2. SYNOPSIS

Name of Sponsor/Company: Amicus Therapeutics, Inc. **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Afegostat tartrate	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:

An Open-Label, Multicenter, Long-term Extension Study to Assess the Safety, Efficacy and Pharmacodynamics of AT2101 in Adult Patients with Type 1 Gaucher Disease

Investigators:

[redacted]

Study Sites[a]:

4. [redacted]
7. [redacted]s
9. [redacted]
14. [redacted]

[a] Study site numbers match the site numbers from GAU-CL-202. Not all sites from GAU-CL-202 participated in GAU-CL-202X. Listed are the study sites that enrolled subjects in GAU-CL-202X.

Publications (reference): None as of the date of this report

Studied period (years):	**Phase of development:** 2
Date first patient enrolled: 11 May 2009 Date last patient completed: 01 May 2012	

Objectives:

Primary:

- The primary objective of the study was to evaluate the long-term safety of orally administered AT2101 in adult patients with type 1 Gaucher disease (GD).

Secondary:

- The secondary objective of the study was to assess the long-term efficacy of orally administered AT2101 in adult patients with type 1 GD.

Tertiary:

- The tertiary objective of the study was to assess the pharmacodynamics (PD) of orally administered AT2101 in adult patients with type 1 GD.

Methodology:

The protocol for this study is provided in Appendix 16.1.1. This was a long-term, multicenter study designed to evaluate subjects with type 1 GD who completed Study GAU-CL-202.

This study was designed include a 1 to 3 day screening period, a 30-month treatment period (Visits 2 through 11), and a 6-month follow-up period (Follow-up Visits 1, 2, and 3). Subjects received 225 mg AT2101, administered orally, and remained in the same (one of two) treatment regimen that they were randomized to in Study GAU-CL-202. One treatment regimen was AT2101 for three consecutive days, followed by no AT2101 for four consecutive days (3-on/4-off); the other possible treatment regimen was AT2101 for seven consecutive days followed by no AT2101 for seven days (7-on/7-off).

The Schedules of Assessments for this study are included in Appendix 16.1.1. The screening visit (Visit 1) occurred from Day 1 to 3, and contained the following assessments and procedures: informed consent, eligibility criteria, prior and concomitant medications, medical history, physical, brief neurological, and ophthalmologic examinations, vital signs (blood pressure, heart rate, body temperature, respiratory rate) and body weight, clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis), PD measures (β-glucocerebrosidase [GCase], glucocerebroside [GlcCer], chitositriosidase [CHITO], and pulmonary and activation regulated chemokine [PARC] concentration), electrocardiogram (ECG), magnetic resonance imaging (MRI) measurement of spleen and liver volume, and 36-Item Short-Form Health Survey (SF-36). Refer to Appendix 16.1.2 for a sample case report form and to 16.1.10 for laboratory information and manuals.

During the treatment period (Visits 2 through 11), visits occurred once every 3 months, ± 7 days. The treatment visits included the following procedures, unless otherwise indicated: physical and brief neurological examination (Visits 5, 9, and 11), vital signs and body weight, clinical laboratory tests, PD measures, ECG, MRI measurement of spleen and liver volume, ophthalmologic examination (Visits 9 and 11), SF-36, concomitant medications, and adverse events (AEs). Visit 11/Early Termination (ET) included all treatment visit assessments.

The follow-up period contained three visits, 3 months apart, with the first visit 1 month ± 1 day after Visit 11/ET. The following procedures were to be completed at all follow-up visits: vital signs and body weight, clinical laboratory tests, PD measures, concomitant medications, and AEs. The SF-36 was to be completed at Follow-up Visit 2 and 3 and MRI measurement of spleen and liver volume was to be completed at Follow-up Visit 3.

