2. SYNOPSIS

Name of Sponsor/Company: Amicus Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page: *(For National Authority Use Only)*
Name of Finished Product: AT1001	
Name of Active Ingredient: Migalastat Hydrochloride	
Title of Study: A Phase 2, Open-label, Single Dose Level, 24-Week Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of AT1001 in Patients with Fabry Disease	
Protocol Number: FAB-CL-203	
Investigators: Perry Elliot, MD (Chief Investigator); Philip Lee, MD; Atul Mehta, MD & Derralynn Hughes, MD; Dominique Germain, MD; Daniel Bichet, MD	
Study Centers: (1) Elliott: The Heart Hospital, London, United Kingdom (UK) (2) Lee: National Hospital for Neurology & Neurosurgery, London, UK (3) Mehta & Hughes: Royal Free Hospital, London, UK (4) Germain: Hôpital Europeen Georges Pompidou, Paris, France (5) Bichet: Université de Montréal, Hôpital du Sacré-Coeur de Montréal, Montréal (Québec), Canada	
Publications (references): None as of the date of this report	
Study Period (years): Date first patient enrolled: 09 May 2006 Date last patient completed: 12 March 2008	**Phase of Development:** 2
Objectives: **Primary:** • To evaluate the safety and tolerability of oral AT1001 in subjects with Fabry disease **Secondary:** • To evaluate the pharmacodynamic (PD) effect on plasma (leukocytes), urine, skin, and renal tissue before and after treatment with oral doses of AT1001 in subjects with Fabry disease An additional objective was to provide a preliminary assessment of functional parameters in subjects with Fabry disease (including cardiac, renal, and central nervous system [CNS] function).	

Methodology:

This was a Phase 2, multicenter, open-label trial in male subjects with Fabry disease. For an individual subject, the minimum study duration was approximately 28 weeks, including a 4-week screening period and 24 total weeks of treatment (150 mg AT1001 once every other day). Subjects who did not enter an optional treatment extension were to attend a follow-up visit at Week 26. For subjects who entered the optional treatment extension, the maximum duration was approximately 48 weeks.

There were two visits during the one month screening period. Following a baseline visit on Day 1, there were visits at Weeks 4 (Visit 1), 8 (Visit 2), 12 (Visit 3), 16 (Visit 4), 20 (Visit 5), and 24 (Visit 6) during the 24-week treatment phase. An additional visit occurred at Week 26 (Visit 7/follow up). During the 24 week treatment extension, there were visits at Weeks 36 (Visit 8) and 48 (Visit 9).

Number of Subjects (planned and analyzed):

Enrollment of up to eight male subjects was planned. A total of five subjects were enrolled. All subjects completed both the treatment and the treatment extension phases and were included in both the safety and pharmacodynamic analysis sets.

Eligibility Criteria:

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

1. Males between 18 and 65 years of age (inclusive)
2. Hemizygous for Fabry disease
3. Had a confirmed diagnosis of Fabry disease with a documented missense gene mutation (individual or familial)
4. Had enzyme activity responsive to AT1001 as defined by meeting one of the following criteria:
    - If residual α-galactosidase A (α-Gal A) activity in lymphocytes was less than 1% of normal, then α-Gal A activity after incubation with AT1001 was required to be at least 2% of normal
    - If residual α-Gal A activity in lymphocytes was between 1% of normal and less than 3% of normal, then α-Gal A activity after incubation with AT1001 was required to be at least 2 times the baseline level
    - If residual α-Gal A activity in lymphocytes was between 3% of normal and less than 10% of normal, then α-Gal A activity after incubation with AT1001 was required to be at least 3% of normal higher than the baseline level
    - If residual α-Gal A activity in lymphocytes was 10% of normal or more, then α-Gal A activity after incubation with AT1001 was required to be at least 1.3 times the baseline level
5. Had end organ dysfunction, even minimal, demonstrated by either abnormal ECG or left ventricular hypertrophy documented by echocardiogram or previous cardiac biopsy, or renal insufficiency documented by common clinical assessments such as creatinine and glomerular filtration rate (GFR), or by renal biopsy

