INTRODUCTION

- Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency in a galactosidase (A or Gal A) activity, leading to progressive accumulation of lysosomal globotriaosylceramide (GL-3) in multiple tissues.

- While enzyme replacement therapy (ERT) with recombinant human 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, that may impact efficacy and tolerability.

- Previously, we demonstrated that the pharmacological chaperone ATB101 (migalastat) improves the pharmacological properties of the manufactured enzymes via binding and stabilization.

- A proprietary recombinant human α-Gal A (rhα-Gal A), ATB101, has recently been developed and is co-formulated with AT1001 (designated as ATB101/AT1001). The co-formulated ATB101/AT1001 as a single intravenously administered product is aimed to improve the pharmacological properties 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

ATB101 Stabilizes ATB101 In Vitro

- 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 ATB101 at pH 7.4 and in the absence of ATB101 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, ATB101 was also significantly less stable (melting temperature (Tm) = 57.8°C). Co-incubation with AT1001 at neutral pH resulted in a concentration-dependent stabilization of ATB101, with 10 µM AT1001 shifting the Tm to 54.6°C, and 100 µM AT1001 shifting the Tm to 57.8°C. The latter was similar to the Tm observed for ATB101 alone at acidic pH.

ATB101/AT1001 Co-Formulation Increases the Circulating Levels of ATB101 in Gla KO Mice

- Approximately 16-week-old male Gla KO mice (n=8/group) were given 2 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 4MU-Gal as the substrate. Co-formulation with AT1001 substantially increased α-Gal A activity in all tissues measured compared with enzyme alone.

CONCLUSIONS

- ATB101 increased the physical stability of a proprietary rhα-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 co-formulation with AT1001, the half-life of active ATB101 in plasma increased up to 2.3-fold compared with enzyme alone.

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