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# Enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase): Novel global treatment response model and outcomes in patients with alpha-mannosidosis

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ABSTRACT

Alpha-mannosidosis is an ultra-rare monogenic disorder resulting from a deficiency in the lysosomal enzyme alpha-mannosidase, with a prevalence estimated to be as low as 1:1,000,000 live births. The resulting accumulation of mannose-rich oligosaccharides in all tissues leads to a very heterogeneous disorder with a continuum of clinical manifestations with no distinctive phenotypes. Long-term enzyme replacement therapy (ERT) with velmanase alfa is approved in Europe for the treatment of patients with non-neurological manifestations of mild to moderate alpha-mannosidosis. The clinical heterogeneity and rarity of the disease limit the sensitivity of single parameters to detect clinically relevant treatment effects. Thus, we propose a novel multiple variable responder analysis to evaluate the efficacy of ERT for alpha-mannosidosis and present efficacy analyses for velmanase alfa using this method.

Global treatment response to velmanase alfa (defined by response to ≥2 domains comprising pharmacodynamic, functional, and quality of life outcomes) was applied post hoc to data from the pivotal placebo-controlled rhLAMAN-05 study and to the longer-term integrated data from all patients in the clinical development program (rhLAMAN-10). After 12 months of treatment, a global treatment response was achieved by 87% of patients receiving velmanase alfa (n = 15) compared with 30% of patients receiving placebo (n = 10). Longer-term data from all patients in the clinical program (n = 33) showed 88% of patients were global responders, including all (100%) pediatric patients (n = 19) and the majority (71%) of adult patients (n = 14). The responder analysis model demonstrates a clinically meaningful treatment effect with velmanase alfa and supports the early initiation and continued benefit of longer-term treatment of all patients with alpha-mannosidosis with this ERT.

## 1. Introduction

Alpha-mannosidosis (OMIM 248500) is an ultra-rare monogenic disorder resulting from deficiency in alpha-mannosidase (Enzyme Commission number: 3.2.1.24), a lysosomal enzyme involved in glycoprotein catabolism. It is an autosomal recessive disease caused by mutations in the *MAN2B1* gene located on chromosome 19 (19 p13.2-q12), with a prevalence estimated at 1:500,000 to 1:1,000,000 live

*Abbreviations:* 3MSCT, 3-min stair climb test; 6MWT, 6-min walking test; BMI, body mass index; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CHAQ-DI, Childhood Health Assessment Questionnaire Disability Index; CHAQ-VAS, Childhood Health Assessment Questionnaire Visual Analog Scale; CLN2, classic late infantile neuronal ceroid lipofuscinosis; DMD, Duchenne muscular dystrophy; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels; ERT, enzyme replacement therapy; FVC, forced vital capacity; GTR, Global Treatment Response; IgG, immunoglobulin G; MCID, minimal clinically important difference; MPS, mucopolysaccharidosis; PD, pharmacodynamic; QoL, quality of life; SD, standard deviation; VAS, visual analog scale

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births [1–3]. The result of alpha-mannosidase deficiency is blockage of the degradation of glycoproteins, leading to an accumulation of mannose-rich oligosaccharides in all tissues.

Accumulation of mannose-rich oligosaccharides manifests in a broad variety of symptoms including skeletal abnormalities, motor function impairment, intellectual disability, hearing loss, respiratory dysfunction, recurrent infections, and cellular and humoral immune defects usually presenting in early childhood [1,4–8]. Alpha-mannosidosis presents as a continuum of clinical symptoms in the very small patient population. This ultra-rare disease manifests as a very heterogeneous disorder due to the large variation in severity and rates of disease progression in terms of neuromuscular and skeletal deterioration [9].

Long-term enzyme replacement therapy (ERT) represents a therapeutic option for alpha-mannosidosis. Velmanase alfa is the first human recombinant form of alpha-mannosidase approved in Europe. The primary pharmacodynamic (PD) action of velmanase alfa is reduction of serum oligosaccharides. In phase I–II studies (rhLAMAN-02, -03, and -04; n = 9) in patients aged 7–17 years, velmanase alfa treatment resulted in improvements in PD biomarkers, motor function, and pulmonary function over 12 months [10]. All patients continued receiving velmanase alfa at the end of study, under compassionate use or after-trial care studies (rhLAMAN-07 and rhLAMAN-09), based on national regulations. In addition, data supporting the use of velmanase alfa as an effective therapy for alpha-mannosidosis have been reported from a 12-month, placebo-controlled, phase III study (rhLAMAN-05 [NCT01681953]; n = 25) [11]. Patients in the placebo arm (n = 10) switched to velmanase alfa treatment at the end of phase III under compassionate use or after-trial care studies; patients in the active treatment arm could continue receiving treatment either under compassionate use or after-trial care studies. The rhLAMAN-10 study [NCT02478840]) [12] is the integrated analysis of long-term data (up to 4 years of treatment) from all patients who participated in the early phase and phase III studies, the compassionate use programme and the after-trial care. The co-primary end points were changes from baseline in 3-min stair climb test (3MSCT). In the rhLAMAN-05 study, post hoc analysis revealed a clear trend towards improved steps per minute in the 3MSCT and secondary outcome measures of the meters walked in the 6-min walk test (6MWT) and forced vital capacity as percentage of predicted normal value (FVC %) in pediatric patients receiving velmanase alfa compared with adults [11]. A greater improvement in 3MSCT, 6MWT, and FVC % was also observed in pediatric patients, compared with adults in the rhLAMAN-10 analysis [12], suggesting that velmanase alfa produces greater clinical benefits in motor and pulmonary function when administered early in the disease course.