There were five amendments to the original protocol. Amendments 2 and 4 altered subject treatment regimens. Amendments 2, 4, and 5 altered visit procedures and/or assessments. All amendments altered the treatment period schedule, follow-up period schedule, or the duration of these periods. Summaries of the changes in each amendment can be found in Appendix 16.1.1. Amendment 2 removed the 7-on/7-off group and added an alternative pattern of 3-on/4-off dosing consisting of AT2101 on Monday, Wednesday, and Friday, with no AT2101 on Tuesday, Thursday, Saturday, and Sunday. Once Amendment 2 was implemented at a site,

any remaining active subjects assigned to the 7-on/7-off regimen were switched to one of the 3-on/4-off regimens. Also with this amendment, the option for active subjects on the initial 3-on/4-off regimen to switch to the MWF 3-on/4-off regimen was made available. Amendment 4 removed the 3 consecutive days of AT2101 followed by 4 consecutive days with no AT2101, such that any subjects still active on that regimen would have been switched to MWF 3-on/4-off.

Amendments 2 and 5 contained changes to the following assessments and procedures. Magnetic resonance imaging of bilateral femoral bones and dual energy X-ray absorptiometry (DEXA) of bilateral femoral bones and the lumbar spine, in those who had DEXA procedures in Study GAU-CL-202, were to be performed at Visits 1, 5, and 11/ET. Amendment 2 removed these procedures, as well as changing α-synuclein levels in plasma from a tertiary PD measure to an exploratory measure. Amendment 2 also increased the frequency of SF-36 administration and MRI measurements of liver and spleen volume from annually to each treatment visit. As per Amendment 5, subjects could have provided consent to undergo two optional procedures at Visit 11/ET. These included a punch skin biopsy and an additional blood collection for peripheral blood mononuclear cell (PBMC). The procedures were allowed to be completed at Visit 12 or Visit 13, if not done at Visit 11.

Number of patients (planned and analyzed):

Subjects who completed Study GAU-CL-202 were eligible to enroll. There were 18 subjects that completed GAU-CL-202, 10 subjects were planned for GAU-CL-202X; 8 enrolled.

Eligibility Criteria:

Each subject was required to meet all of the following eligibility criteria:

1. Male or female subjects, 18 years of age or older
2. Completed Study GAU-CL-202 with no significant protocol violations or safety concerns
3. Clinically stable
4. Has not received enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) in the past 12 months and is willing not to initiate ERT or SRT during study participation
5. All subjects of reproductive potential are required to practice an acceptable method of contraception as defined in the protocol
6. Provides written informed consent to participate in the study

Subjects were excluded from the study if they met any of the following criteria:

1. During the screening period (Visit 1), any clinically significant findings, based on physical and brief neurological examination, ophthalmologic examination, medical history review, laboratory assessment, vital sign assessment, and/or other significant finding which would compromise the safety of the subject, or preclude the subject from completing the study as deemed by the investigator
2. A clinically significant disease, severe complications from GD, or serious intercurrent illness that may preclude participation in the study, in the opinion of the investigator
3. History of allergy or sensitivity to the study drug or any excipients, including any prior serious allergic reaction to iminosugars (e.g., miglustat)
4. Pacemaker or other contraindication for MRI scanning

5. Pregnant or breast-feeding
6. Presence or sequelae of gastrointestinal, liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs
7. Subject is otherwise unsuitable for the study in the opinion of the investigator

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

The test product was 25 mg afegostat tartrate in hard gelatin capsules.

Subjects took 225 mg administered orally according to one of the following treatment regimens:

- 3-on/4-off
  - Three consecutive days on AT2101, four consecutive days off AT2101
  - AT2101 on Monday, Wednesday, and Friday, no AT2101 on Tuesday, Thursday, Saturday, and Sunday
- 7-on/7-off
  - Seven consecutive days on AT2101, Seven consecutive days off AT2101

The lot/batch numbers used in this study were 0177E and 8905.001.

Duration of treatment:

The approximate duration of treatment for an individual subject was designed to be 30 months.

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

Not applicable.

Criteria for evaluation:

Safety: Safety was evaluated by physical, brief neurological and ophthalmologic examinations, vital signs and body weight, clinical laboratory tests, ECG, changes in concomitant medications, and AEs.

Efficacy: Efficacy was evaluated by the change from baseline in hemoglobin levels, platelet count, liver volume, spleen volume, and functional health and well-being status as measured by the SF-36 scale.

