation (GDPR) (EU) 2016/679]). The subject and the subject's parent or legally-authorized representative will be informed that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

14.3. Clinical Study Protocols and Amendments

Any non-administrative changes to the protocol, initiated either by the sponsor or by the investigator, will require a formal amendment procedure. Approval of all amendments must be obtained from the sponsor, relevant IEC/IRB, and regulatory authorities (in accordance with local requirements) prior to implementation. Changes to the administrative aspects of the study will not require formal protocol amendments or IEC/IRB approval, but can be treated as administrative amendments. However, the IEC/IRB should be kept informed of such changes. Changes in study staffing or contact information are examples of administrative changes not requiring formal protocol amendments.

Protocol deviations to eligibility criteria, addition or deletion of tests, dosing, duration of treatment, and/or any other aspect of the study design that may significantly impact subject safety or scientific integrity, are not permitted under GCP or by the sponsor, unless necessary to eliminate an immediate hazard to the subject(s).

Where the sponsor and/or investigator must take urgent safety measures to protect the subjects from an immediate hazard, a protocol deviation may be allowed prior to obtaining approval from the relevant IEC/IRB (and/or regulatory authorities) according to the US Code of Federal Regulations (CFR) Title 21 Part 312.30(b)(2). In such cases, the sponsor and the IEC/IRB must be notified within 1 business day.

The sponsor and the relevant IEC/IRB, where required by local law, must be informed of all protocol deviations and violations and the investigators will document such protocol deviations and violations in subject source documents and eCRFs.

14.4. Delegation of Investigator Duties

The investigator must ensure that all persons assisting with this study are adequately qualified and informed about their study-related duties and functions, the protocol and any amendments to the protocol, and the study treatment.

Investigators must maintain a list of sub-investigators and other appropriately qualified persons to whom they delegate significant study-related duties.

Should the investigator delegate the supervision of the administration of the study drugs to a designated person, the designee should have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

14.5. Liability and Insurance

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

14.6. Financial Disclosure

Before the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the investigational products, migalastat, or Amicus as required by CFR Title 21 Part 54 and outlined in the financial disclosure form provided by the sponsor. The investigator agrees to update this information in case of significant changes during the study and within 1 year of its completion. The investigator also agrees that, where required by law or regulation, the sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Where required by regulation, the investigator or sponsor on behalf of the investigator, will also disclose these financial interests to the IRB/IEC and the investigator will disclose his/her financial interests to the subjects in the informed consent information.

Where required by regulation, the sponsor or the investigator will also submit the financial arrangements for the study to the regulatory authorities or to the IRB/IEC.

Financial disclosures will also be provided by each sub-investigator to whom the investigator delegates significant study-related responsibilities.

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16. APPENDICES

APPENDIX A. TANNER STAGING

Provided by Endotext

Beccuti G and Ghizzoni L. Normal and Abnormal Puberty. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2015 Aug 8. PMID: 25905253

