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Regular Article

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 non-neurological manifestations in patients with 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

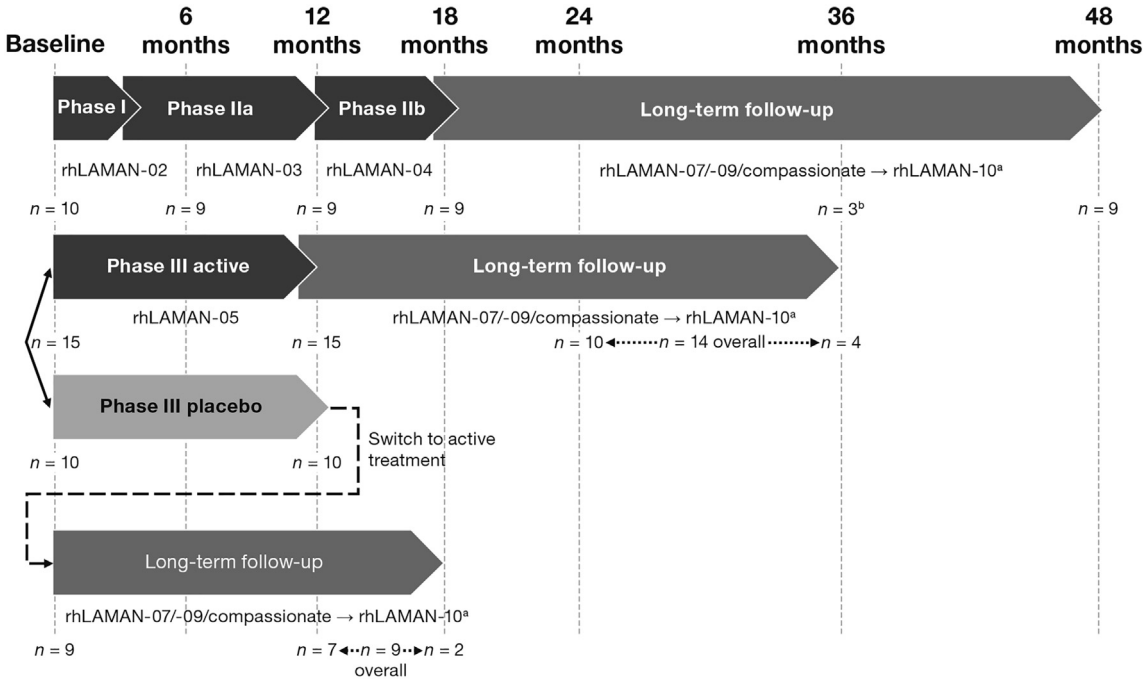

Fig. 1. Database schematic. [a]Integrated analysis of patients who enrolled into the data collection visit as part of the study rhLAMAN-10. [b]Integrated analysis (patients in the compassionate use program were entered into Study rhLAMAN-10 in order to collect data for the integrated analysis; further data for the integrated analysis were obtained from patients in studies rhLAMAN-07 and rhLAMAN-09).

within that domain. The GTR to velmanase alfa was the outcome of interest, and was defined as response in ≥2 domains. This approach enabled a definition of a treatment responder: a patient who in most cases is characterized by a relevant improvement in the key PD biomarker and in at least one clinically relevant end point from at least one clinical domain. The GTR after 12 months of velmanase alfa treatment was compared with placebo using data from the rhLAMAN-05 study. Global response was also analyzed by time (12 months and long-term) and age group (< 18 years and ≥ 18 years).

3. Results

The methods, baseline patient demographics (Table 2), and outcomes of the rhLAMAN-05 and rhLAMAN-10 studies have been previously published [11,12]. Scatter plots showing individual patient data at baseline and changes from baseline are shown in Fig. S2.

3.1. GTR model applied to data from the rhLAMAN-05 study (Fig. 3)

A PD response was achieved by 100% (15/15) of patients receiving velmanase alfa at month 12 compared with 20% (2/10) of patients who received placebo, a functional response was achieved by 60% (9/15) of patients receiving velmanase alfa at month 12 compared with 30% (3/10) of patients who received placebo, and QoL domain responses were achieved by 40% of patients in both groups at month 12 (6/15 in the treatment group, 4/10 in the placebo group). After 12 months of treatment, a GTR (response in ≥2 domains) was achieved by 87% (13/15) of patients receiving velmanase alfa compared with 30% (3/10) of patients in the placebo group.

