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Health Related Quality of Life, Disability, and Pain in Alpha Mannosidosis: Long-Term Data of Enzyme Replacement Therapy With Velmanase Alfa (Human Recombinant Alpha Mannosidase)

Line Borgwardt, MD[1,2], Nathalie Guffon, MD[3], Yasmina Amraoui, MD[4], Simon A. Jones, MD[5], Linda De Meirleir, MD[6], Allan M. Lund, MD[7], Mercedes Gil-Campos, MD[8], Johanna M. P. Van den Hout, MD[9], Anna Tylki-Szymanska, MD[10], Silvia Geraci, MS[11], Diego Ardigò, MD, PhD[11], Federica Cattaneo, MD[11], Paul Harmatz, MD[12], and Dawn Phillips, PT, MS, PhD[13]

Abstract

Alpha-mannosidosis, a rare lysosomal storage disorder caused by deficiency of the lysosomal enzyme alpha-mannosidase, results in accumulation of mannose-rich glycoproteins in the tissues and sequelae leading to intellectual disability, ataxia, impaired hearing and speech, recurrent infections, skeletal abnormalities, muscular pain, and weakness. This study aimed to investigate disability, pain, and overall health using the Childhood Health Assessment Questionnaire (CHAQ) and the EuroQol 5 Dimension-5 Level Questionnaire (EQ-5D-5L) in patients with alpha-mannosidosis participating in rhLAMAN-10, a phase III open-label, clinical trial of velmanase alfa, a recombinant human lysosomal alpha-mannosidase. Long-term prognoses for most patients with untreated alpha-mannosidosis are poor due to progressive neuromuscular, skeletal, and intellectual deterioration, leading to increased dependence in mobility and activities of daily living and increased caregiver and health-care burden. Long-term CHAQ and EQ-5D-5L data highlight improvement trends in health-related quality of life and a reduction in disability and pain in patients receiving up to 48 months of velmanase alfa treatment.

[1] Centre for Inherited Metabolic Diseases, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[2] Center for Genomic Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[3] Centre de Référence des Maladies Héréditaires du Métabolisme, Hôpital Femme Mère Enfant, Lyon, France
[4] University Medical Centre Mainz, Centre for Pediatric and Adolescent Medicine, Villa Metabolica, Mainz, Germany
[5] Manchester Centre for Genomic Medicine, St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, United Kingdom
[6] Paediatric Neurology and Metabolism, Universitair Ziekenhuis, Brussels, Belgium
[7] Centre for Inherited Metabolic Diseases, Departments of Paediatrics and Clinical Genetics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[8] Unidad de Metabolismo e Investigación Pediátrica, Hospital Reina Sofía, Córdoba, Spain
[9] Center for Lysosomal and Metabolic Diseases, Erasmus Medical Center—Sophia Children's Hospital, Rotterdam, the Netherlands
[10] Department of Paediatric, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute, Warsaw, Poland
[11] Chiesi Farmaceutici S.p.A, Parma, Italy
[12] UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA
[13] Evidera, Bethesda, MD, USA

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Corresponding Author:
Dawn Phillips, One Kendall Square, Building 300, Suite 201, Cambridge, MA 02139, US.
Email: DawnPhillipspt@gmail.com

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Keywords
alpha-mannosidosis, recombinant human alpha-mannosidase, CHAQ, EQ-5D-5L, HRQoL, disability

Introduction

Alpha-mannosidosis disease is a rare autosomal recessive disorder caused by mutations in the *MAN2B1* gene, resulting in a deficiency of the lysosomal enzyme alpha-mannosidase. Alpha-mannosidase deficiency blocks the degradation of glycoproteins, which results in the accumulation of mannose-rich oligosaccharides in all tissues; the progressive accumulation of oligosaccharides leads to impaired cell function and apoptosis. The reported prevalence varies from 1:500 000 to 1:1 000 000 worldwide.[1,2] The disease occurs in most parts of the world and is not specific to any ethnic group or gender.[3]

The typical clinical attributes of alpha-mannosidosis include coarse facial features, intellectual disability, ataxia, impaired hearing and speech, immune deficiency with recurrent infections, skeletal abnormalities, muscular pain, and weakness.[1] Most patients are diagnosed in their first or second decade of life with documentation of increased levels of mannose-rich oligosaccharides in urine, reduced activity of alpha-mannosidase in leukocytes, or 2 pathogenic mutations in *MAN2B1*.

Currently, there is no effective treatment for alpha-mannosidosis; rather, patients are dependent on symptom management. Current therapy under investigation includes bone marrow or peripheral blood stem cell transplantation.[4] Velmanase alfa enzyme replacement therapy is approved in the European Union for treatment of nonneurological manifestations in patients with mild to moderate alpha-mannosidosis.[5] The long-term outcome usually involves disease progression and deterioration in motor, cognitive, and musculoskeletal function. Motor function is often impaired due to abnormal balance, hypotonia, ataxia, and pain.[6] The cognitive profiles and activities of daily life (ADL) for children and adults with alpha-mannosidosis have been previously reported by Borgwardt et al[6] from the baseline data in this study (rhLAMAN-10; more details in Methods section). The patients were found to have mild to severe intellectual disability (IQ of 30-81) and variable difficulties with visual function, reasoning, and visuospatial skills. Patients lack independence in ADLs, and caregivers face a considerable burden due to the patient's reduced cognitive capacity, reduced self-care, and limited mobility.[7]

Health-related quality of life (HRQoL) is defined by the European Medicines Agency as "the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological, and social functioning and well-being."[8] Health-related quality of life measures for children and adults are essential tools to capture the impact of impairment on age-appropriate task execution, social and peer interaction, and function within the home, community, work, and school environment.

The Childhood Health Assessment Questionnaire (CHAQ) was adapted from the Stanford Health Assessment Questionnaire (HAQ) as a parent- or self-administered instrument to measure the functional health status of children with juvenile rheumatoid arthritis. The CHAQ has also been utilized to measure disability and functional status in patients with rheumatic or musculoskeletal problems, including juvenile spondyloarthropathy, spina bifida, juvenile idiopathic inflammatory myopathies, juvenile connective tissue disease, hypophosphatasia, and mucopolysaccharidosis types II, III, and VI.[9-12] The CHAQ and the HAQ were used to document ADLs, severity of pain, and extent of disability in a natural history study of children and adults with alpha-mannosidosis.[13] The results indicated that a high level of caregiver assistance was necessary to complete ADLs and that the level of pain was age-dependent; the visual analog scale (VAS) pain scores indicated that a higher level of pain was present in adults compared to children.

