Official Title:	A Long-Term, Open-Label Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Migalastat In Subjects > 12 Years of Age with Fabry Disease and Amenable *GLA* Variants
NCT Number:	NCT04049760
Document Date:	Amendment 2: 19 August 2021

CLINICAL STUDY PROTOCOL

A LONG-TERM, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, PHARMACODYNAMICS, AND EFFICACY OF MIGALASTAT IN SUBJECTS > 12 YEARS OF AGE WITH FABRY DISEASE AND AMENABLE *GLA* VARIANTS

Protocol Number: AT1001-036

Version: 3.0, Amendment 2

Protocol Date: 19 August 2021

Original Protocol: 4 February 2019
Amendment 1: 24 June 2019

EudraCT Number: 2019-000222-21

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

Role	Contact Information
SAE Reporting	**Primary method:** **Safety FAX number:** +1 866-422-1278 **If the primary method fails, please use:** **Safety Email address:** safetyreporting@amicusrx.com

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 (Amicus).

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 Council on Harmonisation (ICH) GCP E6 guidelines

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

Sponsor

Signature: PPD

Date

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 GCP described in the US 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

Signature: _____

Date:

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:
A Long-term, Open-label Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Migalastat in Subjects > 12 Years of Age with Fabry Disease and Amenable *GLA* Variants

Study Centers: Global, multicenter

Protocol Number: AT1001-036

Studied Period:	**Phase of Development:**
Estimated date first subject enrolled: Fourth quarter 2019 Estimated date last subject completed: Second quarter 2022	Phase 3b

Objectives:

Primary

- to assess the long-term 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

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

Methodology:

This is a long-term, open-label, uncontrolled, multicenter study to evaluate the safety, PD, and efficacy of migalastat treatment in subjects over 12 years of age with Fabry disease and with amenable *GLA* variants. Subjects will enroll in this study following completion of migalastat Study AT1001-020.

Enrollment in this study should immediately follow completion of Study AT1001-020 in order to maintain the continuity of treatment. As appropriate, assessments performed at the End of Treatment visit for Study AT1001-020 will be utilized for Visit 1 (baseline) assessments for this study.

Subsequent visits for this study will be scheduled every 6 months with interim telephone contacts at intervening 3-month intervals in order to monitor safety. In general, subjects must have completed Study AT1001-020 to be eligible for enrollment in this study. However, subjects who withdrew from that study for a reason not related to the safety or efficacy of migalastat may be eligible to participate in this study upon approval by the Amicus medical monitor.

Subjects will remain on the same dose of migalastat that they were receiving in Study AT1001-020. 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.

Subjects who are eligible and able to receive reimbursed product at the completion of Study AT1001-020 or during the current study will be switched to Galafold, if continued treatment with migalastat is desired. Subjects who are unable to secure reimbursed product may continue treatment in the study, or via an early access or other program. Regardless of treatment choice, subjects may also enroll in the Fabry Registry that is being conducted under a separate protocol.

Number of Subjects (Planned):

The number of subjects to be enrolled will be dependent on the number of eligible subjects completing Study AT1001-020 and who consent to enroll in this open-label extension study.

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. Male or female subjects diagnosed with Fabry disease > 12 years of age who completed Study AT1001-020
2. Subject's parent or legally-authorized representative 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
3. If of reproductive potential, both male and female subjects agree to use a medically accepted method of contraception throughout the duration of the study and for up to 30 days after their last dose of migalastat

Exclusion Criteria:

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

1. Subject's last available estimated glomerular filtration rate (eGFR) in the previous study was < 60 mL/min/1.73 m^2
2. Subject has advanced kidney disease requiring dialysis or kidney transplantation
3. Subject received any investigational/experimental drug, biologic, or device within 30 days before baseline, with the exception of migalastat
4. Subject anticipates starting gene therapy during the study period
5. Subject has any intercurrent illness or condition at Visit 1 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
6. Subject has a history of allergy or sensitivity to migalastat (including excipients) or other iminosugars (eg, miglustat, miglitol)
7. Subject requires treatment with Replagal® (agalsidase alfa) or Fabrazyme® (agalsidase beta)
8. Subject requires treatment with Glyset® (miglitol) or Zavesca® (miglustat)
9. Female subject 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 150-mg capsules. Migalastat capsules contain 123 mg migalastat free base, which is equivalent to 150 mg migalastat HCl.

Administration

Migalastat will be administered every other day (QOD) during the treatment period. Capsules are to be taken with water at the same time of day during the QOD 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.

Duration of Treatment:

Subjects will continue on the study until the date of regulatory approval or marketing authorization for pediatric patients with Fabry disease and availability of reimbursed product in the participating subject's country, or study termination by Amicus. Since subjects will be entering this study as they complete Study AT1001-020, the duration of treatment will vary among subjects.

Reference Therapy, Dosage and Mode of Administration:

There is no reference therapy for this study.

