Clinical trial results:
A multi-center, un-controlled, open-labeled trial of the long-term safety of velmanase alfa aftercare treatment of subjects with alpha-Mannosidosis

Summary

EudraCT number	2013-000336-97
Trial protocol	DK FR
Global end of trial date	30 September 2022

Results information

Result version number	v1 (current)
This version publication date	21 May 2023
First version publication date	21 May 2023

Trial information

Trial identification

Sponsor protocol code	rhLAMAN-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01908712
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2013-000336-97

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Chiesi Clinical Trial, Chiesi Farmaceutici S.p.A, 0039 05212791, clinicaltrials_info@chiesi.com
Scientific contact	Chiesi Clinical Trial, Chiesi Farmaceutici S.p.A, 0039 05212791, clinicaltrials_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2022
Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: evaluation of safety of repeated velmanase alfa intravenous (i.v.) treatment of subjects with alpha-mannosidosis.
Secondary objectives: evaluating long-term efficacy of velmanase alfa on endurance (6-Minute Walk Test (6MWT), 3-Minute Stair Climb Test (3MSCT)), pulmonary function, serum oligosaccharides, hearing, cognitive development (Leiter International Performance Scale - Revised), motor proficiency (Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition), quality of life (Childhood health Assessment Questionnaire (CHAQ), EuroQoL-5 Dimensions 5-Levels Questionnaire), cerebrospinal fluid (CSF) and 24-hour urine oligosaccharides, central nervous system involvement (imaging and CSF biomarkers (tubulin associated unit, neurofilament light and glial fibrillary acidic proteins)) and in vivo biological activity; evaluating pharmacokinetics; monitoring long-term safety profile including immunogenicity (anti-immunoglobulin (Ig)G) anti-drug antibodies (ADAs)).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and following all other requirements of local laws. Subjects who had enrolled in earlier velmanase alfa trials (rhLAMAN-02/-03/-04, rhLAMAN-05 and rhLAMAN-08) and those not previously enrolled in a velmanase alfa trial were enrolled. Adverse events including infusion-related reactions were collected at every visit. Other safety assessments (performed as per the trial flow chart) including laboratory evaluations (haematology, biochemistry, urinalysis, coagulation tests), physical examination, recording of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature), tests for ADAs and neutralising antibodies (every 12 weeks) and serum IgG/IgM/IgA (every 24 weeks). Electrocardiograms (ECGs) and echocardiograms were recorded at a comprehensive evaluation visit (CEV) performed by 7 subjects who had enrolled in earlier trials. At the first dose visit for subjects not previously enrolled in a velmanase alfa trial, vital signs were monitored immediately prior to infusion, every 30 minutes (±5 minutes) during infusion and during the observation period of 2 hours post-infusion. At other dosing visits, medical personnel continuously observed subjects until 1 hour post-infusion; vital signs were monitored at the Investigator's discretion; and observation periods were prolonged if required. Medical/surgical history was recorded at screening. Concomitant medications and illnesses were collected throughout the trial. During the coronavirus disease 2019 (COVID-19) pandemic, a contingency plan was developed for protection of subjects in treatment phase and appropriate mitigation actions were adopted according to local regulations. These included implementation of a home infusion programme for suitable subjects (as determined by the Investigator) with infusions administered by specialised nurses.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 13

Worldwide total number of subjects	13
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	6
Adolescents (12-17 years)	3
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initially, only subjects who had completed rhLAMAN-04 or rhLAMAN-05 trials were eligible for inclusion and 7 subjects were enrolled. Further to protocol amendments, a subject who had completed the rhLAMAN-08 trial and 5 subjects not previously enrolled in a velmanase alfa trial with confirmed diagnosis of alpha-mannosidosis were later enrolled.

Pre-assignment

Screening details:

An informed consent from subjects/their legally authorised guardians was obtained prior to any trial-related procedures. Inclusion/exclusion criteria were checked, medical/surgical history and concomitant medications and illnesses were collected, demographics were recorded and a serum pregnancy test was performed as applicable.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable, open-label trial.