The EuroQol 5 Dimension-5 Level Questionnaire (EQ-5D-5L) is a generic standardized measure of health that is applicable to a broad range of health conditions and is widely used in health research. Use of the EQ-5D has been recommended in the United States by the Washington Panel on Cost Effectiveness in Health and Medicine and in the United Kingdom by the National Institute for Health and Care Excellence.[14] The EQ-5D-5L was initially developed for adults, but use has been expanded to also include children with orthopedic conditions, arthritis, attention deficit/attention disorder,[14] and trauma.[15] Hendriksz et al[16] used the EQ-5D-5L to document HRQoL in children and adults with Morquio A syndrome, another ultrarare, lysosomal storage disease, with skeletal and joint abnormalities, gait impairment, and reduced independence in ADLs.

Aims

The objective of this study was to investigate the overall HRQoL including level of disability in ADLs, physical function, and pain in patients affected by alpha-mannosidosis during treatment with velmanase alfa. Velmanase alfa is a recombinant human lysosomal alpha-mannosidase developed as an intravenous enzyme replacement therapy for the treatment of alpha-mannosidosis. The aim of treatment is to reduce the mannose-rich oligosaccharide levels in the tissues, altering the progression of the disease and thereby preventing or reducing clinical complications, thus potentially improving the patient's condition and quality of life.

Methods

The HRQoL, disability, and pain data have been obtained from an open-label clinical trial investigating the long-term efficacy of velmanase alfa treatment in patients with

alpha-mannosidosis (rhLAMAN-10; NCT 02478840). The rhLAMAN-10 trial is an integrated collection of all 33 patients from both the early phase (phase I and II [rhLAMAN-02/-03/-04, NCTO1681940], N = 9 of 10 patients in the trials) and the late phase (phase III [rhLAMAN-05, NCTO1681953], N = 24 of 25) studies. All patients continued receiving treatment after study conclusion in either follow-on extension studies (the rhLAMAN-07, NCT01908712; and rhLAMAN-09, NCT01908725 studies) or compassionate use programs (CUP), depending on national legislation. Data collection was not carried on for patients in CUP, so they were invited to sign an informed consent to attend a Comprehensive Evaluation Visit in the frame of the rhLAMAN-10 study protocol. The HRQoL, disability, and pain data for all studies have been collected in a single center in Denmark. Individual patient data from phase I/II[17] and III trials and the subsequent rhLAMAN-07, rhLAMAN-09, and rhLAMAN-10 studies were integrated into a single database. Data were collected for at least 12 months (N = 33), with 48 months of follow-up for a subgroup of pediatric patients (N = 9). Fourteen patients were adult (age range 18-35 years), mean age of 24.6 (5.3) years, and 19 were pediatric (age range 6-17 years) at baseline. The EQ-5D-5L data were collected for only the 24 patients coming from the phase III study who had a mean age of 18.9 (8.3) years.

Parents and caregivers of patients in all age-groups responded to the parent-reported versions of the CHAQ and the EQ-5D-5L at baseline, twice in the first year of their original trial and at LO (defined as the last available value at the end of the study; rhLAMAN-10). Patients initially allocated to the control arm in phase III study rhLAMAN-05 (N = 9 of 10 controls in the trial) started treatment at the end of that trial. For these patients, the start of velmanase alfa treatment at that point was used as a baseline for the data reported in this article. The questionnaires were completed according to the standard administrative guidelines.

A parent/caregiver report was utilized in this study to reliably capture HRQoL and disability in children and adults with considerable intellectual disability. Borgwardt et al[6] previously reported on the cognitive profile of 35 patients from this study and found the baseline LEITER-R visual function and reasoning battery mean age equivalent score (standard deviation [SD]) to be 5.8 (1.55) years, with a mean chronological patient age of 17 (8.3) years.

The CHAQ is designed for use in children and adolescents aged 1 to 19 years. Use was extended to the adults in this study because they present with considerable intellectual and motor impairments, and the CHAQ functional items represent simple ADLs that do not require following directions or learning a new task. A parent/caregiver report was utilized for these adults also, because numerous challenges with self-reporting have been documented in adults with cognitive impairments, leading to increased missing data, decreased internal consistency, and impaired item comprehension.[18] Fujiura et al[19] also noted that the accuracy in self-report of recalling a discrete event, illnesses, or degree of activity can be limited by the cognition or memory.

Health-Related Quality of Life/Disability Measures

The CHAQ measures functional limitations and use of assistive devices in 8 areas, including dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each question is rated on a 4-point scale: without any difficulty (0), with some difficulty (1), with much difficulty (2), and unable to do (3). If aids or assistive devices are used, the minimum score for the corresponding domain is 2 (with much difficulty). The CHAQ classifies ambulatory aids as a cane, walker, crutches, or wheelchair; a category exists for walking that requires assistance from another person. Aids or assistive devices also include devices to assist with dressing, eating, or using a pencil. The maximum response of any of the pertinent questions is the dimension score. A disability index (DI) is then calculated as the mean of the dimension scores. The patient's discomfort is determined by the presence of pain; severity of pain in the last week is measured by a VAS from 0 to 100, with higher scores denoting more limitations. The VAS values are translated to a pain severity code from 0 (no pain) to 3 (very severe pain).

Excellent psychometric properties are present for the CHAQ in juvenile rheumatoid arthritis with a test–retest correlations coefficient of .8 ($P < .002$), internal reliability with Cronbach alpha of .94, and a mean interitem correlation of .6. Face validity instrument evaluation was completed by rheumatologists, health personnel, developmental pediatricians, and child psychologists. Convergent validity was evaluated with correlations to a physician's report of disease activity, and parent–child correlations that support that parents may serve as good proxy reporters for their children (Spearman correlation coefficient of 0.84, $P < .004$).[20]

Moderate to large responsiveness to change with parent report has been reported in pediatric patients with juvenile idiopathic arthritis.[21,22] Dempster et al[23] defined the minimal clinically important difference (MCID) for the CHAQ DI, based on caregiver report, as an improvement of 0.13 in children with juvenile arthritis. Musculoskeletal impairments that are present in both alpha-mannosidosis and juvenile arthritis include muscle weakness, pain, and alignment issues, and both diseases can impact quality of gait and level of independence in ADLs. Dempster et al[23] defined CHAQ levels of disability in children with arthritis as mild, mild to moderate, and moderate disability, with corresponding mean values of 0.24 (interquartile range [IQR]: 0.41), 0.71 (IQR: 0.88), and 1.53 (IQR: 0.59), respectively.