Criteria for Evaluation:

Safety Assessments:

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

Safety endpoints are as follows:

- incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation of study drug
- change from baseline in clinical laboratory test results over time
- change from baseline in vital signs over time
- change from baseline in physical examination findings over time
- change from baseline in body weight and height over time
- change from baseline in ECG results over time
- change from baseline in echocardiogram parameters over time
- change from baseline in Tanner Stage

Pharmacodynamic Assessments:

The primary PD biomarker to be evaluated in this study is lyso-Gb_3 levels in plasma. Exploratory evaluation of lyso-Gb_3 analogues and other potential Fabry biomarkers (non-genetic) also may be explored from these samples.

The PD endpoint is change from baseline in plasma levels of lyso-Gb_3.

Efficacy Assessments:

Efficacy assessments include eGFR, urine protein and albumin levels, left ventricular mass index (LVMi) and other cardiac parameters using echocardiograms, and subject questionnaires (Fabry-Specific Pediatric Health and Pain Questionnaire [FPHPQ], and Pediatric Quality of Life Inventory™ [PedsQL™]).

Efficacy endpoints are as follows:

- change from baseline in eGFR (Schwartz formula)
- change from baseline in urine protein and albumin levels
- change from baseline in LVMi
- change from baseline in FPHPQ scores
- change from baseline in PedsQL scores

For analysis purposes, baseline value for efficacy endpoints for subjects enrolled in this study will be the baseline visit of Study AT1001-020.

Note: Estimated GFR will be calculated using the Schwartz formula throughout the study, regardless of the subject's age at the time of assessment. For subjects ≥ 18 years of age, the Schwartz formula will be applied by the sponsor at the time the value is entered into the database.

Statistical Methods:

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

The intent-to-treat population will include all enrolled subjects. All efficacy analyses will be performed using the 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 age group at baseline, by sex, and combined across all subjects.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
α-Gal A	α-galactosidase A
AE	adverse event
AUC	area under the plasma concentration-time curve
BID	*bis in die* (twice daily)
CFR	Code of Federal Regulations
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EU	European Union
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
IND	Investigational New Drug
IEC	Independent Ethics Committee
IRB	Institutional Review Board
lyso-Gb_3	globotriaosylsphingosine
LVMi	left ventricular mass index
PCS	potentially clinically significant
PD	pharmacodynamic
PedsQL™	Pediatric Quality of Life Inventory™
QOD	*quaque altera die* (once every other day)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
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 live births (Desnick, 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 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, a low molecular weight iminosugar, is an analogue of the terminal galactose of GL-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, Delle 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, Padgett et al. 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 Package Insert 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 150 mg migalastat HCl 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), once every other day (QOD) (50, 150, 250 mg), and 3 days on/4 days off (250, 500 mg). In these studies, 150 mg migalastat HCl 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 migalastat HCl 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 migalastat HCl 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 QOD 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. 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 in a clinical trial being 12.76 years. The subject transferred to commercial migalastat (Galafold®) in 2018.

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 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.

5.4. Study Rationale

This is a Phase 3b, open-label, uncontrolled, multicenter study to evaluate the long-term safety, pharmacodynamics (PD), and efficacy of migalastat treatment in pediatric subjects over 12 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 versus 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). This study provides continued migalastat treatment for pediatric subjects previously enrolled in Study AT1001-020, allowing for continued assessment of safety and efficacy in this population.

5.5. Dose Selection

The dose regimen of migalastat proposed for evaluation in pediatric subjects with Fabry disease (150 mg QOD) weighing ≥ 45 kg (99 pounds) is the same as the adult dose and is supported by simulation results from a population pharmacokinetic 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).

6. OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is as follows:

- to assess the long-term safety of migalastat treatment in pediatric subjects diagnosed with Fabry disease and who have variants in the gene encoding α-Gal A amenable to treatment with migalastat

6.2. Secondary Objectives

The secondary objectives of this study are as follows:

- to characterize the PD of migalastat in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat
- to assess the efficacy of migalastat in pediatric subjects diagnosed with Fabry disease and who have *GLA* variants amenable to treatment with migalastat

7. INVESTIGATIONAL PLAN

7.1. Study Design

This is a long-term, open-label, uncontrolled, multicenter study to evaluate the safety, PD, and efficacy of migalastat treatment in pediatric subjects over 12 years of age with Fabry disease and with amenable *GLA* variants. Subjects will enroll in this study following completion of migalastat Study AT1001-020.

Enrollment in this study should immediately follow completion of Study AT1001-020 in order to maintain the continuity of treatment. As appropriate, assessments performed at the End of Treatment visit for Study AT1001-020 will be utilized for Visit 1 (baseline) assessments for this study.

Subsequent visits for this study will be scheduled every 6 months with interim telephone contacts at intervening 3-month intervals in order to monitor safety. In general, subjects must have completed Study AT1001-020 to be eligible for enrollment in this study. However, subjects who withdrew from the prior study for a reason not related to the safety or efficacy of migalastat may be eligible to participate in this study upon approval by the Amicus medical monitor.