Arms

Arm title	Enrolled subjects

Arm description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the investigational medicinal product (IMP) velmanase alfa (recombinant human alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

Arm type	Experimental
Investigational medicinal product name	Velmanase alfa
Investigational medicinal product code	CHFLMZYM
Other name	Lamzede
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Velmanase alfa was administered as i.v. infusion once weekly at a dose of 1 mg/kg (weight recorded at first dose visit for subjects not previously enrolled in a velmanase alfa trial, and every 4 weeks for all subjects). An i.v. catheter could be implanted to ease delivery. The IMP is supplied as a sterile freeze-dried product in single use vials containing 10 mg, each to be reconstituted with 5.0 mL sterile water for injection. Stability of the reconstituted product is 24 hours at 5°C±3°C and 10 hours at a maximum of 25°C. The solution should reach room temperature prior to infusion. Vials were prepared as per the volume required for the dose and swirled with slow rotations for 10-15 seconds after reconstitution, required volume was withdrawn into one or more large-dose syringes and an infusion set with a mounted filter was filled. Maximum infusion rate was 25 ml/hour. The last empty syringe was replaced with one filled with 20 ml isotonic sodium chloride to infuse the product in set.

Number of subjects in period 1	Enrolled subjects
Started	13
Completed	12
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

Reporting group values	Overall trial	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	6	6	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	4	4	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
The age is presented as at treatment baseline (i.e. age of subjects at the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02, rhLAMAN-05 and rhLAMAN-08).			
Units: years			
arithmetic mean	14.3		
standard deviation	± 9.4	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	8	8	

Subject analysis sets

Subject analysis set title	Paediatric subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Enrolled subjects who were <18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02, rhLAMAN-05 and rhLAMAN-08).

Subject analysis set title	Adult subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Enrolled subjects who were ≥18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02, rhLAMAN-05 and rhLAMAN-08).

Reporting group values	Paediatric subjects	Adult subjects	
Number of subjects	9	4	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	6	0	
Adolescents (12-17 years)	3	0	
Adults (18-64 years)	0	4	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
The age is presented as at treatment baseline (i.e. age of subjects at the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02, rhLAMAN-05 and rhLAMAN-08).			
Units: years			
arithmetic mean	9.4	25.3	
standard deviation	± 4.0	± 8.8	
Gender categorical Units: Subjects			
Female	3	2	
Male	6	2	

End points

End points reporting groups

Reporting group title	Enrolled subjects

Reporting group description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the investigational medicinal product (IMP) velmanase alfa (recombinant human alpha-mannosidase). All enrolled subjects were included in the Full Analysis Set and the Safety Analysis Set.

Subject analysis set title	Paediatric subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Enrolled subjects who were <18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02, rhLAMAN-05 and rhLAMAN-08).

Subject analysis set title	Adult subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Enrolled subjects who were ≥18 years old at treatment baseline (i.e. when they received the first ever dose of velmanase alfa including in earlier trials rhLAMAN-02, rhLAMAN-05 and rhLAMAN-08).

Primary: Number of subjects with infusion-related reactions (IRRs)

End point title	Number of subjects with infusion-related reactions (IRRs)[1]

End point description:

An adverse drug reaction (ADR) was an AE assessed to be related to study treatment by the Investigator. An IRR was defined as an ADR which occurred during or within 2 hours after the end of the infusion of velmanase alfa and was assessed by the Investigator as being infusion-related. The AEs were classified according to the Medical Dictionary for Regulatory Activities Version 23.0. The IRRs were summarised by System Organ Class and Preferred Term (PT) overall and by age group. The number of subjects experiencing events is presented by PT.

End point type	Primary

End point timeframe:

Data for IRRs were collected from enrolment in rhLAMAN-07 until the end of study.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As per protocol, data have been presented through listings and when applicable summarised, with no inferential statistics implemented.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13[2]	9[3]	4[4]	
Units: Subject				
Tachycardia	1	1	0	
Diarrhoea	3	1	2	
Vomiting	2	2	0	
Chills	1	1	0	
Fatigue	1	1	0	
Hypokalaemia	1	0	1	
Increased appetite	1	0	1	
Headache	2	1	1	
Cough	1	1	0	
Rash	1	1	0	

Notes:

[2] - Six subjects experienced 22 IRRs.

[3] - Four paediatric subjects experienced 14 IRRs.

[4] - Two adult subjects experienced 8 IRRs.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for serum oligosaccharides

End point title	Absolute change from treatment baseline to time windows for serum oligosaccharides

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (including in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1) and windowing was performed using the calculated day and a window built around a target day. If >1 time point was reported in the same window, the average of all values was considered in the analysis. Mean (SD) treatment baseline values overall, in paediatric subjects and in adult subjects were 7.925 (3.199), 8.413 (3.902) and 6.950 (0.311) µmol/L, respectively. For 0-12 weeks and time intervals from 156-204, 228-276, 348-372 and 516-612 weeks, data were available for only 1 subject overall. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to time windows from start of treatment (0-12 weeks and 24-weekly intervals thereafter until end of study).

