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Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: Final results of three clinical studies of recombinant human *N*-acetylgalactosamine 4-sulfatase

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ABSTRACT

The objective of this study was to evaluate the long-term clinical benefits and safety of recombinant human arylsulfatase B (rhASB) treatment of mucopolysaccharidosis type VI (MPS VI: Maroteaux-Lamy syndrome), a lysosomal storage disease. Fifty-six patients derived from 3 clinical studies were followed in open-label extension studies for a total period of 97–260 Weeks. All patients received weekly infusions of rhASB at 1 mg/kg. Efficacy was evaluated by (1) distance walked in a 12-minute walk test (12MWT) or 6-minute walk test (6MWT), (2) stairs climbed in the 3-minute stair climb (3MSC), and (3) reduction in urinary glycosaminoglycans (GAG). Safety was evaluated by compliance, adverse event (AE) reporting

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and adherence to treatment. *Results:* A significant reduction in urinary GAG (71–79%) was sustained. For the 12MWT, subjects in Phase 2 showed improvement of 255 ± 191 m (mean ± SD) at Week 144; those in Phase 3 Extension demonstrated improvement from study baseline of 183 ± 26 m (mean ± SE) in the rhASB/rhASB group at Week 96 and from treatment baseline (Week 24) of 117 ± 25 m in the placebo/rhASB group. The Phase 1/2 6MWT and the 3MSC from Phase 2 and 3 also showed sustained improvements through the final study measurements. Compliance was 98% overall. Only 560 of 4121 reported AEs (14%) were related to treatment with only 10 of 560 (2%) described as severe. *Conclusion:* rhASB treatment up to 5 years results in sustained improvements in endurance and has an acceptable safety profile.

Introduction

Mucopolysaccharidosis type VI (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disease in which deficient activity of the enzyme *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B, or ASB; E.C # 3.1.6.12) impairs the stepwise degradation of the glycosaminoglycan (GAG) dermatan sulfate (DS) [1]. Partially degraded GAG accumulates in lysosomes in a wide range of tissues, causing a chronic progressive disorder characterized by significant functional impairment and a shortened lifespan. In addition to supportive care, specific therapies are now available to provide the deficient enzyme, including hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) [2].

The heterogeneity of MPS VI disease was established by a survey of 121 MPS VI-affected individuals [3]. High urinary GAG values (>200 μg/mg creatinine) were associated with an advanced clinical course relative to age, including short stature and low body weight, impaired endurance, compromised pulmonary function and reduced joint range of motion. Rare patients beyond age 20 years were found to have urine GAG >100 μg/mg creatinine, suggesting that longer-term survival is associated with urinary GAG levels below this threshold. Impairment in endurance based on a walk test occurred across all age groups and urinary GAG levels, suggesting that all patients are at risk for developing serious manifestations of the disease. Both physical endurance and urinary GAG values appear to be important parameters to assess treatment options and response to treatment.

Three clinical studies using recombinant human ASB (rhASB) ERT have been reported. A Phase 1/2 study and a Phase 2 Study both demonstrated that weekly infusions of 1 mg/kg rhASB were well tolerated, produced a rapid reduction in urinary GAG levels, and improved endurance in patients with rapidly advancing disease [4,5]. These promising results led to a Phase 3 double-blind, placebo-controlled study, which demonstrated significantly greater improvement in endurance on a 12 MWT after 24 weeks in the treatment as compared to placebo group [6]. The patients treated with rhASB also experienced greater improvement in the 3MSC and greater urinary GAG reduction than the placebo-treated group, and infusions were generally well tolerated. After Week 24, the patients treated with placebo were switched to rhASB, and both groups continued treatment with active drug during an open-label extension phase. Data collection continued in all 3 clinical studies for 97–260 Weeks. Final study results for the 56 MPS VI patients enrolled in the clinical studies were examined to determine whether improvements in endurance were maintained with a continued acceptable safety profile.

Materials and methods

Detailed study design and evaluation criteria have been reported in previous publications of Phase 1/2, Phase 2 and Phase 3 clinical studies of rhASB treatment in MPS VI, but are summarized in Table 1 [4–6]. These reports provide data collected up to 48 weeks of treatment. For the present report, Phase 1/2 and Phase 2 efficacy data are present to 240 and 144 weeks, respectively, and safety data to 260 and 214 weeks, respectively (Table 1). The Phase 3 "extension period" is presented apart from the initial 24 weeks of the Phase 3 study since this initial period involved patients receiving placebo; all patients received rhASB from baseline in the Phase 2 and Phase 1/2 studies. For the Phase 3 Extension, efficacy data are presented to 96 weeks and safety data to 159 weeks (Table 1). All patients received rhASB at a dose of 1 mg/kg/week infused over a 4 h period except three patients in the Phase 1/2 study who received 0.2 mg/kg/wk for the initial part of that study (patients 41 and 45 began the study receiving 0.2 mg/kg rhASB and transitioned to 1.0 mg/kg at Weeks 69 and 59, respectively). Current analysis focuses on long-term endurance and safety outcomes in patients completing these studies.

Observed mean data for endurance measures are presented for the Phase 1/2 and Phase 2 studies, whereas Phase 3 extension endurance results are fitted by means of two separate longitudinal models—one for the group originally given rhASB (rhASB/rhASB), and one for the placebo group switched to active drug after Week 24 (placebo/rhASB). Endurance results include the 53 patients completing the studies, while safety analysis includes all 56 patients enrolled in the clinical studies. Adherence analysis includes all patients until their exit from the study. The 3 MSC was not performed in the Phase 1/2 study.

Adverse events were categorized as mild, moderate, or severe depending on degree of limitation of usual activities. Mild events resulted in no limitation of daily activities, moderate events caused some limitation, and severe events resulted in inability to carry out daily activities. Adverse events were also categorized as serious or non-serious. Serious adverse events (SAEs) were those that resulted in death, were life-threatening, required or prolonged hospitalization, caused significant disability or incapacity, caused congenital anomaly, or were considered "medically significant" by the investigator. AEs that occurred during infusion and judged to be possibly, probably, or definitely related to study drug were considered infusion-associated reactions (IARs). A subset of IARs were termed "anaphylactoid" from their nature, recurrence and response to treatment consistent with immune reactions expected with infused recombinant proteins.

Results

Baseline demographics

An overview of patient demographics by study is presented in Table 1. The age of patients varied from 5 to 29 years; the mean age in each study was approximately 12 years. Of the 56 patients enrolled, 24 (43%) were female and 32 (57%) were male; the majority of patients (71%) were Caucasian. Mean baseline urinary GAG values were similar in each study.

Walk test

A majority of patients completing the clinical studies demonstrated an increase in walk distance; 4 of 5 Phase 1/2 patients, 9 of 10 Phase 2 patients, and 34 of 38 Phase 3 patients showed walk distance improvement at final evaluation as compared to baseline. The patients who did not show improvement at final evaluation all showed transient improvement at some earlier time point.

Long-term walk test results for each study are summarized in Table 2. Results of the 6MWT are provided for Phase 1/2; Phase 2 and Phase 3 results include the 12MWT distance along with the distance measured at the 6-min time point. In each study, improvement from baseline walk distance demonstrated in earlier reports was maintained. Phase 2 12MWT results showed mean ± SD improvement of 246 ± 163 m at Week 96 and 255 ± 191 m at Week 144 ($p = 0.004$); Week 96 Phase 3 Extension data demonstrated mean ± SE improvement from study baseline of 183 ± 26 m ($p < 0.001$) in the rhASB/rhASB group and improvement from treatment baseline (Week 24) of 117 ± 25 m