Subjects will remain on the same dose of migalastat that they were receiving in Study AT1001-020. 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.

Subjects who are eligible and able to receive reimbursed product at the completion of Study AT1001-020 or during the current study will be switched to Galafold, if continued treatment with migalastat is desired. Subjects who are unable to secure reimbursed product may continue treatment in the study, or via an early access or other program. Regardless of treatment choice, subjects may also enroll in the Fabry Registry that is being conducted under a separate protocol.

7.2. Duration of Treatment

Subjects will continue on the study until the date of regulatory approval or marketing authorization for pediatric patients with Fabry disease and availability of reimbursed product in the participating subject's country, or study termination by Amicus. Since subjects will be entering this study as they complete Study AT1001-020, the duration of treatment will vary among subjects.

7.3. Details of Study Treatment

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

7.3.1. Administration of Study Treatment

Migalastat will be administered QOD during the treatment period. Capsules are to be taken with water at the same time of day during the QOD 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.

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.

7.3.2. 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.

7.3.3. 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.

7.4. Concomitant Medications

Concomitant medications, including vaccinations, and any medication taken 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. Medication continuing from the previous study also must be recorded.

7.5. 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
- gene therapy
- Enzyme replacement therapy (eg, Replagal® [agalsidase alfa], Fabrazyme® [agalsidase beta])
- Glyset® (miglitol)
- Zavesca® (miglustat)

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Number of Subjects

The number of subjects to be enrolled will be dependent on the number of eligible subjects completing migalastat treatment in Study AT1001-020 and who consent to enroll in this open-label extension study.

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. Male or female subjects, diagnosed with Fabry disease > 12 years of age who completed Study AT1001-020
2. Subject's parent or legally authorized representative 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
3. If of reproductive potential, both male and female subjects agree to use a medically accepted method of contraception throughout the duration of the study and for up to 30 days after their last dose of migalastat

8.2.2. Exclusion Criteria

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

1. Subject's last available estimated glomerular filtration rate (eGFR) in the previous study was < 60 mL/min/1.73 m^2
2. Subject has advanced kidney disease requiring dialysis or kidney transplantation
3. Subject received any investigational/experimental drug, biologic, or device within 30 days before baseline, with the exception of migalastat
4. Subject anticipates starting gene therapy during the study period
5. Subject has any intercurrent illness or condition at Visit 1 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
6. Subject has a history of allergy or sensitivity to migalastat (including excipients) or other iminosugars (eg, miglustat, miglitol)
7. Subject requires treatment with Replagal (agalsidase alfa) or Fabrazyme (agalsidase beta)
8. Subject requires treatment with Glyset (miglitol) or Zavesca (miglustat)
9. Female subject 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

8.3. Withdrawal Criteria

8.3.1. Reasons for Discontinuation/Withdrawal

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
- failure of the subject to comply with the study visit schedule
- persistent noncompliance, at the discretion of the investigator
- pregnancy
- subject becomes eligible for reimbursed product
- inability to contact subject (ie, subject is lost to follow-up)
- Amicus medical monitor request

8.3.2. Handling of Withdrawals

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. 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 baseline
- intrauterine device that meets the < 1% failure per year rate, as stated in the product label, for at least 12 weeks before baseline
- 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 Amicus.

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 2. Total blood volume to be drawn per subject is presented in Table 3.

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 2: Schedule of Assessments

Assessments	**Baseline**[a]	**Treatment Period**								**EOT/ ET**	**Follow-up**
Visit Interval	**Day 1**	**Month 3 (TC)**	**Month 6**	**Month 9 (TC)**	**Month 12**	**Month 15 (TC)**	**Month 18**	**Month 21 (TC)**	**Month 24**	**--**	**30-Day Safety**
Visit Window (days)	**—**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**+6**
Informed consent/assent	X										
Inclusion/exclusion criteria	X										
Medical history	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Dosing diary[b]	X	→	→	→	X	→	→	→	X		
FPHPQ questionnaire	X		X		X		X		X	X	
PedsQL	X		X		X		X		X	X	
Complete physical examination	X		X		X		X		X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, RR, Temp)	X		X		X		X		X	X	
Body weight	X		X		X		X		X	X	
Height	X		X		X		X		X	X	
Tanner Staging	X		X		X		X		X	X	
12-lead ECG	X		X		X		X		X	X	
Chemistry (including eGFR using Schwartz formula)	X		X		X		X		X	X	
Hematology	X		X		X		X		X	X	

Table 2: Schedule of Assessments (Continued)

Assessments	Baseline[a]	Treatment Period								EOT/ ET	Follow-up
Visit Interval	**Day 1**	**Month 3 (TC)**	**Month 6**	**Month 9 (TC)**	**Month 12**	**Month 15 (TC)**	**Month 18**	**Month 21 (TC)**	**Month 24**	**--**	**30-Day Safety**
Visit Window (days)	**—**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**±6**	**+6**
Plasma lyso-Gb_3, analogs, and exploratory PD biomarkers	X		X		X		X		X	X	
Urinalysis (urine protein, albumin and microalbumin levels)	X		X		X		X		X	X	
Urine pregnancy test or date of LMP (as applicable)[c]	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[d]	

Abbreviations: BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = end of treatment; ET = early termination; FPHPQ = Fabry-Specific Pediatric Health and Pain Questionnaire; HR = heart rate; LMP = last menstrual period; LVMi = left ventricular mass index; lyso-Gb_3 = globotriaosylsphingosine; PD = pharmacodynamic; PedsQL = Pediatric Quality of Life Inventory; RR = respiration rate; TC = telephone call; Temp = body temperature

Note: Following Month 24, visits will continue every 6 months with interim telephone contacts at 3-month intervals. The assessment schedule will repeat starting from Month 3.

