# 2. SYNOPSIS

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| **Name of Sponsor/Company:** Amicus Therapeutics, Inc.<br>**Name of Finished Product:** AT1001<br>**Name of Active Ingredient:** Migalastat hydrochloride | Individual Study Table Referring to Part of the Dossier<br>Volume:<br>Page: | *(For National Authority Use Only)* |

**Title of Study**: Open-label extension study to evaluate the long-term safety, tolerability, and pharcodynamics of AT1001 in patients with Fabry Disease

**Protocol Number:** FAB-CL-205

**Principal Investigators:** [redacted]

**Study center(s):**

01: [redacted]
02: [redacted]
03: [redacted]
04 [redacted]
05: [redacted]
06: [redacted]
07: [redacted]
08: [redacted]

**Publications (reference):** None at the time of this interim report

| **Studied period** | **Phase of development: 2** |
|---|---|
| Date first patient enrolled: 17 September 2007<br>Date last patient completed: 08 September 2012<br>Date of full report: 18 December 2014 | |

**Objectives:**

Primary:

- to evaluate the long-term safety and tolerability of oral migalastat HCl in patients with Fabry disease

Secondary:

- to gain information about the pharmacodynamics (PD) and pharmacokinetics (PK) of orally administered migalastat HCl in patients with Fabry disease

Exploratory:

- to evaluate the effect of migalastat HCl on disease related outcomes.

**Methodology:** An open-label, non-comparative long-term extension study for male and female subjects with Fabry disease who had completed the treatment period of one of four preceding Phase 2 trials (FAB-CL-201,-202, -203 or -204). Subjects could enter this extension trial immediately upon completion of participation in their previous migalastat HCl trial, or at a later time point. Thus some subjects did not necessarily have continuous treatment with migalastat HCl from the original study and this extension study.

The dose and regimen in the original protocol and Amendment 1 was 150 mg migalastat HCl, administered once every other day (QOD). Amendment 2 introduced a 4-month dose escalation period (DEP). In the DEP, all subjects received migalastat HCl administered at 250 mg (3 days on, 4 days off) for the first 2 months. If there were no safety concerns, the dose was then increased to 500 mg (3 days on, 4 days off).

During the DEP, safety was evaluated monthly. Pharmacodynamic (PD) markers (α-Gal A activity in leukocytes and GL-3 levels in plasma and urine) were evaluated monthly on the second day off drug. At the end of the DEP, subjects continued to receive migalastat HCl at 500 mg (3 days on, 4 days off) unless, based on safety review, the investigator and medical monitor agreed to a lower dose level as allowed per protocol. Subjects already enrolled into the study and receiving 150 mg migalastat HCl QOD at the time Amendment 2 was implemented began the revised dosing regimen at their next scheduled visit.

An interim review of safety and PD data was performed after all enrolled subjects had completed at least 4 months of treatment in the DEP. Increase in leukocyte α-Gal A activity and reduction in plasma or urine GL-3 were regarded as PD indicators of a positive response to migalastat. However, because the value of these markers as predictors of clinical outcome was as yet unclear, the decision to continue each subject in the trial and hence on study treatment was based on the PD results and on the respective treating physician (investigator's) best clinical judgement. The results indicated that 150 mg migalastat HCl QOD provided the most favorable benefit-risk profile. In Amendment 4, the dose and regimen of migalastat HCl was returned to 150 mg migalastat HCl QOD for all subjects, except those who were on another dose as previously agreed by the investigator and medical monitor. Note that the 150 QOD regimen did not start exactly at Visit 6 and was staggered from one subject to the next, depending on when Amendment 4 was approved for each site. The first subject switched to 150 QOD at Visit 10, and the last subject switched to 150 QOD by Visit 12 with the exception of 1 subject who continued on 300 mg 3 days on/4 days off for the remainder of the study.

During the remainder of the study, subjects returned to the study center for their regular visits every 3 months.

Amendment 6 provided details for termination of this study, and described a similar open-label, long-term migalastat HCl treatment study AT1001-041 into which eligible subjects from the current study could enroll without treatment interruption.

**Number of patients (planned and analyzed):**

Twenty-three subjects were enrolled and all 23 subjects were included in the safety and PD analysis sets.

**Diagnosis and main criteria for inclusion:**

A subject was required to meet all of the following inclusion criteria to be considered eligible for study participation:

1. Had completed the main treatment period of another Phase 2 trial of migalastat HCl in Fabry disease
2. Women of childbearing potential had a negative result on their pregnancy test
3. Male and female subjects agreed to use reliable methods of contraception during study treatment and for 4 weeks after study treatment termination
4. Was willing and able to provide written informed consent

A subject was considered ineligible for study participation if any of the following exclusion criteria were met:

1. Had a major protocol violation in the preceding migalastat HCl trial and was discontinued
2. Had undergone, or was scheduled to undergo kidney transplantation or was currently on dialysis
3. Was treated or had been treated with another investigational drug (except migalastat HCl) within 30 days of study start
4. Had been treated with Fabrazyme® (agalsidase beta), Replagal® (agalsidase alfa), Glyset® (miglitol) or Zavesca® (miglustat) within 2 weeks prior to enrollment.