PD: Pharmacodynamic assessments included GCase and GlcCer levels in WBCs, and plasma CHITO and PARC concentration.

Statistical methods:

The Statistical Analysis Plan (SAP; Appendix 16.1.9) describes the statistical methodology utilized for this study. Where analyses described in the protocol differ from the final approved SAP, the analysis procedures in the SAP were followed. However, although described in the protocol and SAP, measurement of GlcCer in plasma and calculation of Bazett- and Fridericia-corrected QT intervals (QTcB and QTcF) were not done.

All safety endpoints were summarized by descriptive statistics. Continuous variables were summarized by presenting the number of subjects (N), mean, median, standard deviation (SD),

and minimum and maximum value. Change from baseline was presented for continuous variables, as appropriate. For each change from baseline presented, the visit specific n is included (each baseline comparison was only to the baselines of subjects with data at the later time point). Categorical variables were summarized by presenting the frequency and percentage of subjects in each category. Subjects who received at least one dose of AT2101 in GAU-CL-202X are included in the safety population. All subjects with a baseline and one post-baseline PD measure were included in the PD population. Baseline values are defined as the values recorded during Visit 1 of the study (as per protocol, certain values could have been carried over from the last assessment in the lead-in study, GAU-CL-202).

By-subject listings of all data are provided. All tabular summaries and by-patient listings are provided in Appendix 16.2.

Summary of Results

This study was designed to evaluate the long-term safety, efficacy, and PD of AT2101 in adult subjects with type 1 GD.

Eight subjects were enrolled in this study; seven males and one female. All subjects met eligibility criteria (Listing 16.2.1.2). Age at consent ranged from 19 to 70 years for males; the female was 24 years. All subjects were white; three were Hispanic (Listing 16.2.3). Of the eight subjects, one completed the study, three were withdrawn due to "other" (noted as: failure to respond), three were lost to follow-up, and one withdrew consent (Listing 16.2.1.1). The three subjects withdrawn due to failure to respond all completed Visit 1, Visit 2, Early Termination (ET) Visit, and one follow-up visit. The three subjects lost to follow-up completed Visits 1, 2, and 3. The one subject who withdrew consent completed Visit 1 through Visit 4 and one follow-up visit. Subject [redacted], the one subject that completed this study, completed all treatment and follow-up visits except for Follow-up Visit 1.

Three subjects entered this study on the 7-on/7-off treatment regimen and five entered on 3-on/4-off (Listing 16.2.1.1). Two subjects were changed from the 3-on/4-off regimen to the MWF 3-on/4-off regimen and one was changed from 7-on/7-off to MWF 3-on/4-off. Three subjects were withdrawn from the study during the implementation of Amendment 2 and one withdrew consent; there was no indication of regimen change for these subjects (Listing 16.2.2.2). The subject that completed this study, [redacted], was switched from the 3-on/4-off regimen to the MWF 3-on/4-off regimen at Visit 5.

Five subjects were heterozygous for the N370S genotype; two were homozygous for the N370S genotype; and, one subject had a genotype (R296Q/E365K; Subject[redacted]) which is classified as "other" (see GAU-CL-202 Clinical Study Report, Listing 5). All subjects experienced symptoms related to Gaucher Disease (Listing 16.2.4.1). The most commonly effected system organ classes were blood/lymphatic (eight subjects), musculoskeletal (eight subjects), and gastrointestinal (five subjects). The most commonly reported symptoms were thrombocytopenia (seven subjects) and anemia (four subjects). Easy bruising, hepatomegaly, splenomegaly, bone pain, abdominal pain, nosebleeds, and leukopenia were reported for two or more subjects. Listing 16.2.4.2 provides non-Gaucher disease history.