Note: For the purposes of this study, a month is considered to be 30 days.

[a] End of study assessments from Study AT1001-020 will be used as baseline assessments for Study AT1001-036.

[b] A dosing diary will be completed throughout the treatment period.

[c] Female subjects only; urine pregnancy tests will be conducted at each site visit. For menstruating females, date of LMP will be elicited during telephone contacts.

[d] Return of study drug only.

Table 3: Total Blood Volume to be Collected (as Scheduled) per Subject per Year

	Blood Volume per Test (mL)			
Assessments	**Baseline[a]**	**Month 6**	**Month 12**	**Total**
Chemistry	4	4	4	12
Hematology	2	2	2	6
Plasma lyso-Gb_3 and PD biomarkers	4	4	4	12
			Total:	**30 mL**

Abbreviations: lyso-Gb_3 = globotriaosylsphingosine; PD = pharmacodynamic
Note: Total collection volume does not take into account additional blood samples drawn during potential unscheduled visits.
[a] End of study laboratory assessments for Study AT1001-020 will be used as Visit 1 assessments for Study AT1001-036. The blood volume from baseline assessments should not be counted for subsequent years.

9.1. Description of Study Visits

9.1.1. 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.

9.1.2. Baseline Visit

Baseline assessments will be performed pre-dose on Day 1. Since subjects will be transitioning from a previous migalastat study, the final visit of that study will be utilized to satisfy any duplicate Visit 1 (baseline) procedures required for the current study. The desired intent is for treatment with migalastat to continue without a break. However, any subject who did not receive migalastat for more than 30 days will be required to repeat all Visit 1 procedures.

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.

9.1.3. Treatment Period Visits/Telephone Contacts

Periodic visits are scheduled every 6 months during the treatment period (ie, at Months 6, 12, etc). Telephone contacts are scheduled at 3-month intervals in between site visits (ie, Months 3, 9, 15, 21, etc). A month will be defined as 30 days. After the first year on study, visits will continue at 6-month intervals with interim telephone contact at intervening 3-month intervals. Following Month 24, the schedule of assessments as displayed in Table 2 will repeat starting with the Month 3 telephone contact (which will be Month 27).

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.

9.1.4. Early Termination Visit

Subjects who are withdrawn from the study should complete early termination procedures as soon as possible. If early termination coincides with a scheduled visit, all procedures outlined for the early termination visit should be performed.

9.1.5. 30-day Safety Follow-up Visit

All subjects, 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. This visit may be accomplished by a telephone contact, similar to the scheduled telephone contact. In these instances, in lieu of a urine pregnancy test for female subjects, subjects will be questioned about any pregnancies (ie, including delay in menstrual period for female subjects with regular menses) that may have occurred.

9.2. Description of Study Assessments

All assessments will be conducted according to the schedule presented in Table 2. Assessments may be repeated if requested by the medical monitor.

9.2.1. Medical History

Medical history will be collected by subject interview. Additionally, medical history deemed related to the subject's Fabry disease will be identified in the subject's medical records by the investigator or designee for entry into the appropriate eCRF, including, but not limited to such things as past serum creatinine results.

Since subjects will have participated in a previous migalastat study, historical medical history (ie, events or conditions that had their onset at least 90 days prior to Visit 1) will be considered as medical history for this study.

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 4. Laboratory samples collected on a dose administration day will be collected predose.

Table 4: Clinical Laboratory Parameters

Chemistry	Hematology	Urinalysis
ALT	Hematocrit	Color
Alkaline phosphatase	Hemoglobin	Appearance
AST	Platelet count	Specific gravity
Albumin	RBC count	pH
Bilirubin, total	WBC count (absolute)	Albumin
BUN	Automated WBC differential	Bilirubin
Calcium, total	Basophils	Blood
Carbon dioxide, total (bicarbonate)	Eosinophils	Glucose
Chloride	Lymphocytes	Ketones
CPK	Monocytes	Microalbumin
Creatinine, serum	Neutrophils	Microscopy of sediment
GGT		Nitrite
Glucose		Protein
Lactate dehydrogenase		WBCs
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

Urine pregnancy tests will be performed for all female subjects of childbearing potential (as defined in Section 8.4); 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.