**Test product, dose and mode of administration, batch number:** Migalastat HCl was administered orally by capsule. Before Protocol Amendment 2: 150 mg migalastat HCl QOD. Under Protocol Amendments 2 and 3: Dose escalation period (DEP) – 250 mg (3 days on and 4 days off) migalastat HCl for 2 months and then 500 mg (3 days on and 4 days off). After Protocol Amendment 4: 150 mg migalastat HCl QOD for the remainder of the study. The lot numbers for the migalastat HCl supplies used in this study were: 25 mg capsule (8901.002. 8901.003, 8901.004, 8901.005, and 150E), 150 mg capsule (W004735, W007077, W008778, W008782, W010396, W011194, and W011196), and 250 mg capsule (8907.001).

**Duration of treatment**:

The duration of treatment varied among subjects. In addition, due to the design and implementation of protocol amendments the duration of treatment of the individual dose escalation regimens (250 mg and 500 mg 3 days on 4 days off) varied between subjects. The overall median duration of exposure to migalastat HCl was 4.14 years (range 1.0 to 4.7 years) reflecting 82.7 patient-years of treatment.

**Reference therapy, dose and mode of administration, batch number:**

Not applicable

**Criteria for evaluation:**

**Safety:**

The safety measures were treatment emergent adverse events (TEAEs), vital signs (heart rate, blood pressure), clinical laboratory measurements (hematology, serum chemistry, and urinalysis) electrocardiogram [ECG]), physical examination, and use of concomitant medications.

**Pharmacokinetics:**

Blood samples for measurement of migalastat HCl concentration levels were collected at DEP Visits 1 and 3 at pre-dose and 3 hours post dose. The results are discussed and reported separately in the Population PK Analysis report.

**Pharmacodynamic:**

The PD measures were α-Gal A activity in leukocytes, globotriaosylceramide (GL-3) in urine and kidney, and renal function assessments (eg, creatinine clearance and estimated glomerular filtration rate [eGFR]). Kidney GL-3 was measured by histological scoring of kidney tissue.

**Statistical methods:**

No formal inferential hypothesis testing was performed. Statistical analyses and reporting were performed using Windows SAS version 9.13. Descriptive statistics were used to summarize continuous variables by presenting the number of subjects (n), mean, standard deviation (SD), median, and range. Categorical variables were summarized by presenting the frequency and percentage of subjects in each category. In general, summary tables were not split by dose, and no summaries distinguished between the different dose levels or dosing regimens. No analysis windows were constructed around scheduled visit timepoints; all data were presented by the visit identifier. All subject were included in the safety and PD analysis sets.

An overall summary was presented for total number and percentage of subjects with AEs, TEAEs, treatment related TEAEs, SAEs, fatal SAEs, non-fatal SAEs, treatment related SAEs, deaths, TEAEs leading to discontinuation, and TEAEs leading to a reduction or interruption in study drug dosing. All TEAEs were presented by System Organ Class (SOC) and preferred term. TEAEs were summarized separately for the nominal subgroups of migalastat HCl dose at onset (150 mg QOD, 250 mg 3-on, 4-off, 500 mg 3-on, 4-off) and sex (male, female). Sponsor-defined Potentially Clinically Significant (PCS) laboratory values were identified programmatically and summarized by laboratory parameter: the summary indicated the number of subjects with PCS-low or PCS-high values at any time during the study. PCS changes in vital signs and ECGs were summarized at each timepoint.

In selected PD tables, figures, and listings, each subject was categorized as a “HEK responder” or “HEK non-responder”. This categorization was retrospective and was based on the results of cell-based assays. In the non-GLP assay performed by Amicus, individual mutant forms of α-Gal A were transiently expressed in human embryonic kidney (HEK-293) cells and α-Gal A activity was measured in response to migalastat HCl exposure. Results of these cell based assays were used to construct a pharmacogenetic reference table. Subject categorization was then based on each individual’s genotype and the pharmacogenetic reference table. Hereafter in this document, subjects with mutant forms of α-Gal A predicted to be amenable to migalastat HCL treatment (eg, previously termed “HEK responder”) or non-amenable to migalastat HCl treatment (eg, previously termed “HEK non-responder”) will be referred to as “subjects with amenable mutations” and “subjects with non-amenable mutations,” respectively.

The α-Gal A activity levels in leukocytes and urine GL-3 levles were summarized by presenting the value at baseline and at each post-baseline time point and the change from baseline at each post-baseline time point. Additional summaries included subjects with amenable mutations and subjects with non-amenable mutations. Kidney interstitial capillary (IC) GL-3 was summarized using

descriptive statistics for the averaged across-pathologists' values at baseline and at each post-baseline time point and the percent change from baseline for the averaged-across pathologists' values at each post-baseline time point. Similarly, the pathologists determined whether paired specimens (baseline, Visit 8, and Visit 12) had "equal" levels of GL-3 within podocytes, endothelial, and mesangial cells or whether one specimen in the pair had "less" or "more" GL-3 within each cell type relative to the other specimen. Interstitial Fibrosis Tubular Atrophy (%IFTA ) and glomerular sclerosis was summarized descriptively by presenting the number of subjects, mean, SD, minimum and maximum averaged across pathologists at each time point; change from baseline was computed.

