Phase 3 Study (FACETS) of Migalastat HCl for Fabry Disease: Post hoc GLA Mutation-Based Identification of Subjects Likely to Show a Drug Effect

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Introduction

FABRY DISEASE
• X-linked inborn error of metabolism
• Mutations in the GLA gene lead to a deficiency in α-galactosidase A (α-Gal A) activity
• More than 600 disease-causing mutations in GLA have been identified (~60% nonsense)
• Affects both males and females; females have mosaic of healthy and diseased cells
• 5,000 – 10,000 patients diagnosed worldwide (likely largely undiagnosed)

MIGALASTAT HCl FOR FABRY DISEASE:
• Migalastat is an orally available investigational pharmacological chaperone
• Designed to selectively and reversibly bind and stabilize endogenous α-Gal A
• Facilitates proper folding and cellular trafficking of some mutant forms of α-Gal A to lysosomes where the breakdown of GL-3 substrate can proceed
• In development for the treatment of Fabry disease in patients who express specific mutant forms of α-Gal as identified using an in vitro cell-based assay

Clinical Trial HEK Assay Used as Entry Criteria in FACETS
• Created cDNA constructs of 531 known disease-causing missense or small in-frame deletions. The corresponding α-Gal A mutant forms were transiently expressed in HEK-293 cells. Cells were incubated at 37°C (7.7 mM) for 4 to 5 days. After, α-Gal A levels were measured in cell lysates using a synthetic fluorogenic substrate (ATP-α-Gal) or by western blot.
• ‘Amenable mutation’ criteria: ≥1.2-fold relative increase and ≥3.0% of wild-type (WT) absolute increase after 10 μM migalastat incubation criteria; were developed based on comparison of the mutant α-Gal A responses determined in the clinical trial HEK assay to male Phase 2 subject peripheral blood mononuclear cell α-Gal A responses after oral administration of migalastat.

MIGALASTAT HCl for Fabry Disease:GLA
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Comparison of Clinical Trial and GLP HEK-293 Cell-based Assays
• The Clinical Trial HEK-293 cell-based assay was transferred to a CRO to create a bioanalytically validated version of the assay in compliance with current regulatory guidance and relevant GLP regulations. The “GLP HEK Assay” is similar to the Clinical Trial HEK assay, but includes modifications to increase the level of quality control, rigor, precision, and consistency. Testing of 531 mutant forms was completed prior to the availability of FACETS Stage 1 data.

FACETS (AT1001-011, NCT00925301) Design
• A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Pharmacodynamics of Migalastat HCl in Patients With Fabry Disease and Amenable GLA Mutations (“amenable” mutation is explained in later sections of this poster)

Baseline Characteristics of the Intent-to-treat (ITT) Population
• A total of 67 subjects with Fabry disease (43 female and 24 male) were randomized
• During Stage 1, 33 subjects were randomized to placebo and 34 subjects were randomized to migalastat
• The baseline characteristics of the FACETS intent-to-treat population are shown

Kidney Interstitial Capillary (IC) GL-3
• Total of 67 subjects with Fabry disease (43 female and 24 male) were randomized
• During Stage 1, 33 subjects were randomized to placebo and 34 subjects were randomized to migalastat
• The baseline characteristics of the FACETS intent-to-treat population are shown

Post Hoc Kidney IC GL-3 Analysis: Change from Baseline (Stage 1 mITT, Excluding GLP HEK Non-amenable)
• ANCOVA model on change from baseline excluding 15 subjects with GLP HEK non-amenable mutations
• GLP HEK amenable subjects only showed a statistically significant (p=0.002) decrease in kidney IC GL-3 inclusions with migalastat treatment compared to placebo
• GLP HEK assay subset analyses will be implemented prospectively for Stage 2

Kidney IC GL-3: Impact of Baseline
• Change from baseline to month 6 in the mean number of GL-3 inclusions per interstitial capillary from placebo- and migalastat-treated subjects were plotted as a function of the baseline value
• The results show that many subjects had relatively low kidney IC GL-3 values at baseline
• In migalastat-treated subjects, larger decreases in kidney IC GL-3 were observed with increasingly higher baseline values

Conclusions
• The analysis of the change from baseline in kidney IC GL-3 demonstrates a measurable drug effect during the first 6 months of treatment with migalastat
• The effect of migalastat is more pronounced in subjects with GLP HEK amenable mutations and higher baseline kidney IC GL-3
• The change from baseline in kidney IC GL-3 and GLP HEK assay subset analyses will be implemented prospectively for Stage 2
• Complete Stage 2 (month 12) and open-label extension study (month 24) data are expected in the first half of 2014