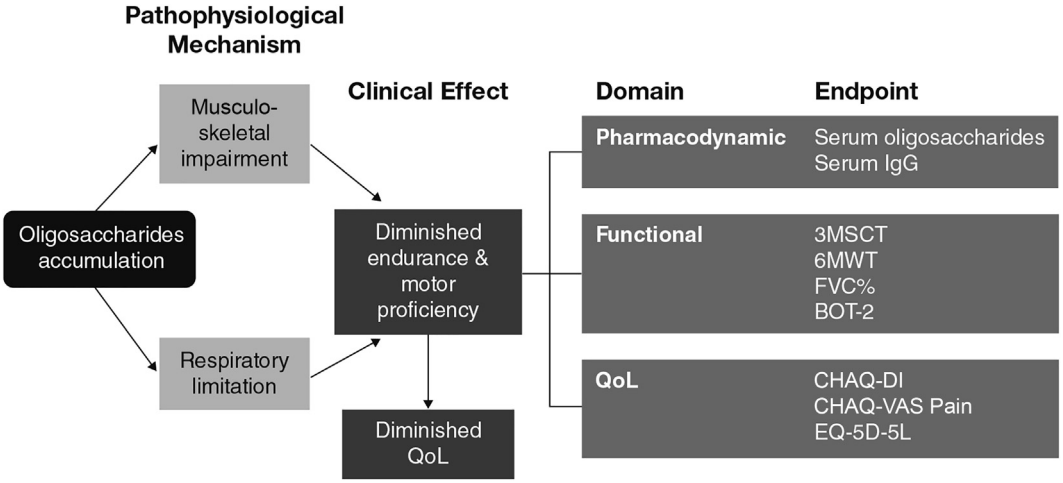

Fig. 2. Alpha-mannosidosis response model. 3MSCT, 3-min stair climb test; 6MWT, 6-min walk test; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CHAQ-DI, Childhood Health Assessment Questionnaire Disability Index; CHAQ-VAS, Childhood Health Assessment Questionnaire Visual Analog Scale; EQ-5D-5 L, EuroQoL 5 Dimensions 5 Levels; FVC, forced vital capacity; IgG, immunoglobulin G; PD, pharmacodynamic; QoL, quality of life.

Table 1
Responder criteria definitions for MCIDs.

Domain	Criterion	MCID threshold	MCID definition	Note on the end point
PD	Serum oligosaccharides	≤ 4 umol/L	Based on baseline data from the 12-month Phase III rhLAMAN-05 study [11] (baseline serum oligosaccharide range 4.4 umol/L to 10.2 umol/L)	The primary PD action of velmanase alfa is reduction of serum oligosaccharides
Functional	3MSCT	Absolute increase from baseline ≥ 7 steps/min	Based on published data from another lysosomal storage disorder, MPS type IVA [21]	Used in ERT studies in long-term follow-up of patients with similar lysosomal storage disorders, MPS [27]
	6MWT	Absolute increase from baseline ≥ 30 m	Based on a literature search, including data on DMD and cystic fibrosis, suggesting that 30 m is a robust measure of clinical meaningfulness [21,25,26,29–32,34]	Used in ERT studies in long-term follow-up of patients with similar lysosomal storage disorders, MPS, and Pompe disease [27]
	FVC (% predicted)	Absolute increase from baseline ≥ 10% of predicted	Based on studies in chronic lung diseases defining an MCID and another lysosomal storage disorder, Pompe disease [24,28,33]	Representative of muscular effort
QoL	CHAQ-DI	Absolute score change from baseline ≤ −0.130	Based on the MCID for the score in juvenile arthritis [22]	Validated scale for patients with musculoskeletal disorders
	CHAQ-VAS	Absolute score change from baseline ≤ −0.246	Based on a reduction of magnitude ≥ 8.2% as an MCID for VAS pain in patients with juvenile arthritis [23]	Validated scale for patients with musculoskeletal disorders

3.2. GTR model applied to data from the rhLAMAN-10 study, overall population

In the rhLAMAN10 integrated analysis at 12 months a PD response was achieved by 97% (30/31) of patients, a functional response was achieved by 65% (20/31) of patients, and QoL domain responses were achieved by 48% (15/31) of patients (Fig. 4a), with 79% of patients classified as global treatment responders. At last observation, these outcomes were achieved by 91% (30/33) of patients, 73% (24/33) of patients, and 67% (22/33) of patients, respectively (Fig. 4b). At last observation, 88% (29/33) of patients were classified as global treatment responders (Fig. 4c).

