2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Amicus Therapeutics, Inc.</td><td rowspan="3">Individual Study Table
Referring to Part of the Dossier

Volume:
Page: (For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
AT2101</td></tr>
<tr><td>Name of Active Ingredient:
isofagomine tartrate</td></tr>
<tr><td colspan="2">Title of Study: A Randomized, Open-Label Study to Assess the Safety and Tolerability of AT2101 in Treatment-Naïve Adult Patients with Type 1 Gaucher Disease</td></tr>
<tr><td colspan="2">Protocol Number: GAU-CL-202</td></tr>
<tr><td colspan="2">Investigators: David Finegold, MD; Nancy Leslie, MD; Paul Fernhoff, MD; Neal Weinreb, MD; Marsha Browning, MD; Timothy Cox, MD, PhD; Ian Cohen, MB, ChB; Hanna Rosenbaum, MD; Atul Mehta, MD; Majed Dasouki, MD; Barry Rosenbloom, MD; Thomas Loew, MD; Rene Heitner, MBBCh</td></tr>
<tr><td colspan="2">Study centers:
1. Finegold: Pittsburgh, Pennsylvania, United States
2. Leslie: Cincinnati, Ohio, United States
3. Fernhoff: Decatur, Georgia, United States
4. Weinreb: Coral Springs, Florida, United States
5. Browning: Boston, Massachusetts, United States
6. Cox: Cambridge, United Kingdom
7. Cohen: Tel Aviv, Israel
8. Rosenbaum: Haifa, Israel
9. Mehta: London, United Kingdom
10. Dasouki: Kansas City, Kansas, United States
11. Rosenbloom: Beverly Hills, California, United States
12. Loew: Iowa City, Iowa, United States
13. Heitner: Morningside, South Africa</td></tr>
<tr><td colspan="2">Publications (references): none as of the date of this report</td></tr>
<tr><td>Study period (years):
Date first patient enrolled: 11 June 2008
Date last patient completed: 20 August 2009</td><td>Phase of development: 2</td></tr>
</table>

Objectives:

Primary:

- To evaluate the safety and tolerability of 2 dose regimens of orally administered AT2101 in treatment-naïve patients with type 1 Gaucher disease

Secondary:

- To assess pharmacodynamic (PD) effects of 2 dose regimens of orally administered AT2101 in treatment-naïve patients with type 1 Gaucher disease

Methodology:

The study was comprised of 3 parts as follows

- Screening (Day -21 to -1; evaluation of eligibility)
- Treatment (Day 1 to Day 169; approximately 24 weeks in duration)
  - Treatment Group 1: For week 1 of treatment, subjects took 225 mg AT2101 once daily for 7 consecutive days followed by no study drug for 7 consecutive days. For the next 22 weeks of treatment, subjects followed a dosing schedule of 225 mg AT2101 for 3 consecutive days followed by no AT2101 for 4 consecutive days (3-days-on/ 4-days-off).
  - Treatment Group 2: Subjects took 225 mg AT2101 once daily for 7 consecutive days followed by no study medication for 7 consecutive days (7-days-on/ 7-days-off). This dosing schedule was followed for 24 weeks.
- Follow-up visit (Day 183; end-of-study)

During screening (Day -21 to Day -1; Visit 1), subjects 18 to 74 years of age were screened and considered for randomization if they met all eligibility criteria and provided written informed consent. On Day 1 (Visit 2), subjects meeting all eligibility criteria were randomized in a 1:1 ratio to either treatment group 1 (3-days-on/ 4-days-off) or treatment group 2 (7-days-on/ 7-days-off).

Beginning on Day 1, all subjects were administered 225 mg of AT2101, orally, once daily for the first 7 days of dosing. All subjects returned to the clinic on Day 8 (Visit 3) so that changes in β-glucocerebrosidase (GCase) levels and other relevant parameters could be assessed in all subjects after following an identical initial treatment regimen. During treatment, clinic visits were scheduled for Days 1, 8, 29, 85, 127, and 169. During these visits safety evaluations were made and samples were collected for safety and pharmacodynamic assessments. A follow-up visit/ end-of-study visit occurred on Day 183; safety and PD assessments were performed.

A Data Safety Monitoring Board (DSMB) reviewed safety data throughout the trial. Safety evaluations including adverse events (AEs), concomitant medication usage, clinical chemistry, hematology, and urinalysis testing, and pregnancy testing (for applicable females only), were assessed at all scheduled visits. Electrocardiograms (ECGs) and vital signs were measured at screening and on Days 1, 8, 29, 85, and Day 169. Height was recorded at screening and weight was recorded at screening and Day 169. Physical examinations and brief neurological examinations were performed at screening, Day 1, and Day 169. A thorough ophthalmologic examination was done at screening and Day 169 (as this was added as part of protocol Amendment 5, subjects enrolled under Amendment 4 of the protocol did not have all of these

assessments).