The CHAQ Pain VAS MCID associated with a significant improvement in quality of life on pediatric rheumatic patients has been defined as 0.82 (8.2%) on a 10 cm VAS.[24] The patient sample included 533 patients aged 9 to 19 years from a full spectrum of rheumatologic diseases and included a calculation of the average change in pain associated with change in quality of life. The diseases in the sample included both common and rare pediatric chronic diseases, such as juvenile rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and the spondylarthropathies. Similar disease impairments are

Table 1. Demographic Characteristics for the Entire Group and by Age.

		Overall (n = 33)		
		<18 years, n = 19	≥ 18 years, n = 14	Total, n = 33
Age, years	Mean (SD)	11.6 (3.7)	24.6 (5.3)	17.1 (7.8)
	Median (min; max)	12.0 (6.0; 17.0)	22.5 (18.0; 35.0)	15.0 (6.0; 35.0)
Sex, N (%)	Male	13 (68.4)	7 (50.0)	20 (60.6)
	Female	6 (31.6)	7 (50.0)	13 (39.4)
Race, N (%)	White	19 (100.0)	14 (100.0)	33 (100.0)
Height, m	Mean (SD)	1.46 (0.20)	1.63 (0.08)	1.53 (0.18)
	Median (min; max)	1.48 (1.12; 1.75)	1.59 (1.53; 1.81)	1.57 (1.12; 1.81)
Weight, kg	Mean (SD)	49.8 (19.7)	70.9 (6.2)	58.8 (18.6)
	Median (min; max)	49.0 (18.7; 95.2)	71.6 (60.0; 84.5)	65.0 (18.7; 95.2)

Abbreviations: Max, maximum; Min, minimum; n, number of patients; N, number of patients with characteristic; SD, standard deviation.

found in alpha-mannosidosis and rheumatic diseases, such as skeletal abnormalities, muscular pain, and weakness.

The EQ-5D-5L is a standardized measure of health designed to provide a simple generic measurement of health through 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is rated on a 5-point scale from no problems (1) to extreme problems or unable to complete (5). The dimension scores can be used to create a single summary health index (range from 0-1). In the CHAQ DI score, a higher value indicates more disability; in contrast, in the EQ-5D-5L, a higher health index score indicates less disability and better health. The EQ-5D-5L also includes a VAS from 0 to 100 with end points labeled as the "best health you can imagine" (100) and the "worst health you can imagine" (0). Kohn et al completed an analysis of EQ-5D-5L MCID in patients with multiple sclerosis (MS) that was based on anchor and distribution methods and found that mean MCID estimates ranged from 0.05 to 0.08.[25] The MCID was found to be largest for patients with the greatest mobility restrictions. In an intervention study for MS, Kohn et al defined the MCID based on 0.33 × the SD, with a responder range from 0.041 to 0.059.[25] Although the disease pathology is different between MS and alpha-mannosidosis, there are similarities in impairments, such as muscle weakness, incoordination, and gait abnormalities.

Data Analysis

The data were analyzed for all patients who were treated with velmanase alfa and whose response was evaluated post-baseline. A total of 33 patients were included in the analysis, and follow-up time points ranged from 1 to 4 years. Data are displayed for the overall group and is divided by age-group for pediatric (<18 years) and adult (≥18 years) patients. Results are presented at baseline, month 12, and LO. The demographic characteristics of the clinical population are described at baseline by age, gender, height, and weight.

The mean, median, and SD of the CHAQ DI; the CHAQ VAS pain scale; and the EQ-5D-5L health index and VAS for best health were examined by time point for the entire sample and by age for the pediatric and adult groups. The EQ-5D-5L health index value and VAS for best health values were available for only 24 patients from the phase III study. The CHAQ and EQ-5D-5L change from baseline was analyzed using paired *t* tests with absolute and percentage values and responder statuses.

Responder categories were defined for the CHAQ DI absolute change as ≤ -0.10 points, ≤ -0.13 points, ≤ -0.15 points, and summarized in frequency tables by time point and age-group. The performance status was characterized on the CHAQ Pain VAS according to 3 classes: mild impairment (0-<1), moderate impairment (1-<2), and severe impairment (2-3). For each parameter, patient status was analyzed by frequency at time point.

A descriptive analysis of CHAQ change from baseline in ambulatory assistive device use was also completed. The assistive devices that were included were walking devices such as a cane, walker, or crutches; wheelchairs; and walking assistance from another person.

A descriptive analysis of EQ-5D-5L individual dimension results is presented as the proportion of the sample size experiencing improvement, stability, or decline from baseline to LO. Sample size for the EQ-5D-5L assessment varied by time period, with 24, 21, and 10 patients at baseline, month 12, and month 24 (LO), respectively.

Results

Baseline demographic characteristics are presented in Table 1. The mean age on the day of the first dose of study treatment (velmanase alfa) for the overall patient population was 17.1 years. All patients were Caucasian, and 61% were male (n = 20).

Length of follow-up of patients differed according to the original trial in which they were enrolled. Mean (SD) duration of exposure to treatment was 29.3 (15.2) months (range: 11.7-53.4 months). All patients included in the study received the intended dose of 1 mg per kg per week by intravenous infusion for at least 12 months, and more than half of the study patients (n = 19, 57.6%) received the intended dose for at least

Table 2. Childhood Health Assessment Questionnaire Disability Index for the Entire Group, and by Age.