3.3. Response in three domains over time (Fig. 5)

At month 12 in rhLAMAN-05, 13% (2/15) of patients receiving velmanase alfa were responders in three domains, compared with zero (0/10) in the placebo group (Fig. 5A). At month 12 in rhLAMAN-10, the percentage of patients with response in three domains who received velmanase alfa was 24% (8/31) (Fig. 5B); at last observation, it was 46% (15/33) (Fig. 5C).

3.4. Model applied to data from the rhLAMAN-10 study, age subgroups

The results from the subanalysis of the data from the rhLAMAN-10 study by age group show that at last observation all pediatric patients (100%, 19/19) were global responders, as were 71% (10/14) of adult patients (Fig. 6). Improvements within in each subgroup by number of domains is shown in Fig. 7.

4. Discussion

These analyses demonstrate the clinical usefulness of a novel alpha-mannosidosis response model for evaluating the therapeutic efficacy of ERT, with global response as an outcome. The model encompasses one PD and two clinically relevant domains (one based on conventional functional tests and the other more patient-centric, based on QoL measures). To be a responder, a patient had to show meaningful improvements in at least two of the three domains, which—generally—translates into PD and pulmonary function improvements, a step-change in clinical test performance or reported clinical outcomes as defined in the analysis. This approach enables treatment effects to be captured across domains of disease manifestation, while ensuring that a clinically relevant response is present. In the specific case of velmanase alfa, the model makes it possible to observe a clear treatment effect over a short duration of treatment (12 months) in a mixed population of pediatric and adult patients, in comparison with placebo. In addition, this model is suitable to assess changes in response at multiple time points. Changes that were defined as a clinically relevant response were seen in a low percentage of patients in the placebo group, which in general terms supports the sensitivity of the approach. Specifically, a total of three patients (1 out of 10) were classified as responders in the placebo group; of these, one patient had decreased levels of serum oligosaccharides and showed a motor function improvement (both in the 3MSCT and 6MWT), whereas the other two were characterized by a combined improvement in FVC and pain scores, but not in motor function. Conversely, all patients who received velmanase alfa achieved a PD response and 10 out of 15 also had a motor function response (in the 3MSCT and/or 6MWT), while 5 of 15 had relevant FVC improvements. These results support the robustness of the approach, despite the small patient numbers and the inherent variability of the disease. Thus, velmanase alfa appears to improve outcomes across multiple variables compared with placebo in both pediatric and adult patients.

Application of the model to the integrated data from rhLAMAN-10 shows how length of exposure to treatment can be relevant in achieving clinically relevant response in functional and QoL domains, with the

Table 2
Baseline characteristics.

	rhLAMAN-05 study			rhLAMAN-10 study		
	All N = 25	Velmanase alfa n = 15	Placebo n = 10	Pediatric n = 19	Adult n = 14	Overall N = 33
Mean age, years (SD)	19.0 (8.8)	18.5 (9.0)	19.7 (8.9)	11.6 (3.7)	24.6 (5.3)	17.1 (7.8)
Male sex, n (%)	14 (56.0)	9 (60.0)	5 (50.0)	13 (68.4)	7 (50.0)	20 (60.6)
Pediatric age (%)	12 (48.0)	7 (46.7)	5 (50.0)			
Mean height, m (SD)	1.6 (0.2)	1.5 (0.2)	1.6 (0.1)	1.46 (0.20)	1.63 (0.08)	1.53 (0.18)
Mean weight, kg (SD)	61.8 (18.1)	60.2 (21.5)	64.2 (12.2)	49.8 (19.7)	70.9 (6.2)	58.8 (18.6)
Mean BMI, kg/m^2 (SD)	24.9 (4.1)	25.1 (4.9)	24.7 (2.7)	22.4 (4.2)	26.9 (2.9)	24.3 (4.3)
Mean 3MSCT, steps/min (SD)	54.0 (13.1)	52.9 (11.2)	55.5 (16.0)	54.04 (13.34)	53.00 (11.82)	53.60 (12.53)
3MSCT, n (%)						
< 30 steps/min	–	–	–	1 (5.3)	–	1 (3.0)
35–45 steps/min	4 (16.0)	1 (6.7)	3 (30.0)	2 (10.5)	2 (14.3)	4 (12.1)
45–55 steps/min	11 (44.0)	9 (60.0)	2 (20.0)	4 (21.1)	7 (50.0)	11 (33.3)
55–65 steps/min	4 (16.0)	3 (20.0)	1 (10.0)	10 (52.6)	1 (7.1)	11 (33.3)
≥ 65 steps/min	6 (24.0)	2 (13.3)	4 (40.0)	2 (10.5)	4 (28.6)	6 (18.2)
Mean 6MWT, m (SD)	462 (102)	460 (72.3)	466 (140)	454.2 (86.3)	483.4 (95,6)	466.6 (90.1)
6MWT, n (%)						
< 200 m	–	–	–	1 (5.3)	–	1 (3.0)
200–400 m	5 (20.0)	2 (13.3)	3 (30.0)	2 (10.5)	2 (14.3)	4 (12.1)
400–500 m	14 (56.0)	11 (73.3)	3 (30.0)	10 (52.6)	8 (57.1)	18 (54.8)
≥ 500 m	6 (24.0)	2 (13.3)	2 (40.0)	6 (31.6)	4 (28.6)	10 (30.3)
Mean FVC, % predicted (SD)	85.4 (17.3)	81.7 (20.7)	90.4 (10.4)	79.6 (16.4)	92.5 (19.4)	84.9 (18.6)
Mean FVC, L (SD)	2.8 (1.1)	2.5 (1.1)	3.3 (0.9)	2.241 (0.933)	3.231 (1.046)	2.651 (1.083)
Mean serum oligosaccharides, μmol/L (SD)	–	6.8 (1.2)	6.6 (1.9)	7.63 (2.52)	5.91 (1.54)	6.90 (2.30)
Mean CHAQ-DI, score (SD)	–	1.4 (0.8)	1.6 (0.6)	1.22 (0.89)	1.55 (0.55)	1.36 (0.77)