6. Were previously untreated by enzyme replacement therapy (ERT) or substrate depletion for Fabry disease or was able to stop ERT for at least 30 weeks or up to 13 months safely (in the judgment of the investigator, it must have been considered safe for the subject to stop therapy for the duration of the study). Was willing to undergo two kidney and three skin biopsies
7. Agreed to be sexually abstinent or use a condom with spermicide when engaging in sexual activity during the course of the study and for a period of 30 days after completion of the study
8. Willing and able to sign an informed consent form

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

1. History of significant disease other than Fabry disease that would impair the subject's ability to participate in the study. For example:
   - End-stage renal disease
   - Heart disease (per clinical history, documented event, testing, or Class III/IV according to the New York Heart Association classification)
   - Current diagnosis of cancer, except for basal cell carcinoma of the skin
   - Diabetes (unless HbA1c was less than or equal to 8)
   - Neurological disease
9. History of organ transplant
10. Serum creatinine greater than 176 mmol/dL on Day -2
11. Screening 12-lead ECG demonstrating QTc > 450 msec before dosing
12. Pacemaker or other contraindication for MRI scanning
13. Taking a medication prohibited by the protocol: agalsidase beta (Fabrazyme®), agalsidase alfa (Replagal™), miglitol (Glyset®), miglustat (Zavesca®), or any experimental therapy for any indication
14. Participated in a clinical trial in the last 30 days
15. Any other condition which, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results

Test Product, dose and mode of administration, batch number:

AT1001 capsules, 25 mg AT1001 per capsule, were administered orally.

The enrolled subjects took 150 mg (6 capsules) once every other day for up to 24 weeks (48 weeks if the subject continued into extension portion of study).

The lot numbers for the AT1001 supplies used in this study were 8901.001, 8901.002, and 8901.003.

Duration of Treatment:

For an individual subject, the minimum planned treatment duration was 24 weeks. With the optional treatment extension, the maximum treatment duration was 48 weeks (24 weeks during the initial treatment phase; 24 weeks during the optional treatment extension).

Reference Therapy, dose and mode of administration, batch number: Not applicable.

Criteria for Evaluation:

Safety:

The primary measures to evaluate the safety and tolerability of AT1001 were adverse events (AEs), clinical laboratory measurements (hematology, serum chemistry, and urinalysis), vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), physical examination, and use of concomitant medications.

Pharmacodynamic:

The PD measures included evaluation of the effect of AT1001 on α-Gal A activity in leukocytes, skin, and kidney, and globotriaosylceramide (GL-3) levels in plasma, urine, skin, and kidney. Functional PD measures included cardiac function (24-hour Holter monitor ECG, cardiac MRI, and brain natriuretic factor), renal function (serum and urine creatinine and creatinine clearance), and central nervous system function.

Statistical Methods:

No formal inferential hypothesis testing was performed. Statistical analyses and reporting were performed using Windows SAS version 8.2 or higher. All subjects who received at least one dose of study drug were included in the safety analysis set. All subjects who received study drug and had at least one post-baseline PD parameter recorded were included in the PD analysis set. Safety data was summarized by treatment and time point and is listed by subject. Safety parameters were summarized using descriptive statistics. Baseline was defined as the last non-missing value before the first dose of study drug for all parameters. Continuous variables were summarized by presenting the number of subjects, mean, median, standard deviation, and range. Change from baseline was presented for continuous variables. Categorical variables were summarized by presenting the frequency and percentage of subjects in each category. AEs were summarized by system organ class (SOC) and preferred term. The number of subjects reporting each AE and the number of AEs reported. Shift analysis tables summarizing changes from normal to abnormal ranges were provided for serum chemistry, hematology, and urinalysis.

SUMMARY:

The five enrolled subjects, after meeting all eligibility criteria, entered a 24-week treatment phase (150 mg AT1001 once every other day). No subject prematurely withdrew from the study. All five subjects completed 24 weeks of treatment and then entered the optional extension phase and completed 48 total weeks of treatment.

All subjects were adult males with Fabry disease. The average age was 41.6 years (range: 31 to 55 years). At the beginning of the study, the average duration of Fabry disease since diagnosis was 3.7 years (range: 0.6 to 6.7 years). All subjects exhibited signs or symptoms of Fabry disease at baseline. The most common of these were angiokeratomas (5 subjects), cold/heat intolerance (5 subjects), reduced sweating (5 subjects), ringing in ears (4 subjects), and pain in hands and feet (4 subjects).