Imaging assessments included an evaluation of liver and spleen volumes by magnetic resonance imaging (MRI) of the abdomen and femoral bones. These were scheduled at screening, Day 85, and Day 169. The femoral bones and the lumbar spine were assessed using dual energy X-ray absorptiometry (DEXA) and radiographs (x-ray) at screening and Day 169. Subject-reported outcomes were assessed using the 36-item Short Form health survey, version 2 (SF-37v2), on Day 1 and Day 169.

Number of patients (planned and analyzed):

Enrollment of up to 16 male and female subjects was planned. The safety population and the PD population both included all 11 subjects randomized to treatment group 1 and all 8 subjects randomized to treatment group 2.

Eligibility Criteria:

Each subject had to meet all of the following criteria to be eligible for the study:

1. Confirmed diagnosis of type 1 GD with a known genotype and documented missense gene mutation in at least one of the two mutated *GBA* alleles
2. Clinically stable
3. Treatment-naïve to enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) or had not received ERT or SRT in the 12 months before screening
4. Willing to not initiate ERT or SRT during study participation
5. Male or female subjects, 18 to 74 years old, inclusive
6. At the screening period (Day -21 to -1), subjects must have met at least 2 of the following criteria:
    - Platelet count less than or equal to 150,000 per microliter (150×10^9 per liter)
    - Hemoglobin less than or equal to 12 g/dL (for females) or less than or equal to 13 g/dL (for males)
    - Liver volume greater than or equal to 1.25 multiples of normal
    - Spleen volume greater than or equal to 2 multiples of normal
7. All subjects of reproductive potential were required to practice an acceptable method of contraception (as defined in Section 5.5 of the protocol)
8. Provide written informed consent to participate in the study

Subjects who met any of the following were excluded from the study:

1. Other clinically significant disease, severe complications from GD, or serious intercurrent illness that precluded participation in the study in the opinion of the investigator
2. During the screening period, any clinically significant findings, based on physical and brief neurological examination, medical history review, laboratory assessment, vital sign assessment, and/or other significant finding which would have compromised the safety

of the subject, or precluded the subject from completing the study as deemed by the investigator

3. Partial or total splenectomy
4. Documentation of moderate or severe pulmonary hypertension, defined as pulmonary arterial pressure less than 35 mmHg, or significant Gaucher-related lung disease
5. History of allergy or sensitivity to the study drug or any excipients, including any prior serious allergic reaction to iminosugars (e.g., miglustat)
6. Pacemaker or other contraindication for MRI scanning
7. Screening period visit (Day -21 to -1) or Day 1 12-lead ECG demonstrating a QTc less than 450 msec for males or less than 470 msec for females
8. Pregnant or breastfeeding
9. Current/recent drug or alcohol abuse
10. Treatment with any investigational product in the last 90 days before study entry
11. Treatment in the previous 90 days with any drug known to have a well-defined potential for toxicity to a major organ
12. Presence or sequelae of gastrointestinal, liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs
13. Subject was otherwise unsuitable for the study in the opinion of the investigator

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

AT2101 capsules, 25 mg AT2101 per capsule, were administered orally.

Subjects took 255 mg once daily.

The lot number of the AT2101 used in this study was 8905.001.

Duration of treatment:

For an individual subject, the approximate treatment duration was 24 weeks.

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 AT2101 were AEs, clinical laboratory measurements (hematology, serum chemistry, and urinalysis), vital signs (blood pressure, heart rate, body temperature, and respiratory rate), ECGs, physical examination, neurological examination, and ophthalmologic examination, and changes in concomitant medications.

Pharmacodynamic Parameters:

The PD measures included β-glucocerebrosidase (GCase) levels in white blood cells (WBC), Glucocerebroside (GlcCer) levels in plasma and WBC, α-synuclein levels in plasma, bone-specific alkaline phosphatase (BAP) activity in plasma, tartrate-resistant acid phosphatase 5b (TRACP 5b) activity in plasma. Plasma markers of GD included: chitotriosidase activity; pulmonary and activation regulated chemokine (PARC) concentration; plasma inflammatory markers, including interleukin 8 (IL-8), interleukin 17 (IL-17), vascular endothelial growth factor (VEGF); change from baseline in liver volume and spleen volume; change from baseline in MRI findings of the left and right femoral bones; change from baseline in hemoglobin concentration, hematocrit, and platelet count; change from baseline in bone mineral density of left and right femoral bones and the lumbar spine; change from baseline in radiographic findings of the femoral bones and the lumbar spine; and change from baseline in physical and mental health status, as measured by the SF-36v2.