3MSCT, 3-min stair climb test; 6MWT, 6-min walking test; BMI, body mass index; CHAQ-DI, Childhood Health Assessment Questionnaire Disability Index; FVC, forced vital capacity; SD, standard deviation.

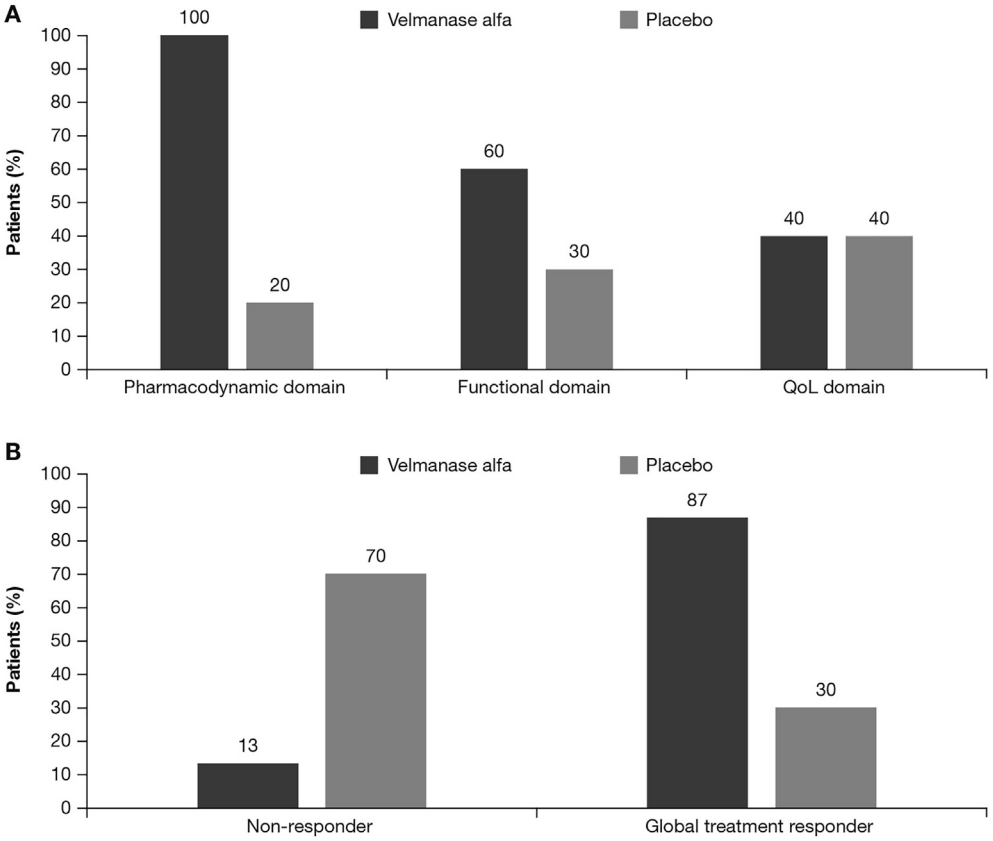

Fig. 3. (A) Multidomain responder analysis at month 12: rhLAMAN-05 study; (B) Global treatment responders in rhLAMAN-05 study.

increase from 65% to 73% responders in the functional domain and from 48% to 67% in the QoL domain from 12 months to last observation. Consequently, the number of global treatment responders increases from 12 months to last observation from 79% to 88%, with higher responsiveness in three domains, from 24% at 12 months to 45.5% at last observation.