Extent of exposure and treatment gaps for all subjects are provided in Listing 16.2.4.3. One subject had no treatment gap between the lead-in study and GAU-CL-202X, seven subjects

had treatment gaps of greater than 2 weeks; three of those subjects had gaps greater than 12 weeks. Gaps ranged from 36 days to 183 days. Exposure to AT2101 in GAU-CL-202X was calculated for all subjects in 6 month intervals. Four subjects had exposure of ≤ 6 months, 3 subjects had exposure > 6 months to ≤ 12 months, 0 subjects > 12 months to ≤ 18 months, and 1 subject had an exposure greater than 24 months (29.9 months). Subject [redacted] had a treatment gap of 127 days between the lead-in study, GAU-CL-202, and GAU-CL-202X. The duration of treatment (first dose to last dose) for Subject [redacted] in GAU-CL-202X was 29.9 months, with total study duration of 35.7 months. Summaries of exposure durations and treatment gaps for all subjects are presented in Table 14.1.4.

There were no deaths or serious AEs (SAEs) in this study (Listing 16.2.9.2).

Subject [redacted] is the only subject to have completed GAU-CL-202X. The subsequent text focuses on the on-treatment results for this subject. All on-treatment and follow-up data for all subjects in GAU-CL-202X are included in Appendix 16.2.

Safety Results:

During the course of this study, Subject [redacted] experienced 9 AEs (Listing 16.2.9.1). No AEs led to a change in dose or an interruption in study drug. Subject [redacted] did not experience any SAEs (Listing 16.2.9.2). Eight of the AEs (pulled flank muscle, twisted neck, herniated disc, sleep apnea, trace bilateral ankle edema, rosacea, small cancer on forearm, and actinic keratosis) were reported as unrelated to study drug. One report of irritated eyes was deemed possibly related to study drug by the investigator; the AE was mild in intensity and resolved within one month with concomitant medication use. One other AE, rosacea, required a concomitant medication.

Concomitant medications for Subject [redacted] were atenolol, aspirin, multivitamin, Benicar HCT, flaxseed, calcium, ibuprofen, Metamucil, losartan, prednisone, Refresh eye drops, Refresh severe gel, and Metrogel 1% (Listing 6.2.4.5.2).

Study drug compliance for Subject [redacted] was calculated as 87.5% over the course of the study (range of by-visit compliance: 89.7% to 99.4%; Listing 16.2.5.1).

There were no clinically significant central laboratory test results for Subject [redacted] (Listings 16.2.10.2, 16.2.10.4, and 16.2.10.5). Serum chemistry at Visit 1 showed elevated blood urea nitrogen (BUN) of 10.35 nmol/L. The level then remained above the upper limit of normal, except for a Visit 2 result of 6.78 nmol/L, until a decrease to 7.5 nmol/L at Visit 5. BUN levels were within the normal range for the remainder of the visits. Bicarbonate level was slightly above the upper range of normal at several visits throughout this study. It ranged from a low of 25 mEq/L to a high of 31 mEq/L. Hematology results at Visit 1 showed a prothrombin time of 13.1 seconds, which was indicated as above the normal range. Prothrombin time was within the normal range until a slight increase above the normal range to 13.4 seconds at Visit 7, then returned to within normal range for the rest of the study. Hematocrit, red blood cell (RBC; erythrocyte) count, and platelet count were reported as low at Visit 1 for this subject. Hematocrit was 38%, RBC count was 3.9 X10E6/UL, and platelet count was 90 X10E6/UL. At the last visit of the treatment period (Visit 11) hematocrit was measured at 40%, RBC count was 3.9 X10E6/UL, and platelet count had risen to 104 X10E6/UL. Local hematology results are in Listing 16.2.10.3.

The physical examination results are in Listing 16.2.8.2. Visit 1 results for body category of

eyes were reported as abnormal (mild injection medial portions both eyes). All other results, over all visits, were normal. Ophthalmologic examination results are in Listing 16.2.8.3. Visual inspection of the conjunctiva was abnormal at each visit. Bilateral pingueculae/pterygia were noted at all study visits. The Humphrey visual field test was abnormal at Visits 1 and 9. The Schirmer test of tear production was normal at all treatment visits.

Vital signs and body weight were recorded for Subject [redacted] at Visit 1 through Visit 11/ET (Listing 16.2.11). No vital signs abnormalities were reported. Visit 2 and Visit 3 showed increases in systolic and diastolic blood pressure from the Visit 1 result of 136/82 mmHg. Visit 2 was recorded as 140/90 mmHg and Visit 3 was recorded as 150/110 mmHg. This is consistent with this subject's medical history of hypertension.