			Overall				
Time Point	CHAQ DI		N	Mean (SD)	Median (Min; Max)	*P* Value	95% CI
Baseline	Actual value		33	1.36 (0.77)	1.50 (0.0; 2.6)		
Month 12	Actual value		31	1.20 (0.70)	1.25 (0.0; 2.5)		
	Change from baseline	Absolute	31	−0.10 (0.36)	−0.13[a] (−0.8; 0.8)	.132	(−0.23 to 0.03)
		%	29	−7.76 (50.68)	−7.14 (−100; 200.0)	.417	(−27.0 to 11.52)
Last observation	Actual value		33	1.23 (0.66)	1.25 (0.1; 2.4)		
	Change from baseline	Absolute	33	−0.13[a] (0.44)	0.00 (−1.1; 0.6)	.095	(−0.29 to 0.02)
		%	31	−2.41 (45.03)	−2.41 (−80.0; 133.3)	.768	(−18.9 to 14.11)

			<18 years			≥18 years		
	Age		n	Mean (SD)	Median (Min; Max)	n	Mean (SD)	Median (Min; Max)
Baseline	Actual value		19	1.22 (0.89)	1.25 (0.0; 2.4)	14	1.55 (0.55)	1.56 (0.6; 2.6)
Month 12	Actual value		18	1.06 (0.78)	1.13 (0.0; 2.5)	13	1.40 (0.55)	1.63 (0.6; 2.1)
	Change from baseline	Absolute		−0.10 (0.37)	−0.13[a] (−0.6; 0.8)		−0.10 (0.37)	0.00 (−0.8; 0.4)
		%	16	−9.74 (66.33)	−14.1 (−100; 200.0)		−5.31 (21.93)	0.00 (−42.9; 27.3)
Last observation	Actual value		19	.97 (0.62)	0.88 (0.1; 2.0)	14	1.57 (0.58)	1.69 (0.6; 2.4)
	Change from baseline	Absolute		−0.24[a] (0.48)	−0.38[a] (−1.1; 0.5)		−0.02 (0.36)	0.13[a] (−0.8; 0.6)
		%	17	−6.82 (57.09)	−17.6 (−80.0; 133.3)		−2.94 (24.73)	6.70 (−42.9; 45.5)

Abbreviations: CHAQ, Childhood Health Assessment Questionnaire; CI, confidence interval; DI, disability index; Max, maximum; Min, minimum; n, number of patients; SD, standard deviation.
[a]MCID ≥ 0.13.

24 months. The patient population originally enrolled in the phase I and II studies, which was entirely pediatric (ages 7-17 years), received velmanase alfa for 48 months.

Most patients had impairments in multiple systems including the nervous (84.8%), auditory (81.8%), speech (78.8%), visual (54.5%), and gastrointestinal (30.3%) systems. Psychiatric (81.8%) and musculoskeletal and connective tissue (60.6%) disorders were also present, and some patients experienced ataxia (24.2%).

Childhood Health Assessment Questionnaire Disability Index

At baseline, the mean (SD) CHAQ DI for the overall group (Table 2) was 1.36 (0.77), with subsequent values of 1.20 (0.70) and 1.23 (0.66) at month 12 and LO, respectively. The CHAQ DI values did not represent a statistically significant change from baseline to LO ($P = .095$); however, the absolute change value from baseline to LO of −0.13 (0.44) represents the MCID established by Dempster et al.[23]

The MCID in the CHAQ DI is particularly relevant when considering the amount of assistance required for ambulation. Overall, 30.3% (n = 10/33) of patients required help from a person, walking aids, or a wheelchair at baseline (representing 26.3% of pediatric patients [5 of 19] and 35.7% of adults [5 of 14]). By the end of follow-up, only 18.3% (6/33) patients required help from a person or an assistive device (representing 15.8% or 3 of 19 pediatric patients and 21.4% or 3 of 14 adult patients; see Table 3). From the original 5 pediatric patients who required assistance at baseline, 4 improved and 1 did not change. At LO, 2 pediatric patients who did not require assistance at baseline required assistance from another person to ambulate. However, both pediatric patients improved in overall function as measured by a reduction in the CHAQ DI.

Also noteworthy, 3 patients (2 pediatric and 1 adult) who used the wheelchair for long-distance mobility by the baseline assessment were able to discontinue use postbaseline (Table 3). Conversely, 2 (22.2%) of 9 adult patients who did not use a wheelchair at baseline required use of a wheelchair at LO (Table 3). Both patients had significant musculoskeletal impairments and previous orthopedic surgeries. One patient underwent a lower limb amputation and required a walker and a wheelchair postsurgery, and the second patient had osteoarthritis and used a walker at baseline but required a wheelchair at LO.

The level of disability at baseline varied by group, with the adults presenting with a higher mean (SD) CHAQ DI (1.55 [0.55]) than the pediatric patients (1.22 [0.89]). The mean (SD) CHAQ DI for the pediatric group decreased from 1.22 (0.89) to 0.97 (0.62), and in the adult group it increased from 1.55 (0.55) to 1.57 (0.58) from baseline to LO, respectively (Table 2). The minimal clinically important improvement of 0.13 was achieved at LO for the pediatric group, with a mean change value of −0.24 (0.48) but was not reached for the adult group with a value of 0.02 (0.36; Figure 1).

Responder status is outlined with the distribution of CHAQ DI variations reported in Table 4. By month 12, the CHAQ DI improved (decreased) by at least 0.10 from baseline in 16 (51.6%) of 31 patients and by at least 0.15 in 12 (38.7%) of 31 patients. By the LO, the CHAQ DI improved (decreased) by

Table 3. Childhood Health Assessment Questionnaire: Patients Who Required Mobility Assistance by Age.

	Mobility Assistance at Baseline				Mobility Assistance at Last Observation				
Age at Baseline	Help From Caregiver	Walking Aids (Cane, Walker, Crutches)	Wheelchair	Overall	Help From Caregiver	Walking Aids (Cane, Walker, Crutches)	Wheelchair	Overall	Baseline to Last Observation
Pediatric									
7	No	Yes	Yes	Yes	No	No	No	No	Improved
7	No	No	No	No	Yes	No	No	Yes	Worsened
9	Yes	No	No	Yes	No	No	No	No	Improved
10	No	No	No	No	Yes	No	No	Yes	Worsened
15	Yes	No	No	Yes	No	No	No	No	Improved
15	No	Yes	Yes	Yes	No	No	No	No	Improved
17	Yes	No	No	Yes	Yes	No	No	Yes	No change
Adult									
22	Yes	No	No	Yes	No	No	No	No	Improved
22	No	No	No	No	Yes	Yes	Yes	Yes	Worsened
25	No	Yes	No	Yes	No	No	No	No	Improved
30	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No change
30	Yes	No	No	Yes	Yes	No	No	Yes	No change
30	Yes	Yes	Yes	Yes	No	No	No	No	Improved

