

**THE PHARMACOLOGICAL CHAPERONE, AT1001, INCREASES LEVELS OF MUTANT AND WILD TYPE  $\alpha$ -GALACTOSIDASE A, THE ENZYME DEFICIENT IN FABRY DISEASE, *IN VITRO*, *IN VIVO* AND IN A PHASE 1 CLINICAL TRIAL.** Elfrida R. Benjamin, Richie Khanna, Hui Hwa Chang, Rebecca Soska, Adriane Schilling, Wei Liang, Brandon A. Wustman, Matthew J. Toth, Jian-Qiang Fan, David J. Palling, David J. Lockhart, and Kenneth J. Valenzano. *Amicus Therapeutics, 6 Cedar Brook Drive, Cranbury, NJ 08512*

Fabry disease is an X-linked lysosomal storage disorder caused by inherited genetic mutations in  $\alpha$ -galactosidase A (GLA). Mutations in GLA lead to reduced cellular enzyme activity as a result of lowered catalytic activity, improper folding, decreased enzyme stability, and/or inefficient trafficking to the lysosome. Consequently, lysosomal accumulation of the natural GLA substrate, globotriosylceramide (GL-3), occurs and contributes to disease pathology. Accumulation of misfolded GLA enzyme in the ER may lead to cellular stress, which may also contribute to cellular dysfunction and disease. Classic Fabry disease patients are males with low GLA activity and disease onset in adolescence. Later onset patients can be males or females presenting with substantial GLA activity, though lower than normal. As females have one mutant and one wild type GLA allele, they have traditionally been thought of as carriers; however, due to X-chromosome inactivation, females may also present with Fabry disease. We and others have previously shown that the pharmacological chaperone, AT1001 (migalastat hydrochloride), can increase the activity of mutant GLA in cultured cells and *in vivo*. We have further characterized the effect of AT1001 on mutant and wild type GLA activity. Our results show that AT1001 increases R301Q GLA activity in Fabry patient fibroblasts. Oral administration of AT1001 (30 mg/kg/day; 4 weeks) to R301Q Tg/KO mice increases mutant GLA activity in liver, heart, kidney, spleen, and skin (5 to 30-fold). AT1001 also mediates a concentration-dependent increase in wild type GLA activity in normal human lymphoblasts (1.5-fold). Similarly, oral administration of AT1001 to wild type mice results in a dose-dependent increase in GLA activity in liver, heart, kidney, and spleen (2.9 to 3.5-fold). Enhancement in wild type and R301Q Tg/KO mouse tissues is specific for GLA, as no effect is observed on acid  $\alpha$ -glucosidase or  $\beta$ -glucocerebrosidase activity in these tissues or in cultured human Fabry fibroblasts *in vitro*. In a Phase 1 clinical study in healthy male volunteers, oral administration of AT1001 (50 and 150 mg twice daily for 7 days) resulted in a dose-related increase in GLA activity in white blood cells (up to 2-fold). Elevated GLA activity persisted for 7 days after drug withdrawal. AT1001 was orally available and was generally well tolerated at all doses, with no serious adverse events occurring in any treatment group. These data suggest that AT1001 merits further evaluation as a treatment for Fabry disease in male and female patients.

American College of Medical Genetics  
Nashville, Tennessee  
March, 2007