Statistical methods:

All inferential hypothesis testing was performed using a 5% significance level. Statistical analyses and reporting were performed using Windows SAS® Version 8.2 or higher. Subjects were randomly assigned to the two treatment groups in a 1:1 ratio across all centers. The randomization was stratified by GD genotype (N370S homozygous, N370S heterozygous and "other"). All subjects who received at least one dose of AT2101 were included in the safety population. The PD population was defined as subjects who were included in the safety population and had a baseline and at least one post-baseline PD measurement.

By-subject data listings are provided for all safety and PD outcome measure. Baseline was defined as the last non-missing value before the first dose of study drug. Safety and PD parameters were summarized by treatment group and by study visit; PD parameters were also summarized by genotype.

Continuous variables were summarized by presenting the number of subjects, mean, median, standard deviation, and range. 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. Shift analysis tables summarizing changes from normal to abnormal ranges were provided for the following outcomes measures: physical examinations; clinical laboratory data (hematology, serum chemistry, urinalysis, and coagulation); and radiographic findings of the femoral bones. Potentially clinically significant vital signs and ECG results were summarized at each time point.

SUMMARY:

A total of 19 subjects were randomized in the study and are included in the safety and PD populations. Eleven subjects were randomized to treatment group 1, and eight subjects were randomized to treatment group 2.

The mean age of subjects was 43.0 years (range: 23-69 years) in treatment group 1, and 39.1 years (range 17-64 years) in treatment group 2. Most subjects were males (7 of 11 subjects, 63%, in treatment group 1; 8 of 8 subjects, 100%, in treatment group 2) and most subjects were white (10 of 11 subjects, 90.9%, in treatment group 1; 8 of 8, 100%, in treatment group 2).

The most common GD genotype in both treatment groups was N370S heterozygous (5 of 11 subjects in treatment group 1; 4 of 8 in treatment group 2), the next most common genotype was N370S homozygous. Three subjects (3 of 11; 27%) in treatment group 1 had a known family history of GD. In treatment group 2, 4 subjects (4 of 8; 50%) had a known family history of GD.

Safety Results:

The safety profile of AT2101 was similar between treatment group 1 and treatment group 2. No subjects died or experienced a serious adverse event (SAE) during the course of the study. One subject in treatment group 1(1 of 11, 9.1%) discontinued due to an AE of bilateral conjunctivitis after about 14 weeks of treatment. All other subjects completed the study.

The incidence of all causality treatment-emergent adverse events (TEAEs) was similar between the two treatment groups. TEAEs were experienced by ten subjects in treatment group 1 (10 of 11 subjects, 90.9%) and eight subjects in treatment group 2 (8 of 8 subjects, 100%).

The most commonly reported treatment-related TEAEs were eye disorders. In treatment group 1, 6 of 11 subjects, (54.5%) experienced a treatment-related TEAE in this SOC. These events were: lacrimation increased (3 events); and abnormal sensation in eye, conjunctivitis, dry eye, eye inflammation, and eye irritation (1 event each). In treatment group 2, 4 of 8 subjects, (50%) experienced a treatment-related TEAE in the SOC of eye disorders. These events were: dry eye (2 events); abnormal sensation in eye, chalazion, conjunctival irritation, eye irritation, and eye pruritus (1 event each). The next most commonly reported treatment-related TEAEs, by SOC, were skin and subcutaneous tissue disorders for treatment group 1 (in 4 of 11 subjects, 36.4%) and gastrointestinal and skin and subcutaneous tissue disorders for treatment group 2 (each in 2 of 8 subjects, 25%). Most treatment-related TEAEs in both treatment groups were mild in severity. One subject, in treatment group 1, experienced a severe AE of urticaria which was considered related to study treatment. There was one additional severe AE (cholelithiasis) in treatment group 1; this event was not considered treatment-related. None of the events in the SOC of eye disorders were severe.

In response to the incidence of AEs in the SOC of eye disorders, the DSMB recommended a thorough ophthalmological examination for all subjects at screening and on Day 169; this was introduced to the protocol in Amendment 5. In addition to the screening and Day 169 examinations, any subject experiencing an AE in the SOC of eye disorders was to have an ophthalmologic examination at the time of the event.

There were no clinically relevant findings on laboratory parameters (hematology, including coagulation, chemistry or urinalysis assessments), ECGs, vital signs, or physical examinations, that contraindicate further investigation of AT2101.

The DSMB reviewed all safety data (with a particular focus on AEs of eye symptoms) and concluded that there were no safety concerns with AT2101, including concern with eye events.

Pharmacodynamic Results:

In response to the 24-week AT2101 treatment period, levels of GCase in WBCs increased. The mean percent change was approximately 59% for both treatment groups. Upon cessation of AT2101, levels of GCase returned to near baseline levels for both treatment groups. The subject (subject 07-01) who had the greatest increase in GCase activity also had a reduction in GlcCer levels in both WBC and plasma. These changes correlated with improvements in this subject's

clinical parameters of GD. He had reductions in his spleen volume, liver volume, chitotriosidase levels, and PARC levels.

