A Novel Phase 2a Study Design to Investigate the Effect of AT2220 (Duvoglustat HCl) on the Pharmacodynamics of Acid β-glucosidase in Subjects with Pompe Disease


Introduction

Pompe disease is caused by mutations in the gene that encodes the lysosomal enzyme acid β-glucosidase (GAA). Pompe Disease presents unique challenges. As a healthy volunteer study can be allowed for a third optional muscle biopsy per patient to be taken on Day 28 of the study for baseline assessment. At both visits the muscle biopsies were examined, vital signs, and muscle strength tests.

Primary Objectives

• To evaluate the safety of single ascending oral doses of AT2220 administered 1 hour prior to IV infusion of rhGAA in Pompe disease.

Secondary Objectives

• Assess GAA activity and protein levels in skeletal muscle at Day 3 or Day 7 following a single enzyme infusion with subcutaneous alfa and after pre-dosing with single ascending doses of AT2220.

• To evaluate the concentration of atorvastatin in skeletal muscle on Day 3 or Day 7.

Study Design and Selection Criteria

AT2220-010 is an ongoing, open-label, non-randomized, single-ascending dose study conducted in 2 stages: AT2220 can be administered 1 hour prior to IV infusion of rhGAA at the standard therapeutic dose and duration as in Period 1. Each period is separated by a washout period to ensure no carryover effects from the previous period. Patients are randomized to one of 5 dose levels of AT2220: 25, 50, 100, 200, and 400 mg administrated as an oral solution.

Pharmacokinetic parameters were calculated using standard non-compartmental procedures (WINNONLIN version 5.0 or higher). Muscle biopsies for rhGAA activity and muscle biopsies were taken on Day 7, for Cohort 1 during Period 1 and 2. Following Cohort 1, the protocol was extended to increase the sample size and for 4 to 6 muscle biopsies so that muscle biopsies could be taken for 3 patients each on Days 3 and 7 for Cohort 2 during Periods 1 and 2, and remaining the cohorts. The amendment also allowed for a third optional muscle biopsy per patient to be taken on Day 30 of the trial for baseline assessment.

Pharmacodynamic Analysis

AT2220 concentrations were taken at intervals of 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours post dose for plasma GAA activity and total rhGAA protein levels. In Period 2 only, serial blood samples for plasma AT2220 concentrations were taken at intervals of 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours post-dose. The AT2220 PK parameters included Cmax, AUC0-t, AUC0-∞, and T½. Pharmacodynamic parameters were calculated using standard non-compartmental procedures (NONMEM version 6.0 or higher).

Bioanalytical Methods and PK Analysis

AT2220 in Plasma and Muscle

An HPLC assay was developed for the determination of AT2220 in plasma and muscle. AT2220 concentrations were determined by HPLC using a 125 mm × 4.6 mm id column of Phenomenex C18 (2.5 μm, 3.0 μl inj, 3 ml/min), with an Applied Biosystems API 4000 LC/MS/MS detector. The instrument was operated in the multiple reaction monitoring mode. The lower limit of quantitation (LLOQ) was 2.00 ng/mL. The assay was validated over a concentration range of 0.5 - 1000 ng/mL. Calibration standards were prepared in blank plasma matrix. The standards were stored at -20°C until analysis.

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Data Safety and Safety Monitoring Board

The safety parameters include adverse events (AEs), vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), electrocardiogram (ECG), physical examination, and use of concomitant medications. A Drug Safety Monitoring Board (DSMB) comprised of external experts in the rare disease field and the Amicus Clinical Team was chartered to monitor and evaluate the safety of all subjects in the trial by periodically reviewing summaries of safety data, evaluating trends, and making recommendations. The DSMB met monthly to review safety data of all patients enrolled in the trial. In addition, an Independent Safety Monitoring Committee (ISMC) which reviewed the trial at regular intervals and for adverse events that de-emphasize the trial or appeared to indicate an unacceptable level of risk.

Disclosure Statement:

Authors footnoted #1 – 11 above are employees of Amicus Therapeutics, Cranbury, NJ USA.