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 1 decimal place. 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 electrocardiogram (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 left ventricular mass index (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. Pharmacodynamic Assessments

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

9.2.4. Efficacy Assessments

9.2.4.1. Estimated Glomerular Filtration Rate

Estimated GFR will be calculated using the Schwartz formula according to the standards of the central laboratory. Subjects who reach the age of 18 and remain on study will continue to have eGFR calculated by this method by the sponsor at the time the value is entered into the database.

9.2.4.2. Urine Protein and Albumin Levels

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

9.2.4.3. 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.

9.2.4.4. Subject Questionnaires

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

9.2.4.4.1. Dosing Diary

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. Subjects will be asked to complete diary entries in order to track migalastat administration beginning on Day 1 and for the duration of the study.

9.2.4.4.2. Fabry-Specific Pediatric Health and Pain Questionnaire

The Fabry-Specific Pediatric Health and Pain Questionnaire (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.

9.2.4.4.3. Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory™ (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 baseline and/or, in the investigator's opinion, represent a clinically significant change in the subject's health during study participation
  - Baseline medical evaluation findings (eg, ECG) that were not previously provided as medical history and can be determined as starting before baseline, 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).

Subjects will be enrolling in this study following completion of Study AT1001-020. Therefore:

- Adverse events that are ongoing as of the last study visit of Study AT1001-020 will be entered in the AE eCRF.
  - The start date recorded in Study AT1001-020 will be the start date entered in the current study AE eCRF.
  - The event will be noted as continuing from Study AT1001-020 in the current study's AE eCRF.

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 baseline should only be reported as AEs if they worsen (ie, increase in severity) since baseline.

Adverse events that begin after the first dose of investigational product in Study AT1001-036 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 baseline.
  - 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 Amicus 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 Amicus 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) or the 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 Amicus 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 Amicus, should be as complete as soon as possible, and should include all information known at the time. 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 Amicus. 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 Amicus 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 Amicus. The subject's study number must be indicated 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 Amicus 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 Amicus 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 Amicus. 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, Amicus 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 Amicus (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 12.3.1) 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 (SAP).

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
- change from baseline in clinical laboratory test results over time
- change from baseline in vital signs over time
- change from baseline in physical examination findings over time
- change from baseline in body weight and height over time
- change from baseline in ECG results over time
- change from baseline in echocardiogram parameters over time
- change from baseline in Tanner Stage

11.1.2. Pharmacodynamic Endpoints

The PD endpoint is the change from baseline in plasma levels of lyso-Gb_3.

11.1.3. Efficacy Endpoints

Efficacy endpoints are as follows:

- change from baseline in eGFR (Schwartz formula)
- change from baseline in urine protein and albumin levels
- change from baseline in LVMi
- change from baseline in FPHPQ scores
- change from baseline in PedsQL scores

11.2. Sample Size Considerations

Since this is a long-term extension study that will enroll subjects from Study AT1001-020, no formal sample size calculation was performed.

11.3. Data Analysis Considerations

11.3.1. Analysis Populations

11.3.1.1. Safety Population

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

11.3.1.2. Intent-to-treat Population

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

11.4. Statistical Methods

For the purpose of statistical analyses, baseline is generally defined as the last non missing measurement obtained on or before the administration of the first dose of study drug. For this study, the baseline value for efficacy endpoints will be obtained from the baseline visit of Study AT1001-020.

Only summary statistics will be provided for data collected from this study. No missing data imputation method is planned to handle missing data. Data will be summarized as observed.

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 age group at baseline, 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.

Full details will be presented in the SAP.

11.4.1. Interim Analysis

No interim analyses are currently planned for this study.

11.4.2. Baseline Demographic and Subject Characteristics

Baseline demographics and subjects' characteristics will be presented for all subjects in the intent-to-treat and Safety Populations. Demographics will be collected from the baseline visit of Study AT1001-020. Age at entry into this study will be re-calculated based on the date of birth recorded in the Study AT1001-020. Subject characteristics will be summarized using descriptive statistics.

Subject characteristics will be updated from Study AT1001-020 and will include height, body weight, body mass index, number of years since diagnosis of Fabry disease, previous use of

enzyme replacement therapy, and previous and current use of angiotensin-converting enzyme inhibitors, renin inhibitors, and angiotensin receptor blockers.

11.4.3. Subject Disposition

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.

Protocol deviations will be listed.

11.4.4. Safety Analyses

Continuous safety data will be summarized using descriptive statistics (number, mean, standard deviation, median, minimum, and maximum). Categorical variables will be presented by number (percentage).

11.4.4.1. Exposure

An exposure table will be presented based on subcategories as defined in the SAP.

11.4.4.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term.

The number and percentage of subjects with AEs will be summarized by SOC and preferred term within each SOC. Additional displays will present AEs by intensity (mild, moderate, severe), relationship to study treatment (Related Events: definite, probable, and possible; Unrelated Events: unlikely and unrelated), and by outcome of events. Moreover, the number of AEs (as opposed to the number and percentage of subjects) will be presented. Listings will also be provided for SAEs and TEAEs leading to discontinuation of study treatment.