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9[5]	4[6]	
Units: µmol/L				
arithmetic mean (standard deviation)				
12-36 weeks	-4.480 (± 1.659)	-4.262 (± 1.798)	-5.350 (± 0.495)	
36-60 weeks	-5.240 (± 2.435)	-5.357 (± 2.973)	-4.967 (± 0.153)	
60-84 weeks	-6.063 (± 4.095)	-6.700 (± 4.766)	0 (± 0)	
84-108 weeks	-6.225 (± 4.938)	-6.225 (± 4.938)	0 (± 0)	
108-132 weeks	-4.215 (± 1.827)	-3.725 (± 1.688)	0 (± 0)	
204-228 weeks	-8.988 (± 4.967)	-8.988 (± 4.967)	0 (± 0)	
324-348 weeks	-4.650 (± 0.636)	0 (± 0)	-4.650 (± 0.636)	
372-396 weeks	-5.140 (± 0.924)	-4.750 (± 1.626)	-5.400 (± 0.361)	
396-420 weeks	-4.840 (± 0.503)	-4.900 (± 0.990)	-4.800 (± 0.100)	

420-444 weeks	-5.160 (± 1.309)	-4.900 (± 2.404)	-5.333 (± 0.651)	
444-468 weeks	-4.900 (± 1.017)	-5.250 (± 1.909)	-4.667 (± 0.208)	
468-492 weeks	-5.733 (± 1.097)	-5.550 (± 1.485)	0 (± 0)	
492-516 weeks	-4.975 (± 1.135)	-5.267 (± 1.193)	0 (± 0)	

Notes:

[5] - No data for 324-348 weeks.

[6] - Available data: 1 subject at 60-84, 108-132, 468-492 & 492-516 weeks; none at 84-108 & 204-228 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to the CEV for CSF oligosaccharides

End point title	Absolute change from treatment baseline to the CEV for CSF oligosaccharides

End point description:

The mean (SD) treatment baseline values for the overall population, paediatric subjects and adult subjects were 14.200 (7.934), 15.840 (9.889) and 11.467 (2.608) µmol/L, respectively. Of note, treatment baseline values were available for the subjects who performed the CEV and the subject who had enrolled in rhLAMAN-08 who did not perform the CEV.

End point type	Secondary

End point timeframe:

The CEV was performed by subjects who had enrolled in earlier trials rhLAMAN-02 and rhLAMAN-05, a mean of 2.2 years from treatment baseline. Absolute change in CSF oligosaccharide concentration from treatment baseline to the CEV was analysed.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	7[7]	4[8]	3[9]	
Units: µmol/L				
arithmetic mean (standard deviation)	-1.171 (± 0.720)	-0.875 (± 0.869)	-1.567 (± 0.115)	

Notes:

[7] - Seven subjects who had enrolled in rhLAMAN-02 and rhLAMAN-05 performed the CEV.

[8] - Four paediatric patients who were enrolled in rhLAMAN-02 and rhLAMAN-05 performed the CEV.

[9] - Three adult subjects who had enrolled in rhLAMAN-02 and rhLAMAN-05 performed the CEV,

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to the CEV for oligosaccharides in 24-hour urine

End point title	Absolute change from treatment baseline to the CEV for oligosaccharides in 24-hour urine

End point description:

Baseline value was available for 1 paediatric subject (604.000 µmol/L).

End point type	Secondary

End point timeframe:

The CEV was performed by subjects who had enrolled in earlier trials rhLAMAN-02 and rhLAMAN-05, a mean of 2.2 years from treatment baseline. Absolute change in oligosaccharides in 24-hour urine from treatment baseline to the CEV was analysed.

End point values	Enrolled subjects	Paediatric subjects		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	1[10]	1[11]		
Units: µmol/L				
number (not applicable)	-451.900	-451.900		

Notes:

[10] - Values at treatment baseline and the CEV are available for 1 subject.

[11] - Values at treatment baseline and the CEV were available for one paediatric subject.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for the 6MWT

End point title	Absolute change from treatment baseline to time windows for the 6MWT

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (including in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 472.1 (96.4), 434.5 (74.7) and 547.3 (98.9) metres, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. Data available for 1 subject at 12 years.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[12]	
Units: metre				
arithmetic mean (standard deviation)				
0-6 months	-17.0 (± 43.8)	-17.0 (± 43.8)	0 (± 0)	
1 year	39.6 (± 48.3)	53.1 (± 54.0)	12.8 (± 17.5)	
2 years	57.0 (± 53.2)	62.7 (± 61.7)	40.0 (± 0.0)	
4 years	16.5 (± 41.5)	21.0 (± 64.5)	12.0 (± 8.9)	
6 years	-3.6 (± 43.9)	31.7 (± 25.7)	-38.8 (± 20.6)	