Alpha-mannosidosis is a progressively debilitating disease, and age at start of treatment could be an impacting factor of treatment outcome.

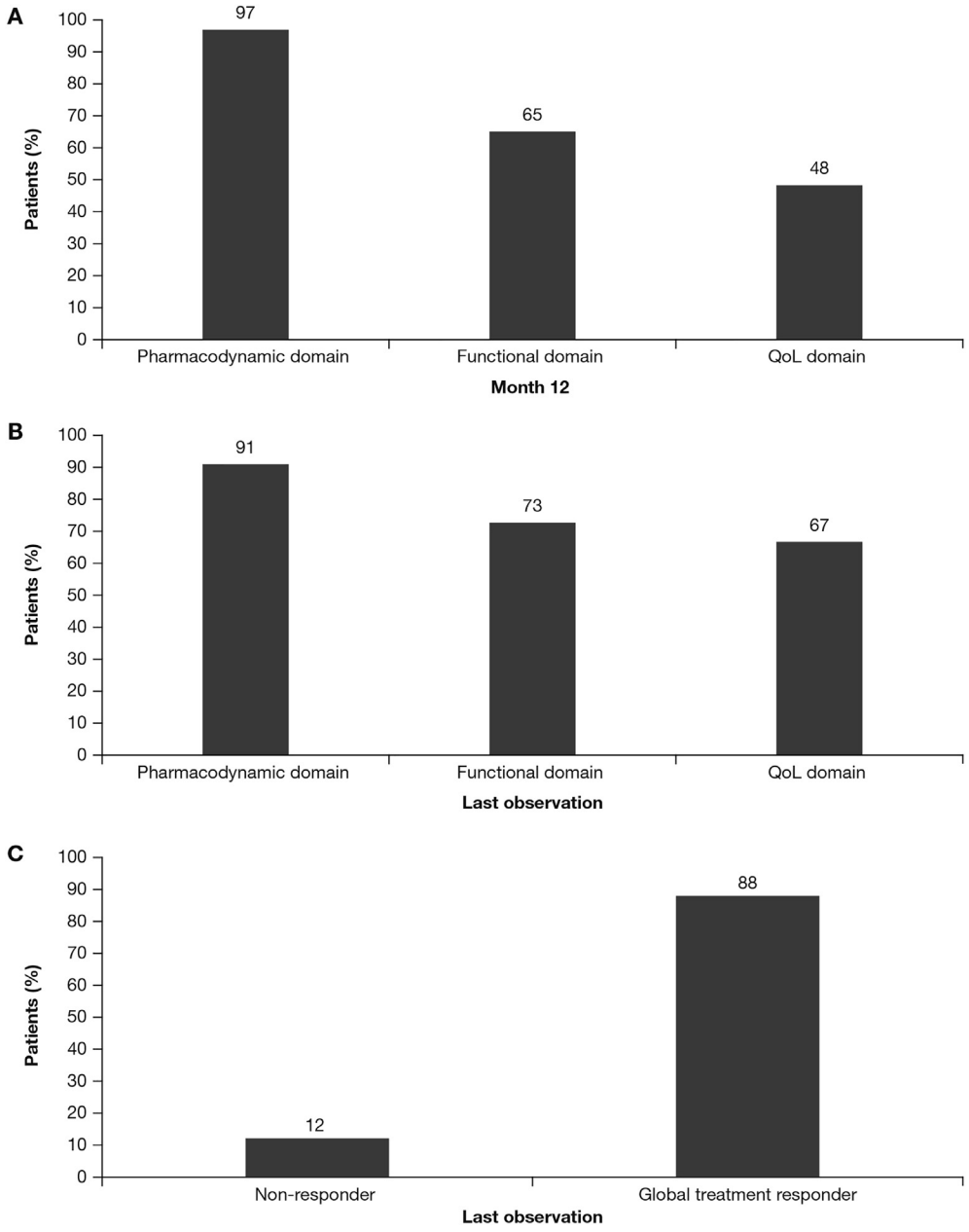

Fig. 4. (A) Multidomain responder analysis at month 12: rhLAMAN-10 study; (B) Multidomain responder analysis at last observation: rhLAMAN-10 study; (C) Global treatment responders at last observation: rhLAMAN-10 study.

