INTRODUCTION

Pompe disease is an inherited metabolic disease of impaired lysosomal glycogen clearance due to acid α-glucosidase (GAA) deficiency, which leads to accumulation of the substrate most prominently in the heart, skeletal muscle, and smooth muscle. Progressive accumulation of glycogen results in a spectrum of disease severity, often leading to organ failure and/or death. Muscle weakness and progressive respiratory involvement are predominant manifestations of late-onset Pompe disease (LOPD).

Current management of LOPD includes enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA), in association with cardipulmonary and gastrointestinal support, musculoskeletal and functional rehabilitation, and dietary therapy.

ATB200 is a next-generation rhGAA ERT designed with optimized glycosylation and high levels of mannose 6-phosphate (M6P) residues for better uptake to target tissues (Figure 1). The pharmacological chaperone AT2221 co-administered with ATB200 stabilize the enzyme in blood and maintain catalytic activity to deliver ERT to lysosomes.

Study ATB200-02 was designed to primarily evaluate the safety, tolerability, and pharmacokinetics (PK) of ATB200 co-administered with AT2221. A PK/pharmacodynamic (PD) translational model from Gaα knockout mice predicted that a combination of ATB200 20 mg/kg with a high dose of AT2221 in humans would provide optimal glycogen reduction.

OBJECTIVE

To evaluate preliminary total GAA protein (ATB200) and AT2221 PK data from patients with LOPD in the phase 1/2 study ATB200-02

METHODS

Study Design

ATB200-02 (NCT02675465) is an open-label, fixed-sequence, ascending-dose, first-in-human, phase 1/2 study to assess the safety, tolerability, PK, and efficacy of intravenous infusions of ATB200 co-administered with oral AT2221 in adults with Pompe disease (Figure 3).

RESULTS

All surviving patients were administered ATB200 and AT2221 at each dose level, except in Cohorts 2 and 3. "During stages 2 and 3, ATB200 was only administered for the first 4 hours of intravenous infusion. For all doses, ATB200 was intravenously infused for a 4-hour duration. The first 2 patients in cohorts 2 and 3 served as sentinel patients for their respective cohorts.

Figure 1. Representative Schematic of ATB200/AT2221

Figure 2. Stabilization of ATB200 by AT2221

Figure 3. ATB200-02 Study Design

Table 1. Baseline Characteristics

Table 2. Total GAA Protein by Signature Peptide T09

CONCLUSIONS

Co-administration of low- and high-dose AT2221 showed dose-related increases in ATB200 exposures and distribution half-life, indicating stabilization of ATB200 in blood by AT2221.

These increases were significantly or highly significantly different from ATB200 administered alone.

High levels of M6P and bis-M6P along with an optimized mixture of glycans may provide enhanced plasma clearance of ATB200 and improved tissue targeting relative to standard of care.

Exposures from ERT-switch patients were not statistically different from those of ERT-naive patients.

REFERENCES

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DISCLOSURE

The authors declare no conflicts of interest.

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