11.4.4.3. Laboratory Data

Actual values and changes from baseline for clinical laboratory test results will be summarized using descriptive statistics (number, mean, median, minimum, and maximum). Categorical variables will be presented by number (percentage). Shift tables will also be provided for clinical laboratory tests.

Potentially clinically significant (PCS) laboratory values will be summarized by laboratory parameter. The PCS criteria for laboratory values will be defined in the final SAP. The summary will indicate the number of subjects with PCS-low or PCS-high values at any time during treatment with migalastat, but will not be presented by visit. It is possible for subjects to appear in both categories (PCS-low and PCS-high) for any parameter. The incidence rates of PCS values will be presented. There will be no statistical testing.

11.4.4.4. Vital Signs

Descriptive statistics for vital signs will be presented for systolic blood pressure, diastolic blood pressure, body temperature, HR, and RR, at each visit. Change from baseline to post baseline visit will also be presented. Data will be attributed to visits as described in the final SAP.

The incidence rates of PCS vital sign changes, by parameter, will be summarized. Potentially clinically significant criteria for vital signs are defined in the SAP. The summary will indicate the number and percentage of subjects with PCS-low and PCS-high values at any time during migalastat treatment and will not be presented by visit. It is possible for subjects to appear in both categories for any parameters.

11.4.4.5. Physical Examinations

Physical examination results will be presented for each body system/category examined; the number and percent of subjects judged to be normal, abnormal, or not performed will be summarized. Similarly, the results of the physical examinations will be summarized for subjects in the Safety Population who had an examination post baseline.

Tanner Stages will be summarized using descriptive statistics.

11.4.4.6. Electrocardiograms

Actual values and changes from baseline for ECG parameters will be summarized using descriptive statistics.

Potentially clinically significant values for quantitative ECG data will be summarized by parameter. The PCS criteria for 12-lead ECGs will be defined in the SAP. The summaries will indicate the number and percentage of subjects with PCS-low and PCS-high values at any time during the study, and will not be presented by visit. It is possible for subjects to appear in both categories for any parameters.

Shift tables will also be provided for clinical laboratory tests and ECG results.

11.4.4.7. Echocardiograms

Echocardiogram parameters (other than LVMi) will be summarized using descriptive statistics.

11.4.4.8. Concomitant Medications

Concomitant medications include all prescription and non-prescription medicinal treatments (including vitamins, supplements, and vaccines) taken during the treatment period. Medications that are ongoing from the Study AT1001-020 or stopped within 2 weeks of the AT1001-020 End of Study Visit, will be recorded as concomitant medications for this study. Medications from Study AT1001-020 that were stopped over 2 weeks prior to the start of this study will not be recorded as concomitant medications. Medications starting after the last dose of study drug will not be considered as concomitant, but will be flagged as post medications on the listing. All concomitant medications will be summarized.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized according to the generic terms and ATC codes (Anatomical therapeutic chemical [classification system]). Medications will be tabulated in decreasing order of the total number of subjects who took each medication. In addition, the total number of subjects to ever take any concomitant medication will be presented.

11.4.5. Pharmacodynamic Analyses

Continuous plasma lyso-Gb_3 levels will be summarized using descriptive statistics. Lyso-Gb_3 analogues and exploratory cardiac biomarkers, if analyzed, will also be summarized using descriptive statistics.

11.4.6. Efficacy Analyses

Actual values and changes from baseline (as applicable) in eGFR, urine levels of protein and albumin, LVMi, FPHPQ scores, and PedsQL scores will be summarized using descriptive statistics.

12. STUDY TREATMENTS

12.1. Description of Study Drug

Migalastat is an iminosugar that functions as a selective pharmacological chaperone. Migalastat will be supplied as a gelatin capsule (Table 5). Migalastat capsules must be swallowed whole and must not be cut, crushed, or chewed.

Table 5: 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 Amicus 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 Amicus (or designee). Product accountability records must be maintained throughout the study.

Subjects will be instructed to return all unused, partially used, or empty study drug containers at each specified visit.

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 Amicus or designee for destruction. Sites may not destroy study drugs on site unless Amicus has provided prior written approval.

12.3.1. 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.

A temperature log must be maintained for the duration of the study, and the temperature of the storage room (or cabinet) in which the study drugs are stored must be recorded for each working day of the week that pharmacy staff (or designated study staff) is available. Temperature is required to be recorded using a standard Min-Max Thermometer that has calibration records available (details usually contained within the device leaflet) and is maintained according to institutions standard maintenance policy.

The study drug is to be stored only at the site listed on the US 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.

12.3.2. Shipment, Return, and Disposal of Investigational Product

The investigator (or designee) will inventory and acknowledge receipt of all shipments of investigational product.

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 Amicus.

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.

At the end of the study, eCRFs (including queries and audit trails) will be retained by Amicus and copies will be sent to the investigator to maintain as the investigator's copy.

