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: AT2220		
Name of Active Ingredient: Duvoglustat hydrochloride		

Title of Study:
An Open-Label, Multi-center, International Study to Investigate Drug-Drug Interactions Between AT2220 and Alglucosidase Alfa in Patients With Pompe Disease

Investigators:
Twelve investigators enrolled subjects into the study and included [redacted] (Site 2001), [redacted] (Site 2008), [redacted] (Site 2017), [redacted] (Site 2027), [redacted] (Site 2028), [redacted] (Site 2029), [redacted] (Site 2030), [redacted] (Site 2031), [redacted] (Site 2033), [redacted] (Site 2304), and [redacted] (Site 6003).

Study sites:
Subjects were enrolled at 11 study sites in Canada, the United Kingdom, and the United States. One site enrolled subjects in Canada (Site 6003; [redacted]). One site enrolled subjects in the United Kingdom (Site 2304, [redacted]). Nine sites enrolled subject in the United States and included the following: Site 2001 [redacted], Site 2008 [redacted] Site 2017 [redacted], Site 2027 [redacted] Site 2028 [redacted] Site 2029 [redacted] Site 2030 [redacted], [redacted], Site 2031 [redacted] and Site 2033 [redacted], [redacted].

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

Studied period (years):	**Phase of development:**
Date first subject enrolled: 31 October 2011 Date last subject completed: 04 January 2013	2a

Objectives:
Primary:

- To evaluate the safety of single ascending oral doses of AT2220 administered 1 hour before administration of recombinant human alpha-glucosidase (rhGAA) in patients with Pompe disease
- To evaluate the effect of single ascending oral doses of AT2220 administered 1 hour before administration of a single intravenous (IV) infusion of rhGAA on the plasma pharmacokinetics of rhGAA in patients with Pompe disease

Secondary:

- To assess total alpha-glucosidase (GAA) activity and total GAA protein levels in skeletal muscle at Day 3 or Day 7 following a single IV infusion with rhGAA alone and after preadministration of single ascending oral doses of AT2220
- To evaluate the concentration of AT2220 in skeletal muscle at Day 3 or Day 7 after preadministration of single ascending oral doses of AT2220. Subjects were assigned to either Day 3 or Day 7 for Treatment Periods 1 and 2

Methodology:
This was an open-label, multicenter, international, 2-treatment period, fixed-sequence crossover study to evaluate the safety and pharmacokinetic (PK) effects of ascending doses (50, 100, 250, and 600 mg) of AT2220 on rhGAA (ie, the drug-drug interactions between AT2220 and rhGAA) in patients with Pompe disease.
During Treatment Period 1, subjects received a single IV infusion of rhGAA. During Treatment Period 2, subjects received a single oral dose of AT2220 one hour before initiation of a single rhGAA IV infusion. Subjects also had a follow-up period. As this was an open-label, single ascending dose study with a fixed crossover treatment sequence, a randomization schedule was not generated, and a placebo was not used.
This study was conducted in males and females who were 18 to 65 years of age, had Pompe disease, and were currently receiving rhGAA every 2 weeks at a stable dose. Approximately 22 eligible subjects were planned sequentially to be enrolled, approximately 4 to 6 subjects per AT2220 dose cohort. During Treatment Period 2, each subject participated in only 1 of the following treatment cohorts:
Cohort 1: A single 50 mg oral dose of AT2220
Cohort 2: A single 100 mg oral dose of AT2220
Cohort 3: A single 250 mg oral dose of AT2220
Cohort 4: A single 600 mg oral dose of AT2220
The initiation of the subject's normal rhGAA infusion occurred 1 hour after administration of AT2220. Administration of rhGAA (Myozyme® or Lumizyme®) occurred at the subject's currently prescribed dose level and was administered as an IV infusion using a calibrated infusion pump.
If 6 subjects were enrolled in a treatment cohort, the first 3 subjects had a muscle biopsy on Day 7 and the next 3 subjects had a muscle biopsy on Day 3 for both Treatment Periods 1 and 2, (Visits 2 and 4). The number of subjects assigned to a treatment cohort and a biopsy day was permitted to vary.
The number of subjects in a treatment cohort and the muscle biopsy day varied depending on PK data from the previous treatment cohort. The additional muscle PK and pharmacodynamic (PD) data were collected to determine if the dose-dependent response was occurring in muscle. An additional optional washout muscle biopsy sample was obtained at the follow-up visit, if the subject consented. This sample evaluated GAA activity in muscle and confirmed the washout of AT2220 from muscle. This biopsy was collected before the subject received their bi-weekly scheduled rhGAA infusion, and the subject should not have received rhGAA for at least 13 days before the optional biopsy. Determination of total GAA activity and protein increase in muscle for each of Treatment Periods 1 and 2 was estimated. Total GAA estimates included both endogenous GAA and exogenous rhGAA.