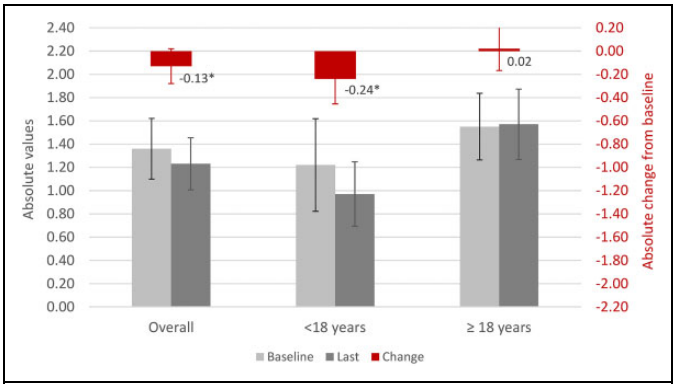

Figure 1. Childhood Health Assessment Questionnaire Disability Index mean change from baseline for the entire group and by age. For patients aged <18 years, n = 19 at baseline, n = 15 at month 6, n = 18 at month 12, n = 10 at month 18, n = 3 at month 24, n = 2 at month 36, and n = 8 at month 48. For patients aged ≥18 years, n = 14 at baseline, n = 9 at month 6, n = 11 at month 12, n = 1 at month 18, n = 5 at month 24, n = 2 at month 36, and n = 0 at month 48. * MCID ≥0.13. MCID indicates minimal clinically important difference; n, number of patients.

Table 4. Childhood Health Assessment Questionnaire Disability Index Responder Analysis for the Entire Group and by Age.

Responder Analysis (Change from baseline)	Patients < 18 years Total = 19, n (%)	Patients ≥18 years Total = 14, n (%)	All Patients Total = 33, n (%)
Month 12	n = 18	n = 13	n = 31
> −0.1	7 (38.9)	8 (61.5)	15 (48.4)
≤ −0.1	11 (61.1)	5 (38.5)	16 (51.6)
≤ −0.13	8 (44.4)	4 (30.8)	12 (38.7)
≤ −0.15	8 (44.4)	4 (30.8)	12 (38.7)
Last observation	n = 19	n = 14	n = 33
> −0.1	8 (42.1)	9 (64.3)	17 (51.5)
≤ −0.1	11 (57.9)	5 (35.7)	16 (48.5)
≤ −0.13	11 (57.9)	3 (21.4)	14 (42.4)
≤ −0.15	11 (57.9)	3 (21.4)	14 (42.4)

Abbreviation: n, number of patients.

at least 0.10 from baseline in 17 (51.5%) of 33 patients and 14 (42.4%) of 33 patients experienced an improvement (decrease) of at least 0.15. In general, a greater proportion of patients experienced a relevant improvement in the pediatric group compared to adults.

Childhood Health Assessment Questionnaire VAS Pain

At baseline, the mean (SD) CHAQ pain score was 0.618 (0.731), with subsequent values of 0.761 (0.931) at month 12 and 0.431 (0.616) at LO. The mean change value (SD) from baseline to month 12 was 0.148 (0.723) and baseline to LO was −0.173 (0.647; Figure 2).There was no statistically significant absolute or percentage change from baseline at any time point, but the mean change of 17% from baseline to LO was greater than the minimal clinically important improvement of ≥8.2% defined by Dhanani et al (Table 5).[24]

The adult group had a higher baseline mean level of pain (0.834 [0.920]) than the pediatric group (0.450 [0.508]). At LO, there was an improvement in the CHAQ Pain VAS that exceeded the MCID in the literature (−8.2%) in the adults (−35.3%) but not in the pediatric group (−0.4%). The adult group mean pain value (0.521 [0.689]) at LO remained slightly higher than the baseline pediatric values.

The performance status was characterized on the CHAQ Pain VAS according to 3 classes: mild impairment (0-<1), moderate impairment (1-<2), and severe impairment (2-3). Decrease of 66% in the number of patients with severe impairment was observed in CHAQ pain from baseline (n = 3, 9.4%

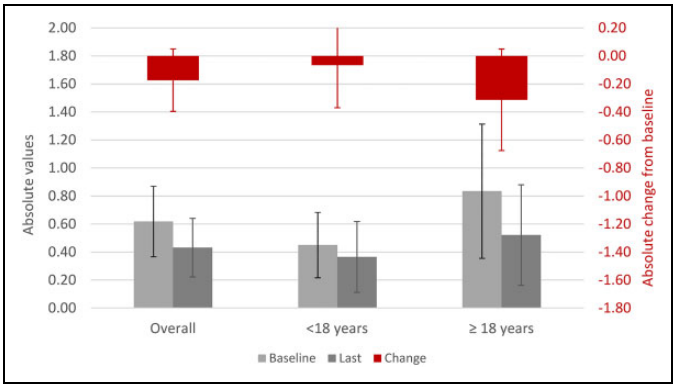

Figure 2. Childhood Health Assessment Questionnaire VAS Pain mean change from baseline for entire group and by age. For patients aged <18 years, n = 19 at baseline, n = 15 at month 6, n = 18 at month 12, n = 10 at month 18, n = 3 at month 24, n = 2 at month 36, and n = 8 at month 48. For patients aged ≥ 18 years, n = 14 at baseline, n = 9 at month 6, n = 11 at month 12, n = 1 at month 18, n = 5 at month 24, n = 2 at month 36, and n = 0 at month 48. n indicates number of patients; VAS, visual analogue scale.

overall population) to LO (n = 1, 3.0% overall population) and a corresponding increase in patients who had mild impairment (n = 24 patients, 75%, to n = 28 patients, 84.8%, respectively; Table 6).

EuroQol 5 Dimension-5 Level Questionnaire: Health Index Value

At baseline, the mean (SD) EQ-5D-5L Health Index value was 0.622 (0.170), while at LO the mean (SD) EQ-5D-5L index value was 0.672 (0.167), representing a mean (SD) absolute change from baseline of 0.050 (0.135) and a mean (SD) percentage change of 11.23% (24.72%). The mean increase reached statistical significance ($P = .036$) at LO for the percentage change (Table 7). Pediatric EQ-5D-5L health index values from baseline to the LO increased from 0.697 (0.184) to 0.780 (0.104) and for the adults from 0.568 (0.142) to 0.595 (0.163).

The mean absolute change value for the entire group of 0.050 is within the responder range defined by Kohn et al, from 0.041 to 0.059, and at the lower end of the MCID estimate by Kohn et al from 0.05 to 0.08.[25] Absolute change values for the pediatric group of 0.083 (0.136) exceed the MCID, but the 0.027 (0.134) observed in the adult group did not (Figure 3).