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 Amicus (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 their site-specific eCRF data as entered into the EDC system for the study in a secure electronic format, 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 Amicus (or designee) for storage.

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

Monitoring and auditing procedures developed or endorsed by Amicus 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 13.5). 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 Amicus 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 Amicus immediately if contacted by a regulatory authority regarding an inspection or audit.

13.4. Study Site Closure

Upon completion or termination of the study, the study monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and Amicus or its designee's Standard Operating Procedures. Amicus or the investigator has the right to close any study site at any time. The reason(s) for closure will be documented in writing. To the extent possible, premature closure would occur after mutual consultation. Completion or premature termination of the study will be reported by Amicus to the regulatory agency and by Amicus or investigator to the IRB/IEC as required by the IRB/IEC or by local regulation. Study materials must be returned, disposed of, or retained as directed by Amicus

13.5. Records Retention

The investigator must obtain approval in writing from Amicus 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 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, Amicus may request retention for a longer period.

Prior to any decision regarding the disposal or destruction of study documents, the investigator should contact Amicus. 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, including all informed consent forms completed following any protocol amendment

- Subject identification code list 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 Amicus or CRO
- A 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/diaries 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 Amicus for permission to make alternative arrangements. Details of these arrangements must be documented in writing.

13.6. Use of Study Findings

All information concerning migalastat as well as any matter concerning the operation of Amicus, such as clinical indications for migalastat, its formula, methods of manufacture, and other scientific data relating to it, that has been provided by Amicus 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 Amicus 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.

Amicus will ensure that a final report on the study is prepared with 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 Amicus to the regulatory authorities and by the investigator to the IEC/IRB.

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. Regulatory and Ethical Considerations

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 ethical principles outlined in the current version of Declaration of Helsinki, and in keeping with local country-specific regulations, including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments
- Subject informed consent
- Investigator reporting requirements

14.1.1. Independent Ethics Committees/Institutional Review Boards/Research Ethics Boards Approval and Study Compliance

Prior to initiation of a study site, Amicus will obtain appropriate favorable opinions/approvals to conduct the study in accordance with ICH GCP and applicable country-specific regulatory requirements.

14.1.2. Informed Consent/Assent Information

Signed written informed consent/assent is to be obtained for each subject prior to enrollment into the study and 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 provided 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. Details about why oral presentation was used, how the information was presented, and how the subject provided consent must be described in the source documentation.

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.

14.1.3. 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 Amicus (or designee) or by the investigator. The parties responsible for submissions will be identified and documented prior to shipment of investigational product.

- Information on AEs and SAEs
- Expedited safety reports
- Periodic reports on the progress of the study
- Revised informed consent forms
- Amendments to the protocol
- Updated Investigator's Brochure

14.1.4. 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 ClinicalTrials.gov and Eudra CT for publication of study results. Investigators contact information will be included in the study listing.

14.1.5. Quality Control

In accordance with applicable regulations, GCP, and sponsor procedures, Amicus 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 Amicus'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.

14.1.6. Quality Assurance

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

14.1.7. Confidentiality

Subject names (and the names of family members, telephone numbers, and addresses) will not be supplied to Amicus. 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 Amicus. 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 (EU) 2016/679). The subject and the subject's parent or legally-authorized representative will be informed that representatives of Amicus, 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.

14.1.8. Protocols Amendments and Deviations

Any non-administrative changes to the protocol, initiated either by Amicus or by the investigator, will require a formal amendment procedure. Approval of all amendments must be obtained from Amicus, relevant IEC/IRB, and regulatory authorities (in accordance with local requirements) prior to implementation.

If a clarification on a procedure or an error is found in the protocol, a protocol clarification memo may be sent to all sites and the IRB/IEC before an amendment is issued.

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 Amicus, unless necessary to eliminate an immediate hazard to the subject(s). Where Amicus 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 CFR Title 21 Part 312.30(b)(2). In such cases, Amicus and the IEC/IRB must be notified within 1 business day.

Amicus 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.

14.1.9. 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.

14.2. Legal and Financial Aspects

14.2.1. Liability and Insurance

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

14.2.2. Financial Disclosure

Before the start of the study, the investigator will disclose to Amicus 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 Amicus. 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, Amicus may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Where required by regulation:

- The investigator will disclose his/her financial interests to the subjects in the informed consent information.

- The investigator or Amicus, on behalf of the investigator, will 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