However, the limited size of the patient population and disease heterogeneity at baseline, as described above, limited the sensitivity of measures such as mean or median values for PD biomarkers or motor function tests to detect the treatment effect in the prospective clinical studies, particularly in adult patients. Thus, a multiple variable responder analysis aimed at incorporating the domains that characterize alpha-mannosidosis and are targeted by ERT may increase the sensitivity of treatment effect evaluation as has been demonstrated in other rare diseases, such as Duchenne muscular dystrophy (DMD), mucopolysaccharidosis (MPS) VII and classic late infantile neuronal ceroid lipofuscinosis (CLN2) [13,14]. We therefore propose a novel multiple variable responder analysis to evaluate the efficacy of ERT for alpha-mannosidosis and present post hoc efficacy analyses for velmanase alfa from clinical studies using this method.

## 2. Methods

A novel alpha-mannosidosis response model was applied post hoc to the data from the 12-month placebo-controlled rhLAMAN-05 study and the integrated data from patients across the clinical program that was analyzed in rhLAMAN-10 (at 12 months and last observation) (Fig. 1) to identify responders to velmanase alfa. In the rhLAMAN-05 study, patients aged between 5 years and 35 years were eligible for inclusion (n = 15 in the velmanase alfa group; n = 10 in the placebo group) [15]. Patients in the placebo arm switched to velmanase alfa treatment at the end of phase III under compassionate use or after-study care; patients in the active treatment arm could continue receiving treatment either under compassionate use or in after-trial care studies. Study rhLAMAN-10 consisted of open-label data collection over 1 week from patients in the compassionate use program (N = 18; mixed population from early phase study and phase III) and was run approximately 1 year after the completion of rhLAMAN-05. One patient in compassionate use did not participate in the rhLAMAN10 study, so he contributed to the integrated analysis for the 12 months of treatment exposure during the phase III study. The study also included an integrated analysis using the last available data from 14 patients treated in the clinical program who were in after-study care (rhLAMAN-07 and rhLAMAN-09) at that time. The integrated analysis (rhLAMAN-10) included patients aged mean (standard deviation [SD]) 17.1 (7.8) years (19 pediatric patients at baseline) who had previously participated in studies of velmanase alfa (n = 33) and who were followed for up to 4 years, with a mean (SD) treatment exposure of 29.3 (15.2) months [10]. The different duration of exposure to velmanase alfa in these patients is shown in Fig. S1. Across the early phase and phase III studies after-study care and compassionate use program, active treatment was with weekly infusions of 1 mg velmanase alfa/kg body weight [10,15].

The velmanase alfa Global Treatment Response (GTR) model was created based on the concept of identifying the clinical domains affected by the disease and potentially responding to systemic ERT. Three main domains were identified. The PD domain encompasses the accumulated substrate of alpha-mannosidase (oligosaccharides), which is considered to be the main pathogenic factor of the disease manifestations. A decrease in oligosaccharides is an essential biomarker to demonstrate a pharmacological effect of the ERT. The second domain includes all functional end points of the disease, including pulmonary function, endurance, and fine and gross motor proficiency. The third domain relates to the quality of life (QoL) of the patient in terms of disease burden, disability, and pain (Fig. 2).

In the response model, end points collected in velmanase alfa clinical studies were grouped into the appropriate PD, functional, and QoL domains, signifying the clinical burden and measurements of benefit to patients (Table 1). To reflect the clinical manifestations of alpha-mannosidosis (limited mobility, diminished activities of daily living, and reduced QoL), the key measures in the GTR analysis were: the number of steps/min in the 3MSCT [16]; the meters walked in the 6MWT [17]; FVC % predicted [18]; the Childhood Health Assessment Questionnaire disability index (CHAQ-DI) score and the CHAQ visual analog scale pain (CHAQ-VAS) score [19,20]. Although included in the disease response model, it was not deemed appropriate to include responder analyses for EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L), serum immunoglobulin G (IgG) and Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) as these data were available only for part of the population, depending on the parental trial of origin. Furthermore, the BOT-2 test did not have the sensitivity needed to define a minimal clinically important difference (MCID). All tests were performed in a single center (Rigshospitalet, Copenhagen, Denmark), using standardized methodologies to eliminate evaluation discrepancies. Response to treatment was based on the presence of clinically relevant improvements in the end points included in the three domains. An MCID for each of these end points was identified on the basis of those used in clinical conditions with the highest similarity to alpha-mannosidosis (proxy diseases). The MCID identified for each variable and used as response criteria in the analysis are shown in Table 1 [11,21–34].

To generate an overall response rate, a response by domain was defined. Patients were considered responders in a domain if they showed a response based on the MCID for ≥1 efficacy parameters