When the GTR model is applied in the rhLAMAN-10 in the two different age groups, the pediatric patients are all global responders (100%), while the adult population has a global responsiveness in 71% of the total 14 patients. Starting treatment in pediatric age is beneficial; a larger magnitude of improvement is likely to be achieved with early treatment, supporting to start therapy as soon as possible. On the other hand, the GTR model does not take into account disease stabilization that could be already relevant, especially for the adult subgroup, given the progressive nature of the disease. Despite this, 71% of adults were global responders at last observation with 35.7% of these responding in three domains.

Application of the model to the data from rhLAMAN-05 and integrated data from rhLAMAN-10 supports the efficacy of velmanase alfa in treating alpha-mannosidosis, and provides a more sensitive evaluation of response than individual, isolated measures used in clinical studies. These findings are consistent with others reported from studies in rare disease using multiple variables for outcome evaluation [13,14,35]. In general, analysis of multiple outcomes, consisting of a combination of aggregated end points into single domains, can be more sensitive than comparing single end points across a patient population with variable symptomatology at baseline and represents an emerging strategy in other rare lysosomal storage disorders. In a study in DMD, a combination of outcome measures (North Star Ambulatory Assessment and 6MWT) was useful for assessing aspects of motor function not usually captured with a single measure in ambulant boys [13]; in CLN2, a disease score has been generated based on mobility and language items that represent a domain for functional decline [35]; in a mucopolysaccharidosis (MPS) type VII case, response to ERT was measured using an index of aggregated scores for 6MWT, FVC, shoulder flexion, visual acuity, and the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) [14]. This approach of combining outcome measures has also been recognized as valuable from regulatory and reimbursement perspectives: a response rate in multiple domains was adopted in support of the approval of elosulfase alfa therapy for MPS