**SUMMARY:**

Of the 23 subjects enrolled, 14 (61%) were male and 9 (39%) were female. The median age at consent was 42 years (range: 19 to 66 years). Sixteen (70%, 11 males and 5 females) subjects had an amenable mutation and 7 (30%, 3 males and 4 females) subjects had a non-amenable mutation. Seventeen subjects completed the study (9 males [all had amenable mutations] and 8 females [4 had amenable mutations, 4 had non-amenable mutations]). At baseline, some subjects exhibited symptoms (temperature intolerance, angiokeratoma, pain in extremity, diarrhea, headache, hypoacusis, tinnitus, abdominal pain and/or proteinuria) commonly reported by subjects with Fabry disease. These events and symptoms generally remained consistent during the study.

**SAFETY RESULTS:**

The evaluation of the long-term safety and tolerability of migalastat HCl was the primary objective of the study.

- All 23 subjects reported at least 1 TEAE during the study. The most common TEAEs were arthralgia, fatigue, back pain, and pain in extremity, influenza and headache.
- Thirteen subjects reported 37 TEAEs that was assessed by the investigator as possible, probable, or definite related to study medication. Most treatment related TEAEs were mild in severity. There was a higher frequency of treatment related TEAEs on the 250 mg (3 days on, 4 days off) and 500 mg (3 days on, 4 days off) dose regimens compared to the 150 mg QOD regimen.
- The only TEAE assessed as definitely treatment-related was an overdose, single extra dose, which was mild in intensity, no AEs related to the overdose were reported, and the subject remained in the study
- Nine subjects reported at least 1 severe TEAE; 3 subjects had a single event and 6 subjects had multiple events.
- No deaths occurred during the study.
- Seven subjects had SAEs, all of which were not considered related to study drug.
    - One subject was withdrawn from the study due to a non-treatment related SAE of cerebrovascular accident (stroke) and ventricular fibrillation.
- Two subjects, all on migalastat HCl 500mg (3 days on, 4 days off), reported TEAEs that resulted in dose reduction.
- There were no consistent trends in clinical laboratory values, vital signs, or ECG qualitative and quantitative results.
- The Fabry disease events and symptoms reported in individual subjects generally remained

consistent during the study

**EFFICACY RESULTS:**

The PD and disease related outcomes were secondary and exploratory objectives of the study, respectively.

- In the overall population, there was a trend of increased α-Gal A activity from baseline during the study. The increase from baseline was greater among male subjects with amenable mutations than in males with non-amenable mutations. Female subjects with and without amenable mutations showed similar increase in leukocyte α-Gal A.
- Leukocyte α-Gal A activity generally increased on the 150 mg QOD dose, and when subjects switched from 150 mg QOD to higher, less frequent doses (250 and 500 mg 3 days on 4 days off) within this study, no notable change in leukocyte α-Gal A activity was observed.
- Urine GL3 generally decreased on the 150 mg QOD dose, and when subjects switched from 150 mg QOD to higher, less frequent doses (250 and 500 mg 3 days on 4 days off) within this study, no notable change in urine GL-3 was observed.
- Kidney histology based on 8 subjects with paired samples (baseline biopsy taken in the previous study and the second taken in the current study in Visit 8) showed a median 78% decline in IC GL-3 inclusions in the 5 subjects with amenable mutations. Based on 7 subjects with paired samples in Visit 12, kidney histology showed a median 27% decline in IC GL-3 in 4 subjects with amenable mutations. In the 3 subjects with non-amenable mutations in Visit 8 and Visit 12, GL-3 inclusions in kidney IC were variable. No consistent trends were seen in GL-3 inclusions in other renal cells, %IFTA, or in glomerular sclerosis.
- A trend in reduction of 24-hr urine protein was seen; however, the reduction was likely confounded by concomitant renal protective therapies (eg, ACEs, or ARBs).
- Median annualized eGFR rate of change for the total population was consistent and showed little change during the study.

**CONCLUSIONS:**

In these male and female subjects with Fabry disease, the long-term use of migalastat HCl appeared to be generally safe and well-tolerated. The dose regimens of 250 mg and 500 mg 3 days on, 4 days off were associated with higher frequency of treatment-related AEs compared to the 150 mg QOD regimen.

Trends noted in the PD evaluations (increased α-Gal A activity, decline in urine GL-3) were generally greatest at the 150 mg QOD dose, without further benefit at either the 250 mg or 500 mg 3 days on, 4 days off regimens. There was little change in annualized eGFR during the study.

The 150 mg QOD dose regimen had the best benefit/risk ratio based on safety and PD data in this study, and therefore this dose was selected for further evaluation in controlled Phase 3 studies.

**Date of the report:** 19 December 2014