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Long-term endurance and safety of elosulfase alfa enzyme replacement therapy in patients with Morquio A syndrome

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ABSTRACT

Long-term efficacy and safety of elosulfase alfa enzyme replacement therapy were evaluated in Morquio A patients over 96 weeks (reaching 120 weeks in total from pre-treatment baseline) in an open-label, multicenter, phase III extension study. During this extension of a 24-week placebo-controlled phase III study, all patients initially received 2.0 mg/kg elosulfase alfa either weekly or every other week, prior to establishment of 2.0 mg/kg/week as the recommended dose, at which point all patients received weekly treatment. Efficacy measures were compared to baseline of the initial 24-week study, enabling analyses of changes over 120 weeks. In addition to performing analyses for the entire intent-to-treat (ITT) population ($N = 173$), analyses were also performed for a modified per-protocol (MPP) population ($N = 124$), which excluded patients who had orthopedic surgery during the extension study or were non-compliant with the study protocol (as determined by ≥20% missed infusions). Six-minute walk test (6MWT) was the primary efficacy measure; three-minute stair climb test (3MSCT) and normalized urine keratan sulfate (uKS) were secondary efficacy measures. Mean (SE) change from baseline to Week 120 in 6MWT distance was 32.0 (11.3) m and 39.9 (10.1) m for patients receiving elosulfase alfa at 2.0 mg/kg/week throughout the study ($N = 56$) and 15.1 (7.1) m and 31.7 (6.8) m in all patients combined, regardless of dosing regimen, for the ITT and MPP populations, respectively. Further analyses revealed that durability of 6MWT improvements was not impacted by baseline 6MWT distance, use of a walking aid, or age. Mean (SE) change at Week 120 in the 3MSCT was 5.5 (1.9) and 6.7 (2.0) stairs/min for patients receiving elosulfase alfa at 2.0 mg/kg/week throughout the study and 4.3 (1.2) and 6.8 (1.3) stairs/min in all patients combined, regardless of dosing regimen, for the ITT and MPP populations, respectively Across all patients, mean (SE) change at Week 120 in normalized uKS was −59.4 (1.8)% and −62.3 (1.8)% in the ITT and MPP

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; AE, adverse event; ERT, enzyme replacement therapy; GALNS, enzyme *N*-acetylgalactosamine-6-sulfatase; IAR, infusion-associated reaction; IgE, immunoglobulin E; ITT, intent-to-treat; KS, keratan sulfate; MPP, modified per-protocol; MorCAP, Morquio A Clinical Assessment Program; NAb, neutralizing antibody; PBO, placebo; QOW, every other week; QW, once weekly; SAE, serious adverse event; TAb, total antibody; uKS, urine keratan sulfate.

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populations, respectively. In the absence of a placebo group, significance of the sustained improvements could not be evaluated directly. However, to provide context for interpretation of results, comparisons were performed with untreated patients from a Morquio A natural history study. In contrast to the results of the extension study, the untreated patients experienced constant uKS levels and a gradual decline in endurance test results over a similar period of time. Differences from the untreated natural history study patients were significant for 6MWT, 3MSCT, and uKS outcomes for the cohort of patients receiving optimal dosing throughout the study and for all cohorts pooled together, for both ITT and MPP populations ($P < 0.05$). Safety findings were consistent with those of the initial 24-week study, with no new safety signals identified.

1. Introduction

Morquio A syndrome (mucopolysaccharidosis IVA) is a rare autosomal recessive disorder caused by mutations in the lysosomal enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS, EC 3.1.6.4). Reduced GALNS enzyme activity results in progressive accumulation of chondroitin-6-sulfate and keratan sulfate (KS) in tissues and organs, leading to dysfunctions in multiple organ systems [1–3]. Due to the rarity of Morquio A syndrome and variations in reporting methods used, accurate prevalence and incidence estimates have not yet been established, with reported birth prevalence ranging widely from 1 in 71,000 to 1,179,000 [4].

Characteristic features of Morquio A include skeletal and joint abnormalities, short stature, cardiorespiratory compromise, nerve entrapment syndromes, impaired vision, hearing loss, and hepatomegaly [1–3]. There is a wide heterogeneity among patients in genotype, clinical presentation, and progression rate. However, regardless of an individual's presentation of the disease, over time, the progressive nature of symptoms ultimately results in deteriorating mobility and endurance, limitations in performing the activities of daily life, and early mortality [5,6].