Number of subjects (planned and analyzed):
Planned: approximately 22 subjects with 4 to 6 subjects per cohort
Analyzed: A total of 27 subjects were enrolled in the study. Of these, 25 subjects completed the study; 6 subjects each in Cohort 1 (50 mg), Cohort 2 (100 mg), and Cohort 3 (250 mg); and 7 subjects in Cohort 4 (600 mg). Two subjects were discontinued from the study prior to assignment to a treatment cohort. Subject [redacted] voluntarily withdrew before receiving study drug. Subject [redacted] was screened twice and enrolled once under subject number [redacted]; therefore, this subject was counted twice under the total number of enrolled subjects.

Diagnosis and main criteria for inclusion:
This study was conducted in males and females who were 18 to 65 years of age, had Pompe disease, and were currently receiving rhGAA every 2 weeks at a stable dose.

Test product, dose and mode of administration, batch number:
AT2220; single oral dose of AT2220 1 hour before initiation of an intravenous infusion of rhGAA in Treatment Period 2. Lot numbers were 003666 for 50-mg bottles and 003836 for 200-mg bottles.

Duration of treatment:
AT2220 was given as a single dose on Visit 3, and subjects were followed through clinical visits up to 24 to 30 days after AT2220 administration and with a telephone contact 24 to 30 days after the follow-up visit.

Reference therapy, dose and mode of administration, batch number:
Intravenous administration of rhGAA was given at the subject's stable dose on Visits 1 and 3. Batch numbers for the commercially available product were not recorded.

Criteria for evaluation:
Efficacy:
Pharmacokinetic and pharmacodynamic outcomes included the following:

- Plasma total GAA maximum observed plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) for activity after an rhGAA IV infusion alone and after

preadministration of single ascending oral doses of AT2220

- Total protein concentration in plasma for each infusion
- The change in total GAA protein levels in muscle at Day 3 or Day 7 after a single IV administration of rhGAA alone and in combination with single ascending oral doses of AT2220 by measuring total GAA activity and protein levels
- The concentration of AT2220 in skeletal muscle tissue homogenate at Day 3 or Day 7 after preadministration of single ascending oral doses of AT2220 in Treatment Period 2

Exploratory outcomes included total GAA activity and total GAA protein levels in peripheral blood mononuclear cells (PBMCs) (the samples from Cohort 4 were not run), anti-rhGAA antibody titers, immunological analyses of cross-reactive immunologic material status, neutralizing antibodies, human leukocyte antigens, and cytokines measured from isolated PBMCs. With the exception of the total GAA activity and total GAA protein levels in PBMCs, the results of the exploratory immunological outcome measures will be presented in a separate report.

Safety:

Safety outcome assessments included the following:

- Adverse events (AEs) (including infusion-associated reactions)
- Clinical laboratory tests (hematology, urinalysis, serum chemistry including creatine phosphokinase, lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase, urine hexose tetrasaccharide [Hex4])
- 12-lead electrocardiograms
- Physical examinations
- Vital sign measurements
- Muscle strength tests

Statistical methods:

The enrolled population included all subjects who were enrolled in the study regardless of whether they received study medication.

All analyses of safety were conducted using the safety population. The safety population consisted of all subjects who were enrolled and received at least 1 dose of rhGAA or AT2220.

The per-protocol population included all subjects who successfully completed both periods, and subjects were analyzed according to the treatment(s) received. The per-protocol population was used for PK and PD analyses.

The total GAA activity and total GAA protein concentrations in plasma, muscle, and PBMC were listed and summarized by treatments in both Treatment Periods 1 and 2. Concentrations of AT2220 in plasma and muscle were listed and summarized by treatments in Treatment Period 2 only.

Arithmetic mean (+SD) and individual total GAA activity, total GAA protein concentrations, and AT2220 concentration in plasma versus time profiles were plotted by treatment on linear and semilogarithmic scales. Composite individual profiles by treatment cohort, with results from both periods on the same plot, were also generated. In addition, Area under the plasma concentration versus time curve from time 0 to the time of the last measurable concentration (AUC_{0-t}) and C_{max} and dose-normalized AUC_{0-t} and C_{max} versus dose were plotted for plasma total GAA activity, total GAA protein, and AT2220. Ratios of AUC_{0-t} and C_{max} were plotted by dose and treatment for total GAA activity and total GAA protein concentration.