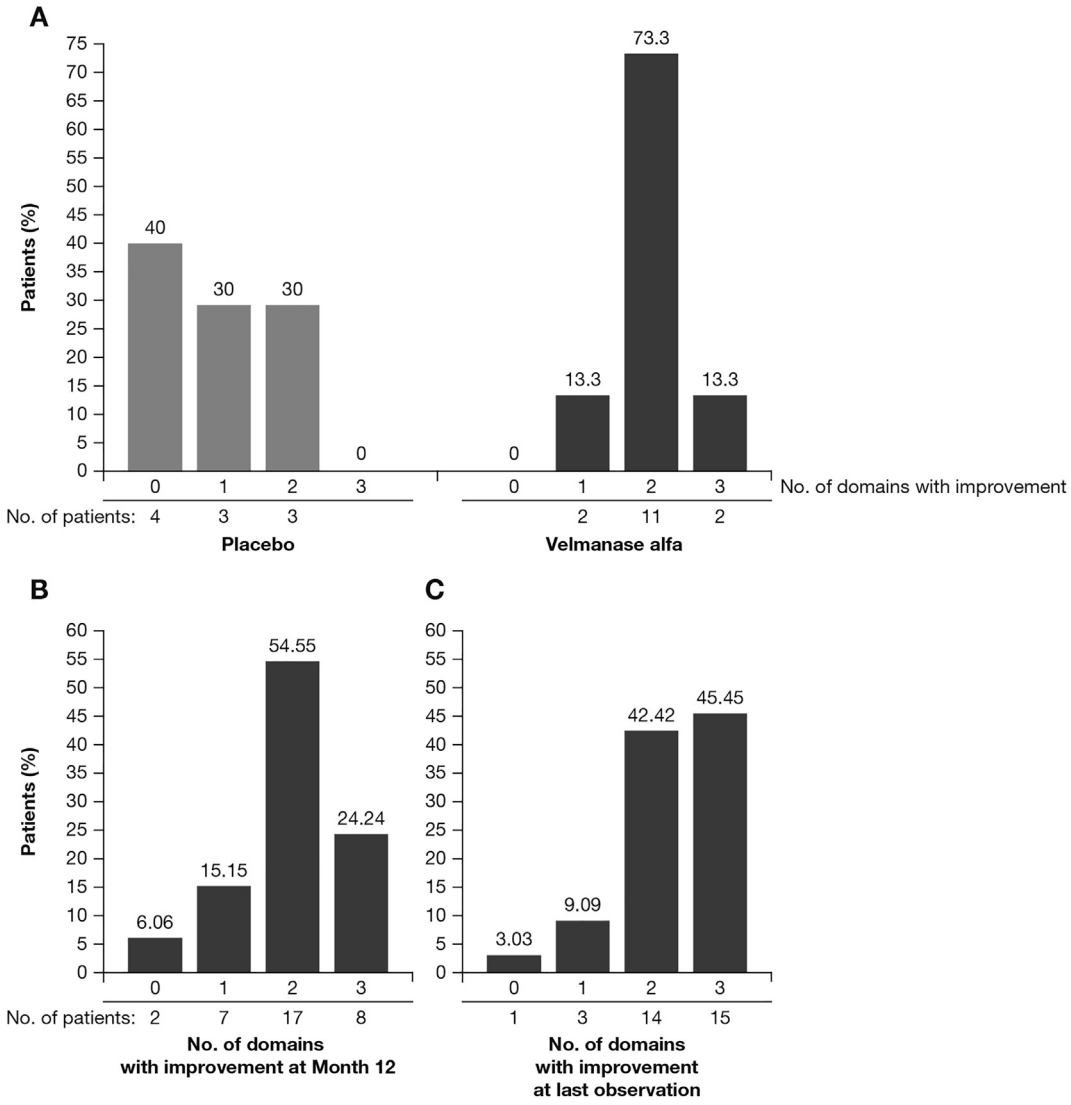

Fig. 5. (A) Multidomain responder analysis at month 12: rhLAMAN-05 study; (B) Multidomain responder analysis at month 12: rhLAMAN-10 study; (C) Multidomain responder analysis at last observation: rhLAMAN-10 study.

type IVA by the European Medicines Agency [26], as well as by the UK's National Institute for Health and Care Excellence [36]. In addition, the US Food and Drug Administration accepted aggregated scores for the approval of vestronidase alfa for MPS VII [37].

To date, there has been no single sensitive outcome measure to quantify a clinically meaningful treatment effect of therapy for alpha-mannosidosis; the novel global response model presented is an important development to meet this need. This type of model also enables

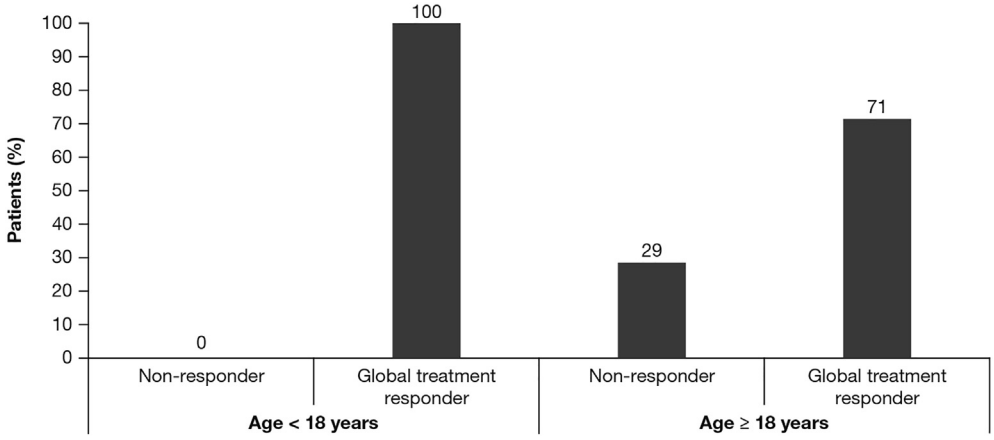

Fig. 6. Results of the model applied to rhLAMAN-10 (age subgroups) at last observation.

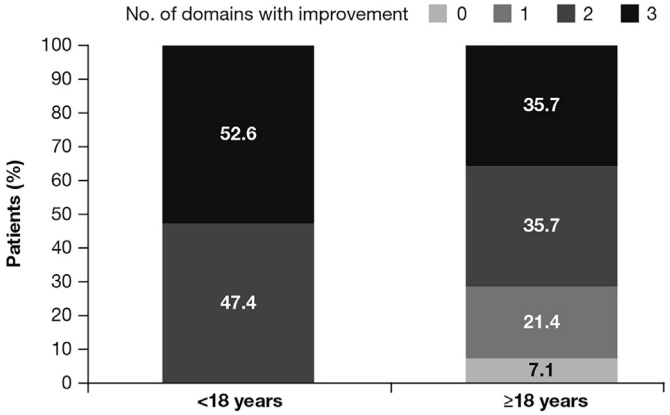

Fig. 7. Number of domains with improvement by age at last observation.