For both treatment groups, mean GlcCer levels in WBCs remained essentially unchanged after approximately 24 weeks of AT2101 treatment, whereas levels in plasma were higher after treatment. For both treatment groups, there were no meaningful changes in BAP activity levels, chitotriosidase levels, PARC concentration, or in any of the plasma inflammatory markers after treatment with AT2101. The majority of the readings for α-synuclein were below the level of detection and thus these results were inconclusive.

The majority of subjects (7 of 11) in treatment group 1 and five subjects in treatment group 2 (5 of 8) had hemoglobin concentrations within the normal range at baseline. In both treatment groups, hemoglobin concentration, hematocrit, and platelet count remained unchanged in response to AT2101.

Subjects in treatment group 1 maintained their spleen and liver volumes over the course of the study while subjects in treatment group 2 experienced an increase in liver and spleen volumes compared with baseline.

There were no clinically meaningful changes in the bone mineral density of the femoral bones or the lumbar spine as measured by MRI. Radiographic findings appeared to be similarly unaltered by treatment with AT2101. SF-36v2 results showed no meaningful changes over the course of the study in either the individual domains or the summary scores.

Subject 07-01, in treatment group 1, had the largest increase in GCase activity of any subject in the study. On Day 8, after 7 days of AT2101 treatment, GCase activity levels were 4-fold higher than baseline (40 pmol/min/mg at baseline, 164 pmol/min/mg on Day 8). On Day 169, GCase activity levels were 2-fold higher than baseline (93 pmol/min/mg). This subject also had a reduction in GlcCer levels in both WBC and plasma. He had a reduction in his spleen volume of approximately 23%, as well as reductions in his liver volume, chitotriosidase levels, and PARC levels.

CONCLUSION:

This randomized, multiple-dose, multiple-regimen, open-label study was designed to evaluate the safety and tolerability of orally administered AT2101 in adult subjects with treatment-naïve type 1 GD. Both treatment groups received AT2101 at a dose of 225 mg.

The primary objective of the study was to evaluate the safety and tolerability of AT2101. The secondary objectives were to assess the PD effects of AT2101. No subjects died and no subjects experienced an SAE during the course of the study. One (1 of 11, 9.1%) subject in treatment group 1 discontinued due to an AE of bilateral conjunctivitis after about 14 weeks of treatment. All other subjects completed the study.

The incidence and types of treatment-related TEAEs were similar for both treatment groups. The most commonly reported treatment-related TEAEs were eye disorders. Most treatment-related TEAEs in both treatment groups were mild in severity. One subject, in treatment group 1, experienced a severe AE of urticaria which was considered related to study treatment. There was one additional severe AE an event of cholelithiasis which was not considered treatment-related. There were no clinically relevant findings on laboratory parameters (hematology, including coagulation; chemistry; urinalysis), ECGs, vital signs, or physical examinations that

contraindicate further investigation of AT2101. The DSMB reviewed all safety data (with a particular focus on AEs of eye symptoms) and concluded that there were no safety concerns with AT2101, including concern with eye events. Treatment with AT2101 was safe and generally well tolerated.

On Day 169, in both AT2101 treatment groups, there was an approximate increase of 59% in GCase activity levels compared with baseline. The increase in enzyme activity did not translate to a reduction in GlcCer levels in plasma or WBCs for either treatment group. Overall, after either AT2101 treatment regimen, there were no meaningful changes to BAP activity levels, chitotriosidase levels, PARC concentration, or any of the plasma inflammatory markers. The majority of the readings for α-synuclein were below the level of detection and thus these results were inconclusive. In both treatment groups, hemoglobin concentration (which was normal at baseline), hematocrit, and platelet count remained unchanged in response to AT2101. Subjects in treatment group 1 maintained their spleen and liver volumes over the course of the study while subjects in treatment group 2 experienced an increase compared with baseline in liver and spleen volumes. There were no clinically meaningful changes in the bone mineral density, or radiographic findings of either the femoral bones or the lumbar spine.

In summary, with the exception of liver and spleen volumes, there were no significant differences in the clinical safety profile of AT2101 administered in either a 3 days on/4-days-off cycle (treatment group 1) or a 7-days-on/7-days-off cycle (treatment group 2).

The subject with the greatest increase in GCase activity levels was subject 07-01. This subject also had a decrease in spleen, and liver volumes as well as a reduction in chitotriosidase activity and PARC levels. The results from subject 07-01 demonstrate that AT2101 can result in clinical benefit for patients with type-1 GD.

Date of the report: 09 August 2010