The plasma PK parameters C_{max}, the time of C_{max} (t_{max}), AUC_{0-t}, Area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{inf}), elimination rate constant, elimination half-life ($t_{½}$), AUC ratio, and C_{max} ratio were calculated for total GAA activity, total GAA protein concentration, and AT2220 using noncompartmental methods. Calculation and summary of PK parameters were performed using Phoenix® WinNonlin® Version 6.2.1 (Pharsight Corporation, St. Louis, Missouri, USA) and SAS® software Version 9.1 or later (SAS Institute, Inc, Cary, North Carolina, USA).

Derived plasma PK parameters for each analyte were tabulated by treatment. Summary statistics presented for the PK parameters include number of subjects (n), mean, geometric mean, SD, coefficient of variation, standard

error, median, minimum, and maximum. For AUC ratio and C_{max} ratio, 90% CI of the mean was also presented. Dose proportionality of AT2220 across the dose range used in this study (50 mg–600 mg) was assessed using the power model approach.
Safety parameters were summarized using descriptive statistics. Frequency and percentages were provided for categorical variables. Sample size (n), mean, standard deviation, quartiles, minimum, and maximum were provided for continuous variables.
Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version 14.0. The number and percent of subjects reporting each AE were summarized by body system and preferred term for each group. Treatment-emergent AEs with an incidence of at least 5% in either group were compared using the Fisher exact test. Pre-treatment AEs will be summarized separately.
Shift tables were produced by treatment cohort to display the hematology, serum chemistry, and urinalysis shifts from baseline to postbaseline values. Clinically notable postbaseline hematology, serum chemistry, and urinalysis values were summarized by treatment period, overall, and treatment cohort. Levels of creatine phosphokinase were shown graphically by treatment cohort and visit for the safety population. Results for Hex4 were shown graphically by treatment cohort and visit for the safety population.
Muscle strength test (shoulder abductors, hip flexors, and knee extensors) findings were summarized by treatment cohort, treatment period, and visit for the safety population. The summary included the number of subjects and percentage in each treatment cohort for each visit and displays the changes from baseline (eg, no muscle movement to normal strength). Muscle strength test findings were also summarized graphically for the shoulder abductors, hip flexors, and knee extensors by treatment cohort and visit for the safety population. These graphs were displayed side-by-side, representing the right and left side for the shoulder abductor, hip flexors, and knee extensors.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

A total of 27 subjects were in the enrolled population. Of these, 25 subjects each were included in safety and per-protocol population. Two subjects were discontinued from the study prior to assignment to a treatment cohort. Subject [redacted] voluntarily withdrew before receiving study drug. Subject [redacted] was screened twice and enrolled once under subject number [redacted]; therefore, this subject was counted twice under the total number of enrolled subjects.
The primary PK outcome measures included plasma total GAA C_{max} and estimated AUC for activity after rhGAA IV infusion alone and after preadministration of single ascending oral doses of AT2220. In addition, plasma rhGAA protein concentration was evaluated for each infusion.

Primary Outcome Measures Analyses:

Activity and Pharmacokinetic Parameters of Total GAA in Plasma

The total GAA activity in plasma was greater for each cohort when AT2220 was coadministered with rhGAA than when the rhGAA treatment was administered alone.
The increase in total GAA activity with AT2220 coadministration occurred both in the maximum observed GAA activity (C_{max}) and the aggregate activity measure of total GAA activity (AUC_{inf} and AUC_{0-t}). For the treatments with AT2220 coadministered, the decline in total GAA activity occurred with a $t_{½}$ of 4.4 to 6.3 hours. For aggregate total GAA activity, the AUC ratio indicates 1.5- to 2.1-fold enhancement of GAA activity with coadministration of AT2220 versus rhGAA infusion alone.
For each subject, regardless of dose of rhGAA, total GAA activity was increased with the coadministration of AT2220.

Protein Concentration and Pharmacokinetic Parameters of rhGAA in Plasma

The results for total GAA protein concentrations in plasma across the treatment cohorts were very similar to the results reported for total GAA activity. For example, the AUC ratios for total protein vary from 1.5 to 2.3 across the AT2220 dose levels compared with 1.5 to 2.1 for the AUC ratios for total GAA activity.

Concentrations and Pharmacokinetic Parameters of AT2220 in Plasma

Median t_{max}, when examined across the 4 treatment cohorts, occurred between 1 and 3 hours after dosing. Mean $t_{½}$ of AT2220 was approximately 3.5 hours for all treatment cohorts.
For AT2220 total exposure (AUC_{inf} and AUC_{0-t}) and peak exposure increased less than proportionally with dose. Assuming the relationship between ln(parameter) and ln(dose) is linear, a value of 1 for the slope (beta) indicates perfect dose proportionality. The upper limit of the 90% CIs for each tested parameter was less than 1, which indicates that increases in total and peak exposure of AT2220 were less than dose proportional over the dose range of 50 mg to 600 mg.

