A Next-Generation Fabry Enzyme Replacement Therapy: A Proprietary Recombinant Human α-Galactosidase A Coformulated With a Pharmacological Chaperone, AT1001, Shows Greater Substrate Reduction Than Standard of Care in Fabry Mice


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INTRODUCTION

- Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency in α-galactosidase A (α-Gal A) activity, leading to progressive accumulation of lysosomal glycosphingolipids (GL-3) in multiple tissues.
- Although enzyme replacement therapy (ERT) with manufactured human α-Gal A, namely agalsidase beta and agalsidase alfa, has brought many therapeutic benefits to patients, the infused enzymes have potential limitations, including low physical stability, short circulating half-lives in blood, and variable uptake into different disease-relevant tissues, which may impact efficacy and tolerability.

Previously, we demonstrated that the pharmacological chaperone AT1001 (migalastat) improves the pharmacological properties of the manufactured enzymes via binding and stabilization of the enzyme and result in improved substrate clearance compared with the standard of care. This concept was tested in preclinical studies using a Fabry mouse model (Gla knockout (KO)).

RESULTS

- The thermal stability of ATB101 was assessed using a fluorescence-based thermal denaturation assay as described previously. The thermal stability scans were performed in the absence and presence of 10 and 100 µM AT1001 at pH 7.4 and in the absence of AT1001 at pH 5.2. Data were normalized to the minimum and maximum fluorescence in each sample. As expected for any lysosomal enzyme at neutral pH, AT1001 was significantly less stable (melting temperature, Tm = 48.9°C) than at acidic pH (Tm = 57.8°C). Coincubation with AT1001 at neutral pH resulted in a concentration-dependent stabilization of ATB101, with 100 µM AT1001 shifting the Tm to 54.6°C, and 100 µM AT1001 shifting the Tm to 54.8°C. The latter was similar to the Tm observed for ATB101 alone at acidic pH.

- Approximately 16-week-old male Gla KO mice (n=8/group) were given two biweekly IV bolus administrations of either ATB101 alone (<10 mg/kg) or ATB101/AT1001. Seven days after the final drug administration, the α-Gal A activity in disease-relevant tissues was measured using an enzymatic method with 4-NM Gal as the substrate. Conformation with AT1001 substantially increased α-Gal A activity in all tissues measured compared with enzyme alone.

- The PK of ATB101 alone was tested in preclinical studies using a Fabry mouse model (Gla knockout (KO)). Following each dosing regimen was calculated using a one-phase decay model. The fitted curves are shown in the graph, and the calculated half-lives are summarized in the table. When administered alone, ATB1001 showed dose-dependent, nonlinear pharmacokinetics, as the half-lives increased with increasing doses. Coformulation with AT1001 increased circulating α-Gal A activity levels, with an up to 3.5-fold increase in ATB101 half-life. N/A = not applicable, PK = pharmacokinetics.

CONCLUSIONS

- AT1001 increased the physical stability of a proprietary rha-Gal A, ATB101, currently in nonclinical development.
- In mice, following IV administration, ATB101 showed dose-dependent, nonlinear pharmacokinetics, as the half-lives increased with increasing doses. Upon coformulation with AT1001, the half-life of active ATB101 in plasma increased up to 3.5-fold compared with enzyme alone.
- In Gla KO mice, coformulated ATB101/AT1001 led to substantially increased α-Gal A activity in disease-relevant tissues compared with enzyme alone.
- Importantly, under a repeat IV administration regimen, coformulated ATB101/AT1001 achieved robust GL-3 reduction in kidney, heart, and skin tissues, reaching or even exceeding the levels achieved with 10 mg/kg agalsidase beta (ie, 10 times the standard-of-care dose).
- In plasma, a similar effect on the lyso-Gb3 levels was observed, and levels correlated well with kidney GL-3.
- Collectively, these results indicate that ATB101/AT1001 coformulation increased the stability of the enzyme, resulting in greater substrate reduction in preclinical models compared with the current standard therapy. Therefore, ATB101/AT1001 coformulation has the potential to represent a promising next-generation treatment for Fabry disease and warrants further investigation.

REFERENCES


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DISCLOSURES

Conflicts of Interest
All of the authors are employees of and hold stock in Amicus Therapeutics, Inc.