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Safety, immunogenicity, and clinical outcomes in patients with Morquio A syndrome participating in 2 sequential open-label studies of elosulfase alfa enzyme replacement therapy (MOR-002/MOR-100), representing 5 years of treatment

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ABSTRACT

Elosulfase alfa is an enzyme replacement therapy for Morquio A syndrome (mucopolysaccharidosis IVA), a multisystemic progressive lysosomal storage disorder. This report includes the primary treatment outcomes and immunogenicity profile of elosulfase alfa in patients with Morquio A syndrome from 2 sequential studies, MOR-002 (ClinicalTrials.govNCT00884949) and MOR-100 (NCT01242111), representing > 5 years of clinical study data. MOR-002 was an open-label, single-arm phase 1/2 study that evaluated the pharmacokinetics, safety, immunogenicity, and preliminary efficacy of 3 sequential doses of elosulfase alfa (0.1, 1.0, and 2.0 mg/kg/week) in patients with Morquio A syndrome (n = 20) over 36 weeks, followed by an optional 36- to 48-week treatment period using elosulfase alfa 1.0 mg/kg once weekly (qw). During the 0.1 mg/kg dosing phase, 1 patient discontinued due to a type I hypersensitivity adverse event (AE), and that patient's sibling voluntarily discontinued in the absence of AEs. An additional patient discontinued due to recurrent infusion reactions during the 1.0 mg/kg continuation phase. The remaining 17 patients completed MOR-002 and enrolled in MOR-100, an open-label, long-term extension study that further evaluated safety and clinical outcomes with elosulfase alfa administered at 2.0 mg/kg qw. During the course of MOR-100, patients were given the option of receiving elosulfase alfa infusions at home with nursing assistance. Over the course of both studies, all patients experienced ≥1 AE and most patients experienced a drug-related AE, generally of mild or moderate severity. Hypersensitivity reactions reported as related to study drug occurred in 25% of patients. Thirteen patients who chose to receive infusions at home had the same tolerability and safety profile, as well as comparable compliance rates, as patients who chose to receive on-site infusions. All patients developed antibodies to elosulfase alfa. Positivity for neutralizing antibodies was associated with increased drug half-life and decreased drug clearance. Despite formation of anti-drug-binding (total antidrug antibodies, TAb) and in vitro neutralizing antibodies (NAb) in all patients, these types of immunogenicity to elosulfase alfa were not correlated with safety or clinical outcomes. In contrast with the reported natural history of Morquio A, no trends toward decreasing endurance, respiratory function, or ability to perform activities of daily living were observed in this cohort over the 5-year period.

Abbreviations: 3MSCT, 3-min stair climb test; 6MWT, 6-min walk test; AE, adverse event; AUC_{0-t}, area under the curve from time 0 to last measurable concentration; AUC_{inf}, area under the curve from time 0 to infinity; CI-M6PR, cation-independent mannose 6-phosphate receptor; CL, clearance; C_{max}, maximum observed concentration in plasma; ERT, enzyme replacement therapy; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GALNS, *N*-acetylgalactosamine-6-sulfatase; HAQ, Health Assessment Questionnaire; IgE, immunoglobulin E; IR, infusion reaction; IV, intravenous; KS, keratan sulfate; MedDRA, Medical Dictionary for Regulatory Activities; MorCAP, Morquio A Clinical Assessment Program; MPS, mucopolysaccharidosis; MVV, maximum voluntary ventilation; NAb, neutralizing antibodies; PD, pharmacodynamics; PK, pharmacokinetics; qw, once weekly; SAE, serious adverse event; SMQ, standardized MedDRA query; $t_{1/2}$, terminal half-life; TAb, total antibodies; T_{max}, time to reach C_{max}; uKS, urine keratan sulfate; V_{dss}, volume of distribution at steady state; V_{dz}, volume of distribution based on the terminal rate constant

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1. Introduction

Morquio A syndrome (mucopolysaccharidosis [MPS] IVA; OMIM #253000) is a rare lysosomal storage disease caused by an autosomal recessive mutation in the gene encoding the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS; EC 3.1.6.4), which catalyzes the degradation of glycosaminoglycans, keratan sulfate (KS), and chondroitin-6-sulfate. The accumulation of glycosaminoglycans in the lysosome gives rise to a heterogeneous but progressive disorder. Clinical manifestations include skeletal dysplasia, cardiac and pulmonary compromise, short stature, pectus carinatum, spinal abnormalities, joint instability, corneal opacity, and impaired hearing [1–3]. This combination of symptoms gives rise to a progressive decline in functional abilities, including endurance. One natural history study has estimated progressive impairment of endurance at a rate of -4.86 ± 3.25 m per year in the 6-min walk test (6MWT) [1].

Elosulfase alfa (recombinant humanized GALNS; BMN 110; Vimizim®; BioMarin Pharmaceutical Inc., Novato, CA, USA) is an enzyme replacement therapy (ERT) approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of Morquio A syndrome. In MOR-004 (ClinicalTrials.gov NCT01275066), the pivotal 24-week randomized, placebo-controlled phase 3 clinical trial, intravenous elosulfase alfa 2.0 mg/kg once weekly (qw) demonstrated efficacy on the primary endpoint, the 6MWT. In the long-term extension study, MOR-005 (NCT01415427), elosulfase alfa demonstrated an acceptable safety profile at the 2.0 mg/kg qw dose over approximately 2 years, and mean improvements were reported for 6MWT distances [4], 3-min stair climb test (3MSCT) outcomes [4], and respiratory function (maximum voluntary ventilation [MVV], forced vital capacity [FVC], and forced expiratory volume in 1 s [FEV_1]) [5]. The levels of the pharmacodynamic (PD) marker KS, which are elevated in the urine of patients with Morquio A syndrome, were significantly reduced during treatment with elosulfase alfa [4,6].