Secondary Outcome Measures Analyses:

Total GAA Activity and Protein Concentration in Muscle at Day 3 or Day 7

At Day 3 the total GAA activity in muscle for each treatment cohort was greater with coadministration of AT2220 than when rhGAA was administered alone. For Cohorts 1, 2, 3, and 4 the increases in activity were 38.5%, 20.5%, 4.7%, and 43.6%, respectively. The total GAA activity levels in muscle were lower on Day 7 than on Day 3, and the effect of coadministration of AT2220 also appeared reduced in comparison to Day 3.

Concentration of AT2220 in Muscle at Day 3 or Day 7

Based on the observed mean concentrations, there were increases in concentrations with dose and decreases in concentrations of AT2220 in muscle from Day 3 to Day 7. The sample sizes were small, and there was only 1 sample from an individual subject. Therefore, these observations need to be combined with other sources of similar information for confirmation.

SAFETY RESULTS:

Overall, a total of 70 treatment-emergent AEs (TEAEs) occurred in 16 subjects (64%) during the study: 11 TEAEs in 5 subjects in Cohort 1 (50 mg), 10 TEAEs in 3 subjects in Cohort 2 (100 mg), 31 TEAEs in 4 subjects in Cohort 3 (250 mg), and 18 TEAEs in 4 subjects in Cohort 4 (600 mg).

Overall, all TEAEs across treatment cohorts were either unrelated or unlikely related to study drug. Of total 70 TEAEs reported in 16 subjects (64%), 55 were unrelated in 11 subjects (44%) and 15 were unlikely related in 5 subjects (20%). The majority of TEAEs were unrelated across treatment cohorts, except in subjects in Cohort 4 (600 mg), in which 6 were unrelated and 12 were unlikely related.

In Treatment Period 1, all TEAEs were unrelated. In Treatment Period 2, two subjects (33.3%) in Cohort 2 (100 mg), 1 subject in Cohort 3 (250 mg), and 2 subjects (28.6%) in Cohort 4 (600 mg) had at least 1 unlikely related AE; no subjects in Cohort 1 (50 mg) had any unlikely related AEs.

Overall, the following TEAEs were considered to be unlikely related to study drug in both treatment periods, reported in 1 subject each (4.0%): palpitations, constipation, nodule, edema peripheral, fall, electrocardiogram QT prolonged, weight increased, back pain, neck pain, pain in extremity, ovarian neoplasm, nephrolithiasis, urinary incontinence, and uterine enlargement.

The majority of reported TEAEs in both treatment periods were mild or moderate in intensity except for 4 severe TEAEs in Cohort 4 (600 mg) in 1 subject in Treatment Period 2. Of the total 70 TEAEs reported, 53 were mild (10 subjects [40%]), 13 were moderate (5 subjects [20%]), and 4 were severe (1 subject [4%]) in intensity across all treatment cohorts in both treatment periods.

In Treatment Period 1, all reported TEAEs were mild or moderate in intensity, with the only 2 moderate events reported in Cohort 4 (600 mg). No severe event was reported in subjects in Treatment Period 1.

In Treatment Period 2, 34 events were mild and 11 events were moderate reported in 5 subjects (20%), each. Four severe events occurred in Cohort 4 (600 mg) in 1 subject (4%). The TEAEs that were considered severe included constipation, back pain, neck pain, and urinary incontinence, reported in 1 subject each.

None of the subjects died during the conduct of the study. One serious AE (SAE) was reported. A brief summary of the SAE is as follows: on 16 May 2012, during Treatment Period 2, one female subject (Subject [redacted]) in Cohort 2 (100 mg) experienced a moderate SAE of electrocardiogram QT prolonged of 20 milliseconds that was considered unlikely related to study drug. No treatment for this event was reported and no action was taken with the study drug. The event resolved by 07 June 2013.

There were no trends in laboratory results or vital signs. The majority of out-of-range values were considered not clinically significant.

CONCLUSIONS:

- The AUC ratios across all AT2220 doses administered indicates 1.5- to 2.1-fold enhancement of plasma GAA activity with coadministration of AT2220 versus rhGAA infusion alone.
- The AUC ratios across all AT2220 doses administered indicates 4.7% to 43.6% enhancement of muscle GAA activity with coadministration of AT2220 versus rhGAA alone.
- Dose-related increases in mean muscle AT2220 concentrations were observed on Days 3 and 7. Muscle AT2220 concentrations on Day 3 or Day 7 do not suggest clinically significant accumulation would occur from coadministering AT2220 with rhGAA every 14 days.
- In patients with Pompe disease, AT2220 was safe and well tolerated when administered in single ascending oral doses 1 hour before infusion with rhGAA.

Date of the report: 12 December 2014