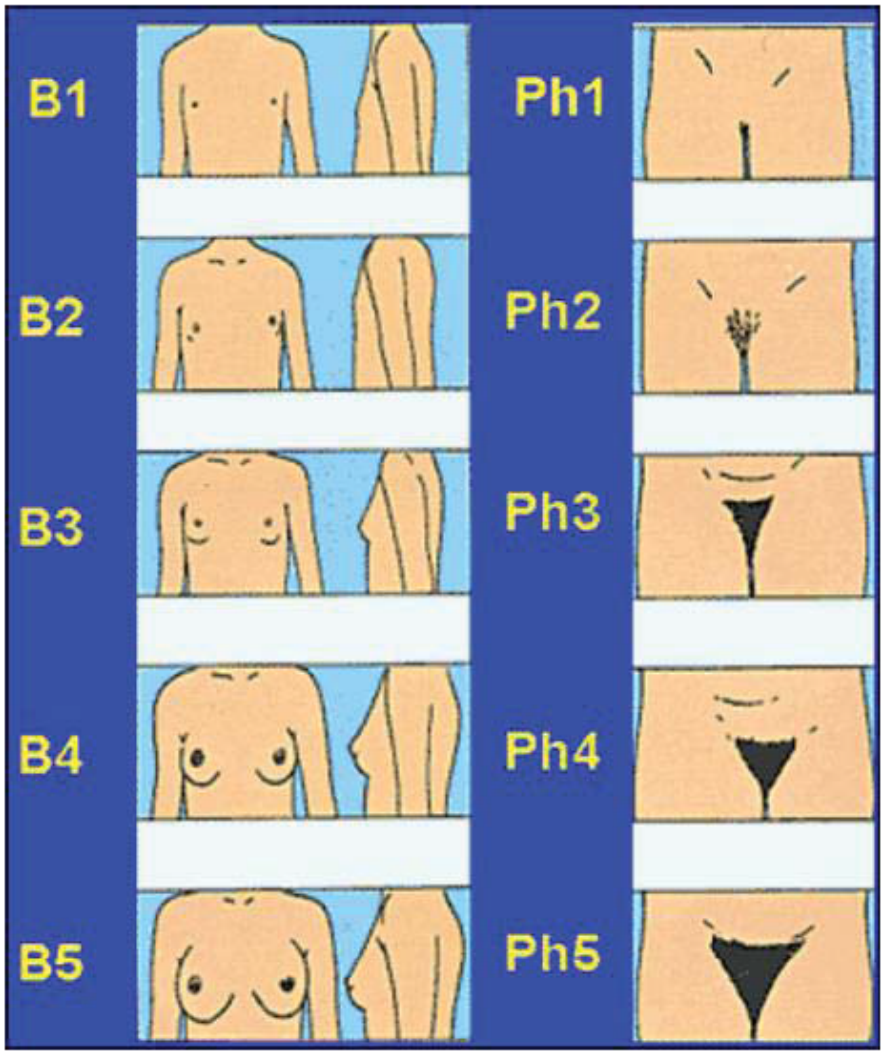

Figure 1. (Left) Stages of breast [B] development. **B-1**: pre-pubertal; **B-2**: breast bud; **B-3**: enlargement of beast and areola with no separation of the contours; **B-4**: projection of areola and papilla to form a secondary mound above the level of the breast; **B-5**: recession of the areola to the general contour of the breast with projection of the papilla only. (Right) Stages of pubic hair [Ph] development in females. **Ph-1**: pre-pubertal; **Ph-2**: sparse growth of long slightly pigmented hair usually slightly curly mainly along the labia; **Ph-3**: the hair is darker, coarser, and curlier and spreads over the junction of the pubes; **Ph-4**: the hair spreads covering the pubes; Ph-5: the hair extends to the medial surface of the thighs and is distributed as an inverse triangle.

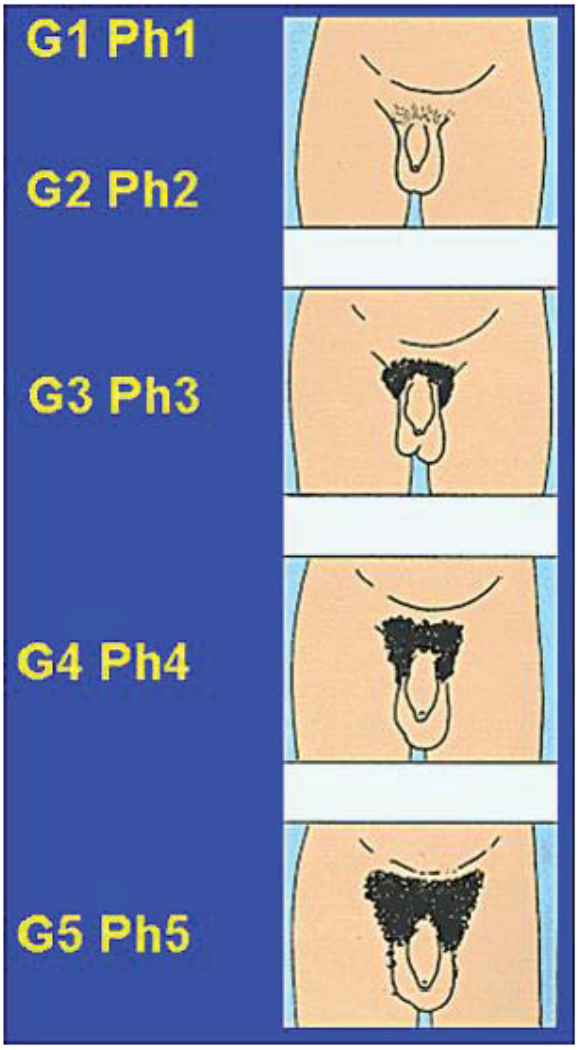

Figure 2. Stages of genital [G] and pubic hair [Ph] development in the male. **G-1, Ph-1**: pre-pubertal; **G-2**: the testis and scrotum enlarge, and the skin of the scrotum shows some reddening and change in the texture. Sparse growth of pigmented hair usually slightly curly, mainly at the base of the penis (Ph-2); G-3: Testis and scrotum enlarge further, the penis grows mainly in length but also in breadth. The hair is darker, coarser and curlier and spreads over the junction of the pubes (Ph-3); G-4: Scrotum, testis, and penis grow further with development of the glans, and further darkening of the scrotal skin. The hair spreads covering the pubes; G-5: adult stage with spreading of the hair to the medial surface of the thighs (Ph-5).