Individual EQ-5D-5L dimension results were consistent with the increase in disease severity with age that was found on the CHAQ. At baseline, 50% (n = 7) of adult patients and only 20% (n = 2) of pediatric patients had moderate problems with walking. The pediatric patients remained relatively stable with no patients demonstrating a decline in mobility function. Of the adult patients, 21.4% (n = 3) had improved mobility, 42.9% (n = 6) were stable, and 35.7% (n = 5) had increased difficulty at LO (Table 8).

Pain severity also varied by age on the EQ-5D-5L with adults comprising 6 of the 7 patients identified with moderate or severe pain. The level of pain in adults was reduced for 28.6% (n = 4) patients, remained unchanged in 57.1% (n = 8), and increased in severity for 14.3% (n = 2; Table 8). The pediatric patients had less pain at baseline with 40% (n = 4) of patients experiencing no pain, 50% (n = 5) had slight pain, and 10% (n = 1) had moderate pain. At LO, 80% (n = 8) of pediatric patients had no pain.

Similarly, adult patients also had more difficulty than pediatric patients in completing usual activities. Nine of the 12 patients with moderate or severe problems in usual activities were adults. A reduction was present in the overall number of patients presenting with severe problems in usual activities from a baseline value of 16.7% (n = 4) to 4.2% (n = 1) at LO. Usual activities were the most notable area of improvement for adults, with 50% (n = 7) of patients improving, 35.7% (n = 5) remaining stable, and 14.3% (n = 2) presenting with increased problems in usual care (Table 8). Ten percent (n = 1) of pediatric patients improved, 70% (n = 7) remained stable, and 20% (n = 2) declined.

More adult patients than pediatric patients presented with anxiety or depression. At baseline, 42.9% (n = 6) adults presented with slight anxiety or previous depression and 21.4% (n = 3) had moderate anxiety or depression. In comparison, 40% (n = 4) pediatric patients were slightly anxious or depressed, and only 10% (n = 1) were moderately anxious or depressed. At LO, 35.7% (n = 5) adult patients had reduced anxiety, 35.7% (n = 5) were stable, and 28.6% (n = 4) had increased anxiety. Forty percent (n = 4) of pediatric patients had reduced anxiety, 60% (n = 6) were stable, and no pediatric patients had increased anxiety at LO.

In the self-care dimension, 1 adult patient was unable to dress or wash himself at all time points and 1 pediatric patient had severe problems with self-care at baseline but had only moderate problems at LO. The level of difficulty with self-care remained stable for the majority of adult and pediatric patients, with 70% (n = 7) of pediatric and 64.3% (n = 9) of adult patients demonstrating no value change.

EuroQol 5 Dimension-5 Level Questionnaire: VAS for Best Health

At baseline, the mean (SD) EQ-5D-5L VAS for Best Health score was 67.9 (18.2). There was an increase in the mean score (SD) at LO of 3.3 (18.1), but the change did not reach statistical significance. There was no clear difference between subgroups based on age in the change in EQ-5D-5L VAS score over time.

Discussion

The CHAQ and EQ-5D-5L help to provide a more comprehensive picture of alpha-mannosidosis disease and to capture the effect of the disease on HRQoL and functioning in home, school, and community environments. This study shows that alpha-mannosidosis has a major impact on HRQoL, physical functioning, and level of independence in ADLs. In this study, the mean CHAQ DI value of 1.36 falls within the moderate

Table 5. Childhood Health Assessment Questionnaire Pain VAS Values for the Entire Group and by Age.

			Overall			
Timepoint	CHAQ Pain VAS		n	Mean (SD)	Median (Min; Max)	*P* Value	95% CI
Baseline	Actual value		32	0.618 (0.731)	0.465 (0.00; 2.52)		
Month 12	Actual value		31	0.761 (0.931)	0.210 (0.00; 2.55)		
	Change from baseline	Absolute	30	0.148 (0.723)	0.030 (−1.44; 1.80)	.271	−0.122 to 0.418
		%	20	3.697 (107.3)	−4.167 (−100.0; 320.0)	.879	−46.5 to 53.91
Last observation	Actual value		33	0.431 (0.616)	0.180 (0.00; 2.55)		
	Change from baseline	Absolute	32	−0.173 (0.647)	0.015 (−1.83; 1.59)	.139	−0.407 to 0.060
		%	21	−17.00[a] (109.8)	−44.2[a] (−100; 400.0)	.485	−67.0 to 32.94

			<18 years			≥18 years	
Timepoint	Age		n	Mean (SD)	Median (Min; Max)	n	Mean (SD)	Median (Min; Max)
Baseline	Actual value		18	0.450 (0.508)	0.210 (0.00; 1.53)	14	0.834 (0.920)	0.540 (0.00; 2.52)
Month 12	Actual value		18	0.623 (0.828)	0.105 (0.00; 2.40)	13	0.951 (1.062)	0.270 (0.00; 2.55)
	Change from baseline	Absolute	17	0.221 (0.705)	0.030 (−1.02; 1.80)	13	0.053 (0.763)	0.030 (−1.44; 1.44)
		%	10	−13.7 (82.59	−34.0 (−100; 116.2)	10	21.07 (129.6)	−3.57 (−100; 320.0)
Last observation	Actual value		19	0.365 (0.566)	0.150 (0.00; 1.68)	14	0.521 (0.689)	0.315 (0.00; 2.55)
	Change from baseline	Absolute	18	−0.065 (0.603)	0.015 (−1.14; 1.59)	14	−0.313 (0.696	−0.015 (−1.83; 0.42)
		%	17	−0.399 (144.3)	−68.0[a] (−100; 400.0)	10	−35.3[a] (54.27)	−38.7[a] (−100; 38.10)

Abbreviations: CHAQ, Childhood Health Assessment Questionnaire; CI, confidence interval; max, maximum; min, minimum; n, number of patients; SD, standard deviation; VAS, visual analogue scale.
[a]MCID ≥ 8.0%.

Table 6. Childhood Health Assessment Questionnaire Pain VAS Patients Status for the Entire Group.

		Patients Status		
Timepoint	n	Mild, Impairment 0-1	Moderate, Impairment >1-2	Severe Impairment >2-3
Baseline	32	24 (75.0)	5 (15.6)	3 (9.4)
Month 12	29	18 (62.1)	7 (24.1)	4 (13.8)
Last observation	33	28 (84.8)	4 (12.1)	1 (3.0)

Abbreviations: n, number of patients; VAS, visual analogue scale.

disability range of 1.53 (IQR: 0.59) as defined by Dempster et al[23] for children with arthritis. Twenty-two (67%) of 33 patients had baseline CHAQ DI values <1.0, confirming the impact of alpha-mannosidosis on physical function and the level of independence in ADLs.