the theoretical possibility of an approach that allows individual end points to be substituted over time as long as they target the same feature within the domain and an MCID can be identified, for example, any time-dependent planar walking test, or a 12MWT could replace the 6MWT, or another QoL questionnaire (such as the Health Assessment Questionnaire) could replace the CHAQ. This "plug in" approach means that the model can be adapted to different national needs, preferences, and availability of tests, as well as to changes in medical practice, evolution of testing methods, and changing test availability over time. Further advantages of such an approach are that the model can evolve in response to, and be enhanced by, new developments in disease modeling efforts, consensus on the most relevant domains of pathological manifestations and sub-domains that can be covered by various clinical/ biochemical tests, and the subset of domains potentially targeted by a specific therapeutic approach for each target disease. This advance in medical and therapeutic understanding would also improve comparability of results across studies, tests, and clinical studies by providing a conceptual skeleton for each disease.

5. Limitations

Several limitations of our study and the proposed model must be acknowledged. First, the model was applied post hoc to clinical study data and therefore lacks prospective validation. This limitation is also shared by some of the other successful cases of multi-parameter approaches used in MPS and DMD. Additional prospective studies are therefore needed to confirm the approach in alpha-mannosidosis. In addition, the model does not take into account stabilization of disease but only improvement. Stabilization over the long term could be considered clinically relevant given the slowly progressive nature of alpha-mannosidosis and it is not surprising that many individual parameters appeared to remain generally unchanged in adult patients during long-term follow-up. However, despite this limitation to the model, the percentage of global treatment responders in the adult subpopulation was high and could therefore be considered conservative considering disease stabilization is not captured. Although the FVC and CHAQ-DI tests were normalized for patient age, the oligosaccharide measure, 3MSCT, and 6MWT were not; this discrepancy may have impacted upon the interpretation of data obtained regarding the overall population. In addition, the absence of a validated disease-specific QoL assessment tool required the use of a specific questionnaire designed for a proxy disease (juvenile arthritis). The small population and the inherent differences between juvenile arthritis and alpha-mannosidosis may have impacted on the accuracy of the assessment in the QoL domain.

Other end point parameters may still be relevant to the model, but insufficient data were available for inclusion in the domains from the small sample size in this analysis (e.g., serum igG level, BOT-2 score, [EQ-5D-5L] score); the adaptability of the model, with a "plug-in" approach, may allow this limitation to be overcome in due course. For some clinical parameters in patients, response can be quite limited and, as the MCID is based on a measure of improvement, a "ceiling effect" may mean that an MCID can never be reached, even if the patient has normalized. Finally, the sensitivity of the measures for each parameter and of each domain require validation. The selection of thresholds for MCIDs was generally conservative, however, and this makes the model more robust.

6. Conclusions

The complexity of alpha-mannosidosis symptomology in multiple body systems with differing severity and progression rates may be better assessed by the grouping of outcomes into domains to inform a global response measure. The novel responder model uses a response in at least two relevant domains to identify global responders to velmanase alfa, and demonstrates a clinically meaningful treatment effect in both the controlled and uncontrolled data analyses, supporting the continued benefit of longer-term treatment of alpha-mannosidosis with velmanase alfa. In addition, the model is sensitive to clinically meaningful improvements in adult patients compared with classical single metrics of efficacy that are less able to demonstrate treatment effects in this age group [10,15]. The analyses suggest that starting treatment in childhood is beneficial and, as a larger magnitude of improvement is likely to be achieved with early treatment, timely initiation of velmanase alfa ERT in both pediatric and adult patients should be recommended.

Competing interests

CJH is the owner of FYMCA Medical Ltd. and a consultant for Chiesi, Actelion, Audentes, Biomarin, Genzyme Sanofi, Inventiva, Shire, as well as various patient organizations.

NG received grants for clinical studies from Chiesi, BioMarin, Genzyme Sanofi, and Shire HGT, and fees concerning expert and board meetings.

AL received grants for clinical studies and consulting fees from Alexion, Biomarin, Genzyme Sanofi, Shire, and Chiesi.

FC, DA, and SG are full-time employees of Chiesi.

JBH received travel support from Shire, Genzyme Sanofi, and Biomarin, and honoraria from Shire. Her institute received grants from Shire.

PH received grants and consulting fees from Shire, Biomarin, Alexion, Armagen, and Inventiva Orphazyme; consulting fees from Genzyme, PTC, Chiesi, REGENXBIO; and grants from Sangamo.

LB received travel reimbursement and speakers fee from Chiesi.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2018.04.003.

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