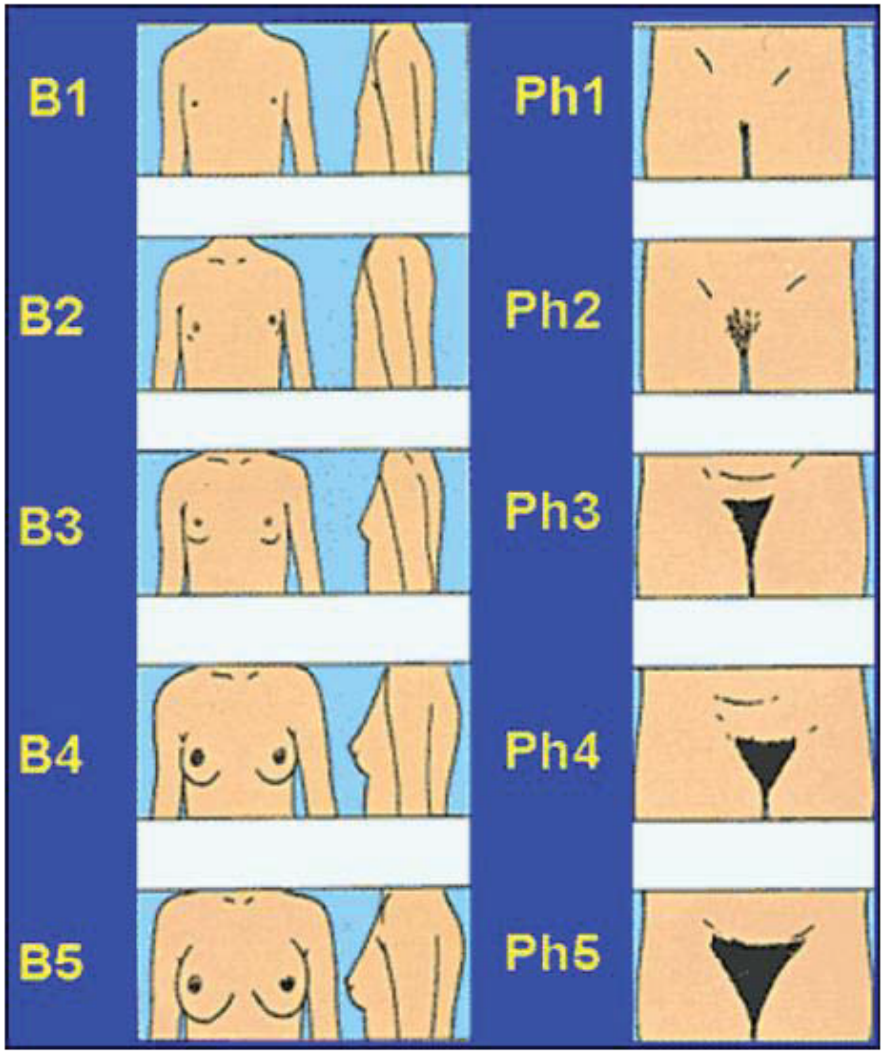

Figure 1. (Left) Stages of breast [B] development. **B-1**: pre-pubertal; **B-2**: breast bud; **B-3**: enlargement of beast and areola with no separation of the contours; **B-4**: projection of areola and papilla to form a secondary mound above the level of the breast; **B-5**: recession of the areola 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.

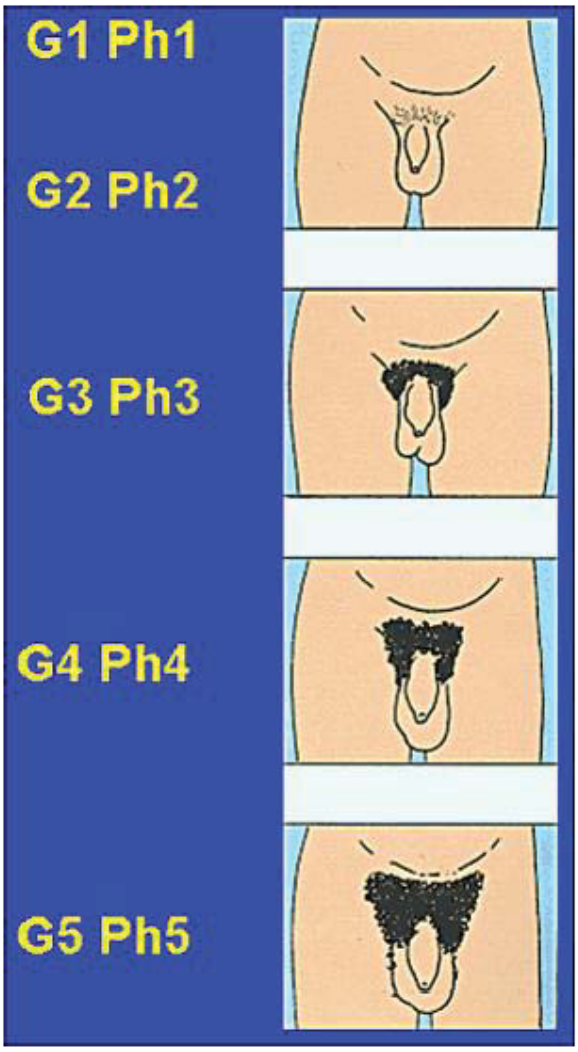

Figure 2. Stages of genital [G] and pubic hair [Ph] development in the male. **G-1, Ph-1**: pre-pubertal; **G-2**: the testis and scrotum enlarge, and the skin of the scrotum shows some reddening and change in the texture. Sparse growth of pigmented hair usually slightly curly, mainly at the base of 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).