A Phase 2a Study to Investigate the Effect of AT2220 (Duvoglustat HCl) on the Pharmacokinetics of Acid α-Glucosidase in Subjects with Pompe Disease


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Pompe disease is caused by mutations in the gene that encodes the lysosomal enzyme acid α-glucosidase (GAA), which hydrolizes glycogen. AT2220 (duvoglustat HCl) is a pharmacological chaperone that reversibly binds and stabilizes endogenous and exogenous forms of GAA. When co-administered with an Enzyme Replacement Therapy (ERT), such as recombinant human GAA (rhGAA), AT2220 is intended to bind to the inactivated enzyme, stabilizing it in its properly folded and active form. AT2220-010 is an open-label, non-randomized, 4-dose cohort, Phase 2a drug-drug interaction study to evaluate the safety and pharmacokinetic (PK) effects of a single oral dose of AT2220 (50 mg, 100 mg, 250 mg or 600 mg) co-administered with intravenous rhGAA in patients with Pompe disease. Patients received an IV infusion of ERT alone during Period 1. A single oral dose of AT2220 was co-administered 1 hour prior to the next IV infusion of ERT at the same dose and regimen during Period 2.

### Objectives and Study Design

- To investigate the PK of rhGAA in combination with AT2220
- To determine if AT2220 interacts with rhGAA
- To evaluate the safety and pharmacokinetics (PK) effects of a single oral dose of AT2220 (50 mg, 100 mg, 250 mg or 600 mg) in patients with Pompe disease

### Disposition and Demographics

- Thirteen subjects were male and 12 were female with Pompe Disease aged 33-65 years, and weight ranged from 55.8 - 109 kg.

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- Twenty-five patients gave consent and were enrolled into one of 4-dose cohorts as follows: 50 mg (N=4), 100 mg (N=4), 250 mg (N=4), and 600 mg (N=7).

### Summary of Results and Conclusions

- Preliminary results show single doses of 50 mg, 100 mg, 250 mg and 600 mg AT2220 with an rhGAA dose of approximately 20 mg/kg increased active plasma rhGAA AUC levels by 1.5 to 2.8-fold in all Pompe patients (100%) relative to rhGAA administered alone.
- Following co-administration with AT2220, approximately 70% (16 out of 23) of patients had increased muscle rhGAA activity from Days 3 or 7 biopsy samples.
- The increased rhGAA activity suggests more active rhGAA is taken up in muscle.
- Increases in active rhGAA levels following co-administration appeared to be dose-dependent.
- Plasma AT2220 exposures (AUC) increased in a dose-related manner, however, were nonlinear.
- Dose-related increases were observed for muscle rhGAA concentrations on Days 3 and 7.
- However, all evaluable follow up samples (Day 28) were below the limit of quantification (8 ng/g).
- Although complete clearance is desired, these data suggest AT2220 is gradually cleared from muscle to levels near or below the LOQ by Day 14.
- The single-dose pharmacokinetics in these Pompe patients were similar to results from healthy volunteers.
- Co-administration of AT2220 at doses of 50 mg, 100 mg, 250 mg and 600 mg with rhGAA was generally well-tolerated.
- No changes in key safety data (e.g., urine glucose tetrasaccharide, CK, liver transaminases) were observed.
- One serious adverse event (SAE) occurred in one subject. The SAE was deemed unrelated to study drug by the investigator.
- The SAE was a QTc prolongation (473-493 msec) due to armodafinil-citalopram CYP2C19 interaction.
- All other AEs were deemed unrelated to AT2220.

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