Enzyme replacement therapy (ERT) with recombinant human GALNS (elosulfase alfa, Vimizim®, BioMarin Pharmaceutical Inc., Novato, CA) has recently been approved as a treatment option for Morquio A [7]. The pivotal 24-week, randomized, placebo-controlled, phase III study showed significant improvements with weekly elosulfase alfa infusions (2.0 mg/kg) on the primary efficacy measure, i.e. distance walked in the 6MWT [8]. After 24 weeks of treatment, 6MWT distance increased by 22.5 m versus placebo ($P = 0.017$). No effect was seen with elosulfase alfa administered every other week. In addition, the study demonstrated non-statistical increases in the 3MSCT and pulmonary function tests versus placebo [8,9]. Normalized urine KS (uKS) was reduced at 24 weeks with both treatment regimens. Long-term safety and efficacy data from an extension of this pivotal study are reported in this manuscript.

2. Methods

2.1. Study design

The study (MOR-005, #NCT01415427) was a multi-national, multicenter, open-label extension of a randomized, double-blind, placebo-controlled, 24-week, phase III study (MOR-004, #NTC01275066) of 176 Morquio A patients [8,9]. The inclusion and exclusion criteria and study design have been published previously [8,9] and included requirements that patients were ≥5 years of age, had a baseline average 6MWT distance ≥30 and ≤325 m at baseline, and did not have major surgery within the 3 months prior to MOR-004 entry. For consistency, both MOR-004 and MOR-005 protocols mandated uniform walking aid use during endurance tests from baseline through last visit. All patients completing MOR-004 were eligible for enrollment in MOR-005. Before entering MOR-005, all participants, and/or their legally authorized representative (as required), provided written informed consent.

In part 1 of MOR-005, patients initially randomized to elosulfase alfa remained on their assigned dosing regimen of 2.0 mg/kg/week (QW-QW cohort) or 2.0 mg/kg/every other week (QOW-QOW cohort); placebo-treated patients were re-randomized (1:1) to one of the two dosing regimens (Fig. 1). Unlike randomization at initiation of MOR-004, re-randomization was not stratified by age or baseline 6MWT. After review of final efficacy and safety results from MOR-004 by an independent data monitoring committee, the recommended dose was established as 2.0 mg/kg/week. As pre-specified in the protocol, all patients were switched to the recommended dose for part 2 of study. Specific study week of transition depended on study enrollment timing and ranged from MOR-004/005 Week 36 to 96.

Although surgeries were not allowed during MOR-004, due to the long-term nature of the extension study, they could not reasonably be prohibited during MOR-005. However, endurance test results can be impacted by the occurrence of orthopedic surgery and the subsequent recovery period. Therefore, the per-protocol population for analysis excluded data on or after orthopedic surgery, as well as 24 week intervals of data where ≥3 infusions were missed and all data subsequent to such intervals. However, at a meeting on February 9, 2015 in Orlando, FL, USA, study investigators determined that the pre-specified per-protocol population was unnecessarily restricted and excluded too many patients (95 patients excluded; 51 patients due to missing ≥3 infusions) and established the modified per-protocol (MPP) population. The MPP population excluded patients who underwent orthopedic surgery during the study ($N = 38$) and/or exhibited recurrent non-compliance with the study protocol. Missed infusions were used as an indicator of compliance; patients missing ≥20% of their scheduled elosulfase alfa infusions during MOR-005 were identified as non-compliant ($N = 14$). In total, 49 patients were excluded, thereby allowing inclusion of an additional 46 patients as compared to the per-protocol population. To reveal the impact of orthopedic surgeries and lack of compliance on endurance, MPP population results are presented alongside results from the entire intent-to-treat (ITT) population (all patients who were previously included in the 24-week phase III study and received at least one dose of elosulfase alfa).

2.2. Efficacy evaluation

The primary efficacy variable of this extension study was distance walked in a 6MWT, which provides a measure for endurance. The 3MSCT, also a measure of endurance, and normalized uKS were secondary efficacy variables. The uKS measurements were normalized by dividing by urine creatinine levels, resulting in μg/mg creatinine units.

In part 1 of MOR-005, the 6MWT and the 3MSCT were performed at Week 12 and Week 24, and at 24-week intervals thereafter. Normalized uKS was assessed every 12 weeks. In part 2 of MOR-005, the 6MWT