The Validation of Pharmacogenetics in the Identification of Target Fabry Patients for Treatment with Migalastat

Benjamin ER², Della Valle C¹, Wu X¹, Katz E¹, Valenzano KJ¹, Bichet DG², Germain DP³, Giugliani R⁴, Hughes DA⁵, Schiffrin RN⁶, Wilcox WR⁷, Yu J¹, Kirk J¹, Barth J¹, Castelli J¹

¹Amicus Therapeutics, Cranbury, NJ, USA; ²Hôpital du Sacré-Coeur, Montréal, Québec, H4I1S1, Canada; ³Division of Medical Genetics, University of Versailles, University Paris-Saclay, Montigny, France; ⁴Medical Genetics Service, CHUP/IFR76, Porto Alhevere, Brazil; ⁵Royal Free Campus, Univ College London, London, London, UK; ⁶Baylor Research Institute, Dallas, TX; ⁷Dept of Human Genetics, Emory Univ, Atlanta, GA, USA

Introduction

Fabry Disease (FD) • Progressive X-linked lysosomal storage disorder caused by a deficiency in α-galactosidase A • Estimated FD incidence of approximately 1 in 100,000. Actual prevalence may be higher • More than 80% disease-causing mutations in GLA have been identified; ~60% of these are missense mutations • Affects males and females; females have a mosaic of healthy and diseased cells • Glutarate from lysosomally stored Gb3 is elevated in plasma of male and female patients with FD Migalastat for FD: • Orally administered investigational pharmacological chaperone for patients with amenable mutations • Increases stability, folding, and cellular trafficking of amenable mutant forms of α-GAL A to lysosomes where the breakdown of substrate can proceed • Amenable mutant forms of α-GAL A are identified using a GLP-validated HEK-293 cell-based assay (Migalastat Amenability Assay) • 30-50% of patients with FD are estimated to have amenable mutations; the majority of amenable mutations are associated with the classic phenotype of the disease

Objectives

• To assess the clinical validation of the Migalastat Amenability Assay, the mutant α-GAL A responses to migalastat in the assay were compared to Fabry patient pharmacodynamic responses to treatment with migalastat in Phase 2 and 3 clinical studies

Materials & Methods

Migalastat Amenability Assay (GLP HEK Assay): • A biologically validated assay used to individually express FD mutations in human embryonic kidney-293 (HEK) cells and measure increases in mutant α-GAL A activity in response to 10 μM migalastat • Known FD associated missense, carboxyl terminal nonsense, small-in-frame insertion, deletion, and complex mutant forms of the enzyme qualify for testing in the Migalastat Amenability Assay • Amenable mutant forms are defined as those having a ≥1.2 fold increase in α-GAL A activity • Patient samples are not required and the approach is applicable to both males and females • To date, 600 FD mutations have been tested; 268 have met the amenable mutation criteria

Data From Three Phase 2 Studies of Migalastat: • FAB-CL-201 (NCT00214500), FAB-CL-202 (NCT00283959), FAB-CL-203 (NCT00283933)
- The objectives were to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of migalastat in patients with FD
- All three studies included males only
- Study 201 evaluated different dosages; Studies 202 and 203 evaluated 150 mg migalastat HCI once every other day
- All three studies were open-label and included initial 12-24 week treatment periods and optional treatment extensions

Data From Phase 3 Study AT1001-001 (NCT00925301):
- A double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and pharmacodynamics of migalastat HCI in patients with FD and amenable GLA mutations
- Key Inclusion Criteria
  - Male or female, diagnosed with FD
  - Amenable GLA mutation (during screening the GLA mutation was confirmed by gene sequencing; the ‘amenable’ category was determined by a preliminary HEK-293 cell based assay)
  - Naeve to enzyme replacement therapy (ERT) or has not received ERT for at least 6 months before screening

Data From Phase 3 Study AT1001-012 (NCT01218659):
- A randomized, open-label study to compare the efficacy and safety of migalastat HCI and ERT in patients with FD and amenable mutations who were previously treated with ERT
- Key Inclusion Criteria
  - Male or female, diagnosed with FD
  - Amenable GLA mutation (during screening the GLA mutation was confirmed by gene sequencing; the ‘amenable’ category was determined by a preliminary HEK-293 cell based assay)
  - Initiated treatment with ERT at least 12 months prior to the baseline visit

Comparison to α-GAL A Responses in Phase 2 and 3

- The mutant α-GAL A responses to migalastat in the Migalastat Amenability Assay and in white blood cells (WBCs) of male Fabry patients orally administered migalastat in clinical studies were compared
- The degree of consistency was evaluated by calculating the sensitivity, specificity, positive predictive value, and negative predictive value

Comparison to Substrate Responses in Study 011

- Male and female kidney interstitial capillary Gl-3 (IC Gl-3) and plasma lysyl-Gb3, absolute changes after six months of treatment were grouped by GLA mutation category
- Patients with amenable mutations showed consistent decreases in these substrate levels; larger decreases were observed with increasingly higher baseline values
- In patients with non-amenable mutations, no consistent reductions in lysyl-Gb3 were observed

Conclusions

• The results indicate that the Migalastat Amenability Assay and the amenable mutation criterion have high predictive value in identifying FD patients who show a pharmacodynamic response to oral administration of migalastat based on assessment of α-GAL A in WBCs, kidney interstitial capillary Gl-3 deposition, and plasma lysyl-Gb3 concentrations
• The results indicate that the amenable mutations evaluated in the migalastat Phase 2 and 3 clinical studies are representative of the larger subset of amenable mutations
• These results support the clinical validation of the Migalastat Amenability Assay and its utility in identifying the target population for treatment with migalastat: patients with FD who have amenable mutations
• Approximately 30-50% of patients with FD are estimated to have amenable mutations; the majority of amenable mutations are associated with the classic phenotype of the disease
• As new GLA mutations are identified, they can readily be tested in the Migalastat Amenability Assay to determine amenability to treatment with migalastat