Preceding the pivotal phase 3 trial that led to approval, a 72- to 84-week phase 1/2 dose-finding trial (MOR-002; NCT00884949) was conducted in patients with Morquio A syndrome to identify the optimal efficacious dose of elosulfase alfa and assess its safety and tolerability. Following MOR-002, patients were invited to enroll in a long-term extension study (MOR-100; NCT01242111) to receive elosulfase alfa 2.0 mg/kg qw for an additional 192 weeks, which included its use as a home-infused therapy. This report describes the findings of the dose-escalation and long-term extension trials that together comprise 5 years of elosulfase alfa treatment outcomes in Morquio A syndrome.

2. Methods

2.1. Study design

MOR-002 was a multicenter, open-label, phase 1/2 clinical study designed to assess safety, dose, and preliminary efficacy of elosulfase alfa in individuals with Morquio A syndrome aged 5–18 years. To be eligible for enrollment, patients were required to have a diagnosis of MPS IVA based on reduced GALNS enzyme activity or confirmed by genetic testing. The dose-escalation period was 36 weeks, divided into 3 consecutive 12-week intervals, at doses of 0.1, 1.0, and 2.0 mg/kg qw. Weekly elosulfase alfa was administered intravenously (IV) over 4–5 h. Antihistamines were administered to patients before infusion as prophylaxis for potential hypersensitivity reactions. Patients who completed the dose-escalation period were eligible to enter the continuation period, receiving elosulfase alfa 1.0 mg/kg qw for an additional 36–48 weeks. Patients who completed MOR-002 were eligible to enter MOR-100, an optional long-term extension study evaluating 2.0 mg/kg qw elosulfase alfa treatment over 192 weeks.

In MOR-002 and at the start of MOR-100, all infusions were performed at study sites. However, following a protocol amendment, patients were given the option to continue receiving qw infusions in the home setting, provided the treating physician deemed that home infusions were appropriate. Home health nurses met with the patient at his/her home and provided the same care as the study site, including pretreatment with antihistamines and other agents as necessary and administration of study drug according to the same infusion rate schedule.

2.2. Pharmacokinetics and PD

Pharmacokinetic (PK) analysis was performed for samples collected at weeks 1, 12, 24, and 36 of MOR-002, and noncompartmental analyses were performed for elosulfase alfa 0.1 mg/kg qw, 1.0 mg/kg qw, and 2.0 mg/kg qw. The parameters measured were area under the curve from time 0 to last measurable concentration (AUC_{0-t}) and time 0 to infinity (AUC_{inf}), maximum observed concentration in plasma (C_{max}) and time to reach C_{max} (T_{max}), clearance (CL), volume of distribution based on the terminal rate constant (V_{dz}) and at steady state (V_{dss}), and terminal half-life ($t_{1/2}$) [7]. For determination of the PD effect of elosulfase alfa, urine KS (uKS) levels, normalized to creatinine levels, were measured at baseline and every 12 weeks for up to 72 weeks in the MOR-002 study and every 24 weeks for up to 168 weeks in the MOR-100 trial.

2.3. Clinical evaluation

Endurance was assessed using the 6MWT according to American Thoracic Society guidelines [8] and the 3MSCT [9]. Pulmonary function was assessed by FVC, FEV_1, and MVV tests. Initially, these assessments were conducted at baseline, every 12 weeks for up to 72 weeks in MOR-002, and every 24 weeks up to 192 weeks in MOR-100. Following a protocol amendment implemented in the last year of the study, the frequency of the 6MWT, 3MSCT, and respiratory function tests was changed to every 48 weeks, and the frequency of weight measurements, physical examinations, clinical laboratory tests, pregnancy tests, uKS measurements, and creatinine tests was changed from every 12 weeks to every 24 weeks.

The intent-to-treat population consisted of all patients who enrolled in the study, including 2 patients who were unable to perform the 6MWT at baseline or during treatment: 1 due to physical reasons, who was imputed as 0 m, and the other, who could not perform the assessment for developmental reasons, was imputed as missing.

The MPS Health Assessment Questionnaire (MPS-HAQ) [2], a 52-item survey that assesses self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting), mobility skills (dexterity, mobility, walking, stair climbing, and gross motor skills), and the extent of required caregiver assistance in the performance of these activities was completed every 24 weeks. For patients < 14 years of age, the MPS-HAQ was completed by a parent or guardian.

2.4. Safety evaluation

The safety of elosulfase alfa in the MOR-002 study and the MOR-100 long-term extension was assessed by evaluating treatment-emergent adverse events (AEs) and changes in physical examination results (including neurological examinations and corneal clouding), vital signs, standard clinical laboratory tests (including serum chemistry, hematology, and urinalysis), cervical spine (flexion-extension) radiographs, electrocardiograms and echocardiograms, concomitant medications, and immunogenicity tests. AEs occurring after the onset of the infusion and within 1 day following the end of the infusion were considered to be temporally related to study drug infusion. These AEs were categorized by the following: did they occur during infusion, was the infusion interrupted or discontinued, and was medical intervention with IV steroids, IV antihistamines, IV fluids, or oxygen required. AEs were coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 and tabulated by system organ class, preferred term, and severity (Common Terminology Criteria for Adverse Events

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