The adult group had a higher level of disability and pain on the CHAQ when compared to the pediatric group, indicating disease progression with age. Similarly, on the EQ-5D-5L health index wherein a higher value indicates better health, adults presented with slightly lower values than the pediatric patients. Patients with alpha-mannosidosis always present with diverse complications to the disease, so it is challenging to hypothesize on the source of the pain. Beck et al[13] suggest that the pain may be due to progressive bone and joint disease. Beck et al found that skeletal deformities such as scoliosis, genu valgum, hip dysplasia, and joint contractures were present in a higher percentage of adults than children.[13] Disease progression with age as measured by HRQoL, disability, and pain may suggest the need to start treatment as soon as possible.

Pain is a prominent component of alpha-mannosidosis that affects HRQoL. This study did not specifically measure the association between pain and physical function measures, but previous research in Hunter Syndrome (HS), a rare disease with many musculoskeletal and cognitive impairments similar to those found in alpha-mannosidosis, supports the concept that pain and discomfort are key impairments that affect physical function and ability to perform ADLs.[26] Raluy-Callado et al found that the CHAQ values correlated with the 6-minute walk test and with function as measured by the HS-Functional Outcomes for Clinical Understanding Scale.[26] The mean CHAQ pain value for the adults in this study of 0.83 and the CHAQ DI of 1.55 are similar to the values published for adolescents with HS (0.80 and 1.49, respectively).[26]

Caregiver burden is an important consideration in the management of patients with rare diseases, especially when disability and pain are paired with cognitive impairment, and disease severity progresses with age. Additional research would be beneficial to understand the caregiver perspective and to identify caregiver challenges related to managing children and adults with alpha-mannosidosis.

Improvement trends in HRQoL and a reduction in disability following velmanase alfa treatment were detected overall and were most notable in the pediatric group versus the adult patient group. Pain was reduced in all groups and the mean value for adult and median value for pediatric patients exceeded the established MCID. The lack of statistically significant changes in any CHAQ end point (CHAQ DI and

Table 7. EuroQol 5 Dimension-5 Level Questionnaire Health Index Score Absolute Values and Change From Baseline for the Entire Group and by Age.

			Overall				
Timepoint	EQ-5D-5L		n	Mean	Median (Min; Max)	*P* Value	95% CI
Baseline	Actual value		24	0.622 (0.170)	0.612 (0.268; 1.00)		
Month 12	Actual value		21	0.668 (0.178)	0.6420 (0.275; 1.00)		
	Change from baseline	Absolute	21	0.0346 (0.1044)	0.000 (0.137; 0.264)	.145	−0.0130 to 0.082
		%	21	6.932 (19.098)	0.000 (−21.373; 63.20)	.112	−1.761 to 15.625
Last observation	Actual value		24	0.672 (0.1674)	0.655 (0.279; 1.000)		
	Change from baseline	Absolute	24	0.050 (0.135)	0.022 (−0.260; 0.302)	.080	0.0066 to 0.1075
		%	24	11.23 (24.72)	5.242 (31.4; 67.87)	.036	0.790 to 1.668

			<18 years			≥18 years		
Timepoint	Age		n	Mean (SD)	Median (Min; Max)	n	Mean (SD)	Median (Min; Max)
Baseline	Actual value		10	0.697 (0.184)	0.722 (0.439; 1.00)	14	0.568 (0.142)	0.584 (0.268; 0.827)
Month 12	Actual value		8	0.720 (0.182)	0.771 (0.436; 1.00)	13	0.636 (0.176)	0.641 (0.275; 1.00)
	Change from baseline	Absolute	8	−0.005 (0.065)	−0.005 (.111; 0.128)	13	0.059 (0.118)	0.029 (−0.137; 0.264)
		%	8	−.513 (8.538)	−1.01 (12.3; 18.08)	13	11.51 (22.49)	4.739 (−21.4; 63.20)
Last observation	Actual value		10	0.780 (0.104)	0.771 (0.587; 1.00)	14	0.595 (0.163)	0.561 (0.279; 1.00)
	Change from baseline	Absolute	10	0.083 (0.136)	0.045 (−0.111; 0.302)	14	0.027 (0.134)	0.022 (−0.260; 0.264)
		%	10	17.49 (28.27)	6.182 (12.3; 67.87)	14	6.754 (21.82)	5.242 (−31.4; 48.00)

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5 Dimension-5 Level questionnaire; max, maximum; min, minimum; n, number of patients; SD, standard deviation.

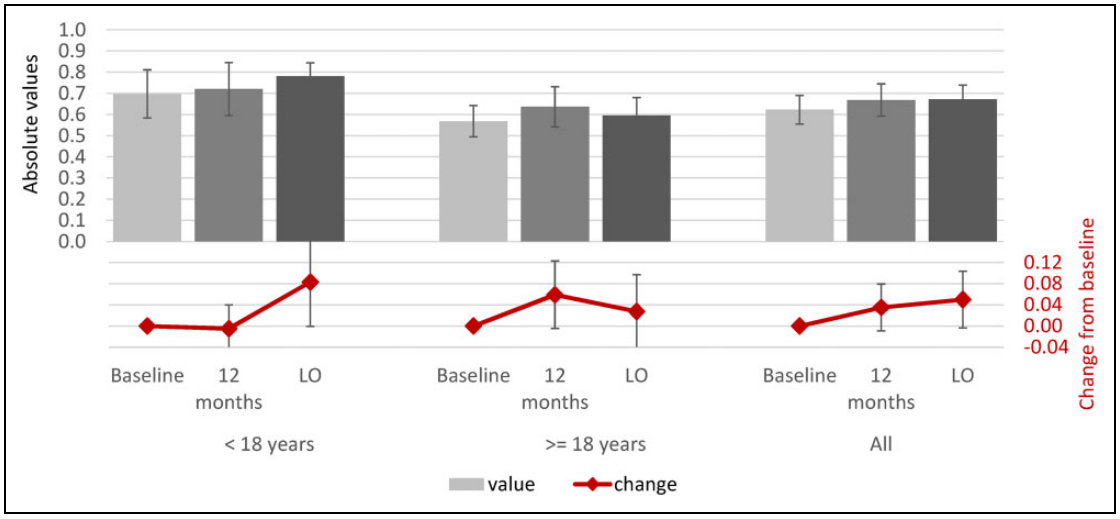

Figure 3. EuroQol 5 Dimension-5 Level questionnaire Health Index Score absolute values and changes from baseline overall and by age.