Safety Results

There were no deaths in the study. There were a total of three SAEs in two subjects; all three SAEs occurred during cardiac biopsy procedures during screening, prior to treatment with AT1001. With protocol amendment 4, all cardiac biopsies were removed from the study. There

were no SAEs during or after treatment with AT1001, including during the optional treatment extension. None of the subjects had an interruption or reduction in study drug dosing due to an AE, and no subject discontinued study drug due to an AE.

All subjects reported at least one treatment-emergent adverse event (TEAE). A total of 20 TEAEs were reported. Of these 20, 16 were assessed as related to treatment (none were reported as definite or probable, 6 were reported as possible, and 10 were reported as unlikely related to treatment). All of the TEAEs were mild or moderate. The only treatment-related TEAE reported by more than one subject was mild proteinuria (two subjects). In the Fabry disease history for both of these subjects, protein in the urine was reported as a daily occurrence.

For the clinical laboratory evaluations, most shifts were from abnormal at baseline to normal. The one shift considered clinically significant was for proteinuria and haematuria in one subject. This subject had a medical history including proteinuria and, during the review of Fabry disease symptoms at the screening visit, reported protein in urine as a daily occurrence. For vital signs, there were no changes that met the pre-set criteria to be considered potentially clinically significant (PCS). Although ECG abnormalities were seen during treatment, three of five subjects had abnormalities at screening and changes reported at Visit 9 were assessed as not clinically significant. The abnormalities in cardiac, renal, or CNS function present at the beginning of the study typically either remained stable or resolved by the end of study.

In these subjects, no trends were detected in clinical laboratory findings or safety assessments that contraindicate further investigation of AT1001 as a treatment for Fabry disease.

Pharmacodynamic Results:

As measured in Study FAB-CL-102, the average leukocyte α-Gal A activity in healthy adult male volunteers is 22 ± 5.7 nmol 4-MU nmol/hr/mg protein (mean ± standard deviation). In this study, leukocyte α-Gal A activity at baseline ranged from approximately 0.23% to 15.5% of normal. AT1001 increased leukocyte α-Gal A activity in all subjects through 48 weeks of treatment. At Week 48, leukocyte α-Gal A activity was increased 1.7 to 17-fold over each subject's individual baseline. Increases in α-Gal A activity were also seen in skin tissue in all five subjects and in kidney tissue in four of the five subjects. For urine GL-3, baseline levels were elevated from 3.5 to 79-fold over the average level in healthy male volunteers. During AT1001 treatment, no consistent trends were identified from baseline to the subsequent time points in GL-3 measurements in urine, plasma, and skin tissue samples. Even within individual subjects, both decreases and increases were observed. For the cardiac and renal function assessments, the abnormalities present at baseline remained relatively stable after 48 weeks of AT1001 treatment and thus did not exhibit the further declines in function that would be expected over this period of time in patients with Fabry disease.

CONCLUSION:

The primary objective of the study was to evaluate the safety and tolerability of AT1001. The secondary objectives were to gain information about the effects of AT1001 on PD outcomes. Overall, treatment with AT1001 at 150 mg once every other day for 48 weeks was generally safe and well tolerated. There were no safety results that contraindicate further investigation of AT1001 as a treatment for patients with Fabry disease.

The PD outcome measures in this study included a range of approaches, from the biochemical (α-Gal A activity and GL-3 levels) to the functional (including cardiac and renal). Baseline leukocyte α-Gal A activity levels were substantially lower in male subjects with Fabry disease relative to activity levels previously measured in healthy volunteers (0.23% to 15.5% of normal). AT1001 increased leukocyte α-Gal A activity in all subjects through 48 weeks of treatment. Further, increases in α-Gal A activity were seen in skin in all subjects and in kidney tissue in most subjects. No consistent trends were identified from baseline to the subsequent time points in GL-3 measurements in urine, plasma, and skin tissue samples during treatment with AT1001. For the cardiac and renal function assessments, the abnormalities present at baseline remained relatively stable after 48 weeks of AT1001 treatment and thus did not exhibit the further declines in function that would be expected over this period of time in patients with Fabry disease.

Date of Report: 22 October 2010