A Phase 2a Study to Investigate the Effect of a Single Dose of Migalastat HCl on Active Agalsidase Activity in Fabry Patients Receiving Enzyme Replacement Therapy


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Objectives and Study Design

Fabry disease is an X-linked lysosomal storage disease caused by mutations in GLA, the gene encoding α-Gal A. Migalastat HCl (AT1001, GR181413A) is a pharmacological chaperone that reversibly binds and stabilizes endogenous and exogenous certain forms of α-Gal A. When co-administered with an Enzyme Replacement Therapy (ERT), such as agalsidase alfa or beta, migalastat HCl is intended to bind to the infused α-Gal A enzyme, stabilizing it in its properly folded and active form. AT1001-013 (NCT #01968771) is an open-label, non-randomized, Phase 2a drug-drug interaction study to evaluate the safety and pharmacokinetic (PK) effects of a single oral dose of migalastat HCl (150 mg or 450 mg) co-administered with intravenous agalsidase alfa or beta in male patients with Fabry disease. Patients received an IV infusion of ERT alone. A single oral dose of migalastat HCl was co-administered 2 hours prior to the next IV infusion of ERT at the same dose and regimen. Patients also received 150 mg migalastat HCl alone 7 days after the next IV infusion of ERT.

Preliminary Results

Twenty-three patients completed the study. Twelve received 150 mg migalastat HCl and 11 received 450 mg migalastat HCl.

- 150 mg Cohort: Eight patients received agalsidase beta alone and 4 patients received agalsidase alfa alone during Period 1. Migalastat HCl was co-administered two hours prior to their next IV infusion of the same ERT at the same dose and regimen during Period 2. All patients received a single dose of 150 mg migalastat HCl alone 7 days after their next regularly scheduled ERT visit during Period 3.

- 450 mg Cohort: Seven patient received agalsidase beta alone and 4 patients received agalsidase alfa alone during Period 1. Migalastat HCl was co-administered two hours prior to their next IV infusion of the same ERT at the same dose and regimen. Period 2: 450 mg migalastat HCl was not administered alone.

Alone and when co-administered with migalastat HCl, agalsidase alfa 0.2 mg/kg was infused for ~40 minutes; agalsidase beta 0.5 mg/kg or 1.0 mg/kg was infused for ~2 hrs.

During the study period, 22 SAEs occurred in 18 patients (16% of patients). One of the SAEs was a transient ischemic attack (TIA) at screening. The other was a hospitalization for acute pain and acroparesthesia due to Fabry Disease which occurred approximately 5 months after the most recent dose of study drug.

Summary of Results and Conclusions

- Preliminary results show single doses of 150 mg and 450 mg migalastat HCl with agalsidase doses of 0.2 mg/kg, 0.5 mg/kg, and 1.0 mg/kg increased active plasma α-Gal A activity from baseline by 50-60% and 70-80%, respectively.

- Relative increases in active plasma α-Gal A activity were agalsidase dose-dependent. The largest increases occurred at the lowest dose (0.2 mg/kg) and the smallest increases occurred at the highest dose (1.0 mg/kg).

- Relative to baseline, increases in active α-Gal A levels were generally agalsidase dose-dependent.

- Co-administration of migalastat HCl at doses of 150 mg and 450 mg with agalsidase was generally well-tolerated.

- Two serious adverse events (SAEs) occurred in one subject. Both SAEs were deemed unrelated to study drug by the investigator.

- One of the SAEs was a transient ischemic attack (TIA) at screening. The other was a hospitalization for acute pain and acroparesthesia due to Fabry Disease which occurred approximately 5 months after the most recent dose of study drug.