CHAQ Pain VAS) or the EQ-5D-5L health index absolute value may be accounted for by the rarity of alpha-mannosidosis. The low prevalence means that only a small sample size is available for studies, and further, that sample will always display significant patient heterogeneity. Again, because of the rarity, we cannot reduce the heterogeneity by altering the inclusion criteria. The EQ-5D-5L mean health index percentage did reach statistically significant change, and those change values fall within the responder ranges in the literature. The CHAQ mean change values for the entire group from baseline to LO met the MCID as defined by Dempster et al.[23] Pain reduction in both adults and children was evident on the CHAQ VAS and supported by a reduction in the proportion of patients with pain or discomfort on the EQ-5D-5L.

The rationale for ambulatory assistance from another person is not defined on the CHAQ. When interpreting the increase in ambulatory assistance required by 2 pediatric patients, it may be important to consider that assistance may have been necessary due to behavioral or cognitive challenges. Both patients had an overall improvement in function as measured by a reduction in the CHAQ DI.

Table 8. EuroQol 5 Dimension-5 Level Questionnaire Dimension Problems for Adult and Pediatric Patients From Baseline to LO.

	Improvement, Decreased Problems in Dimension				Stability, No Change in Dimension Score				Decline, Increased Problems in Dimension			
	Pediatric		Adult		Pediatric		Adult		Pediatric		Adult	
Dimension	n = 10	%	n = 14	%	n = 10	%	n = 14	%	n = 10	%	n = 14	%
Mobility	1	10%	3	21.4%	9	90%	6	42.9%	0	0%	5	35.7%
Self-care	3	30%	1	7.1%	7	70%	9	64.3%	0	0%	4	28.6%
Usual activities	1	10%	7	50%	7	70%	5	35.7%	2	20%	2	14.3%
Pain/discomfort	5	50%	4	28.6%	3	30%	8	57.1%	2	20%	2	14.3%
Anxiety/depression	4	40%	5	35.7%	6	60%	5	35.7%	0	0%	4	28.6%

Abbreviations: n, number of patients; LO, last available value at the end of the study.

A limitation of this study is the relatively small sample size with a very wide range of ages and functional presentations. Rare disease research often requires use of smaller sample size and a heterogeneous sample of patients. A broad inclusion of disease phenotypes allows better characterization, for which therapy may be feasible but adds increased design and analysis complexity. A wide heterogeneity in functional presentation and level of pain was present in both the adult and the pediatric patients and is consistent with what has previously been described in the literature.[13] The threshold for change on the CHAQ may vary with disease severity, and a smaller change may be more relevant in patients with mild disease.[23] The CHAQ has limited sensitivity to detect positive change in patients with low disability.[23] Despite the moderate level of disability observed on average at baseline, 11 of our 33 patients had a CHAQ DI of <1 and several of them had a score of 0. A ceiling effect may be present with patients who have a low score because only a small amount of improvement is possible. Ceiling effects reduce data variability and may further reduce the power of statistics in such a small sample size. Additional research would help to define the impact of functional heterogeneity on MCID in patients with alpha-mannosidosis.

Patients with alpha-mannosidosis present with moderate intellectual disability and limitations in problem-solving and memory that can impact their level of independence in activities of daily living.[7] An additional study limitation is that we are not able to attribute impacts to a single impairment like cognition, and we are able only to consider the complex interaction between multiple systems in our assessment of ADLs, physical function, and pain. Generic measures such as the CHAQ and EQ-5D-5L can be used to capture the composite impact of multiple systems and define a level of disability (CHAQ) and function relative to a normative population (EQ-5D-5L). Development of a disease-specific measure may be beneficial to capture increased sensitivity to change but would be inherently challenging to develop given the heterogeneity in the disease presentation, small sample size, and international patient distribution. In addition, comparability of EQ-5D-5L MCID between published and study values may be limited by variations between proxy and self-report.

Conclusions

This study helps to define the impact of alpha-mannosidosis on HRQoL, disability level, and pain. Baseline values illustrate that a moderate level of disability was present in the overall alpha-mannosidosis patient population and that a greater level of disability and poorer overall health was present in adult versus pediatric patients. The mean adult CHAQ VAS for pain was almost double the value for the pediatric group, and more adult than pediatric patients presented with severe pain on the EQ-5D-5L. Disability and pain values indicate a disease progression in the initial phase of the disease and may suggest the need to start treatment as soon as possible.

The long-term prognosis for untreated alpha-mannosidosis is poor due to progressive neuromuscular and skeletal deterioration that lead to increased dependence in mobility and ADLs and increased caregiver and health-care burden. The long-term data highlight improvement trends in HRQoL and a reduction in disability and pain, following up to 48 months of treatment with velmanase alfa. Although statistically significant change was present for only the mean EQ-5D-5L health index percentage score, the mean CHAQ DI, CHAQ VAS, and EQ-5D-5L health index absolute change values all fell within responder ranges as defined in the literature. The proportion of patients who experienced moderate or severe problems with pain, mobility, and usual activities was reduced from baseline to last observation. The CHAQ DI and EQ-5D-5L health index changes were most notable in the pediatric group, but the reduction in pain in adults on the CHAQ VAS was also relevant and fell within defined responder ranges. Moreover, both adults and children comprised the sample of patients who presented with their ambulatory dependence on a device or third party reduced at LO. The rhLAMAN-10 study results clearly communicate the challenges of daily living for patients with alpha-mannosidosis. The improvement trends observed in their HRQoL under velmanase alfa treatment, the impressive length of the follow-up period in this study, and the progressive deterioration that must be foreseen when such patients are not treated, should all be factors when assessing the clinical relevance of these results.

Authors' Note

Written informed consent was obtained from the patient or his/her legally authorized guardian(s) prior to performing any trial-related activities. The clinical trial, rhLAMAN-10, was conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practice guidelines, and following all other requirements of local laws. The trial was registered with the following agencies:

ClinicalTrials.gov trial registration: NCT02478840 Evaluation of Long-term Efficacy of Treatment with Lamazym (rhLAMAN-10). Study start date: February 2015. URL: https://clinicaltrials.gov/ct2/show/study/NCT02478840?cond=Alpha-Mannosidosis&draw=1&rank=10.

The EudraCT Trial Registration Number: 2014-003950-15 (Sponsor Protocol Number: rhLAMAN-10). Start Date: 2015-01-22. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-003950-15.

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