Ten of the eleven ECGs performed on subject [redacted] were recorded as normal (Listing 16.2.12). The final ECG, at Visit 11, was indicated as abnormal, but not clinically significant. No description of this not-clinically-significant abnormality was provided or is apparent.

Efficacy Results:

Subject[redacted] received nine spleen and liver MRI measurements throughout the treatment period (Listing 16.2.7.1). The baseline spleen volume was 615 cm^3, the Visit 11 volume 477 cm^3; a decrease of 138 cm^3. There was no consistent increase or decline in volume, over more than two consecutive assessments, in the study period. Baseline liver volume was recorded as 2121 cm^3; Visit 11 volume was 2178 cm^3. The Visit 5 through Visit 9 measurements each showed a decline in volume from the previous measurement (2085 cm^3 to 1967 cm^3). At Visit 10 and Visit 11 liver volume was increased to 2067 cm^3 and 2178 cm^3, respectively.

Magnetic resonance imaging of bilateral femora was performed at Visit 1 for Subject [redacted] (Listing 16.2.7.2). Abnormal marrow signal involving the metaphyses of both femora was reported for this test. No additional MRIs of bilateral femurs were performed, as per Amendment 2.

Subject [redacted] received DEXA scans of the left femur and lumbar spine at Visit 1 (Listing 16.2.8.1). A DEXA scan of the right femur was not performed and is noted as a protocol deviation. The T-score for his left femur was -1.98 and the Z-score was -0.28. The T-score for the lumbar spine was -0.66 and the Z-score was -0.47. No other DEXA scans were performed, as per Amendment 2.

The SF-36 was administered to Subject [redacted] on Visit 1, Visits 4 through 11. Raw scores and norm-based scores are presented for the 8 domains of the SF-36 in Listing 16.2.6.

Pharmacodynamic Results:

Pharmacodynamic blood samples were taken for Subject [redacted] at all visits (Listing 16.2.13). During the treatment period, GCase levels in WBC increased from 32.2 pmol/min/mg at Visit 1 to 39.4 pmol/min/mg at Visit 11. The highest value of 52.25 pmol/min/mg was reported at Visit 8.

The measurement of GlcCer levels in WBCs for Subject [redacted] showed an initial result of 0.594 µg/mg at Visit 1 and a measurement of 0.561 µg/mg at Visit 11. Results ranged from 0.513 µg/mg min to 1.85 µg/mg max over all treatment visits.

The CHITO levels at Visit 1 for Subject [redacted] were recorded as 563.7 nmol/hr/mL. Levels remained below this level until Visit 5 at which a result of 581.8 nmol/hr/mL was reported. At

Visit 11, the CHITO level was recorded as 437.7 nmol/hr/mL; a decrease of 126 nmol/hr/mL from Visit 1. The PARC concentration for Subject [redacted] was 339.21 ng/mL at Visit 1, with a range from a minimum value of 193.20 ng/mL at Visit 11 to a maximum value of 423.07 ng/mL at Visit 4. Relative to Visit 1, PARC concentration showed a decrease of 146.01 ng/mL over the treatment period.

CONCLUSIONS:

This open-label, multicenter, long-term extension study was designed to assess the safety, efficacy, and PD of AT2101 in adult patients with type 1 GD. Subjects who had completed the lead-in study, GAU-CL-202, were eligible to enroll.

The primary objective of this study was to evaluate the long-term safety of AT2101. The secondary objective was to evaluate the long-term efficacy of AT2101. The tertiary objective was to evaluate the PD of AT2101.

Of the eight subjects enrolled, one completed (Subject [redacted]). There were no reports of clinically significant adverse events for this subject throughout the duration of this study.

Due to the early withdrawals of seven of the eight study subjects, there are no comparative data for Subject [redacted] results. This being the case, no definitive conclusions regarding AT2101 safety, efficacy, or PD effects can be based on this information.

Date of the report: 03 April 2013