8 years	-28.4 (± 53.0)	7.5 (± 25.2)	-64.3 (± 50.2)	
10 years	-45.8 (± 103.2)	3.7 (± 36.5)	0 (± 0)	

Notes:

[12] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for 3MSCT

End point title	Absolute change from treatment baseline to time windows for 3MSCT

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline results for enrolled, paediatric and adult subjects were 61.12 (11.06), 59.05 (10.69) and 65.27 (12.14) steps/minute, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. Data available for 1 subject at 12 years.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[13]	
Units: steps/minute				
arithmetic mean (standard deviation)				
0-6 months	-0.50 (± 10.14)	-0.50 (± 10.14)	0 (± 0)	
1 year	5.48 (± 5.25)	5.53 (± 5.10)	5.39 (± 6.35)	
2 years	5.40 (± 7.39)	6.70 (± 7.40)	1.51 (± 8.25)	
4 years	2.26 (± 5.28)	2.33 (± 6.17)	2.19 (± 5.63)	
6 years	1.83 (± 7.49)	4.74 (± 8.99)	-1.08 (± 5.85)	
8 years	1.92 (± 3.69)	3.78 (± 4.82)	0.07 (± 0.75)	
10 years	-4.16 (± 7.49)	-2.54 (± 8.27)	0 (± 0)	

Notes:

[13] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for forced

vital capacity (FVC) in litres

End point title	Absolute change from treatment baseline to time windows for forced vital capacity (FVC) in litres

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 2.663 (1.185), 2.102 (1.071) and 3.505 (0.852) litres, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. At 12 years, data were available for only 1 subject.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[14]	
Units: litre(s)				
arithmetic mean (standard deviation)				
0-6 months	0.475 (± 0.431)	0.475 (± 0.431)	0 (± 0)	
1 year	0.508 (± 0.524)	0.650 (± 0.592)	0.295 (± 0.373)	
2 years	0.698 (± 0.802)	0.888 (± 0.794)	0.320 (± 0.948)	
4 years	0.552 (± 0.703)	0.953 (± 0.760)	0.150 (± 0.419)	
6 years	0.550 (± 0.731)	0.940 (± 0.785)	0.160 (± 0.515)	
8 years	0.738 (± 1.213)	1.637 (± 0.993)	-0.160 (± 0.522)	
10 years	1.013 (± 1.218)	1.463 (± 1.003)	0 (± 0)	

Notes:

[14] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for FVC percent predicted

End point title	Absolute change from treatment baseline to time windows for FVC percent predicted

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of

assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were were 83.2 (21.9)%, 73.0 (21.0)% and 98.5 (13.4)%, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. At 12 years, data were available for only 1 subject.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[15]	
Units: percentage				
arithmetic mean (standard deviation)				
0-6 months	11.0 (± 7.1)	11.0 (± 7.1)	0 (± 0)	
1 year	11.7 (± 10.1)	13.5 (± 10.0)	8.9 (± 11.0)	
2 years	15.0 (± 18.0)	16.8 (± 14.8)	11.5 (± 30.4)	
4 years	8.5 (± 13.0)	12.5 (± 12.6)	4.5 (± 14.8)	
6 years	7.8 (± 20.2)	16.8 (± 16.4)	-1.2 (± 22.5)	
8 years	2.1 (± 20.1)	17.0 (± 9.8)	-12.8 (± 15.8)	
10 years	3.4 (± 15.0)	9.8 (± 9.4)	0 (± 0)	

Notes:

[15] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for forced expiratory volume in the first second (FEV1) (litres)

End point title	Absolute change from treatment baseline to time windows for forced expiratory volume in the first second (FEV1) (litres)

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Averages of values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 2.372 (1.050), 1.928 (0.969) and 3.038 (0.871) litres, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. At 12 years, data were available for only 1 subject.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[16]	
Units: litre(s)				
arithmetic mean (standard deviation)				
0-6 months	0.425 (± 0.233)	0.425 (± 0.233)	0 (± 0)	
1 year	0.438 (± 0.507)	0.602 (± 0.549)	0.193 (± 0.367)	
2 years	0.568 (± 0.690)	0.728 (± 0.590)	0.250 (± 1.018)	
4 years	0.380 (± 0.516)	0.735 (± 0.658)	0.143 (± 0.327)	
6 years	0.493 (± 0.663)	0.777 (± 0.825)	0.210 (± 0.422)	
8 years	0.568 (± 1.062)	1.260 (± 1.051)	-0.123 (± 0.531)	
10 years	0.663 (± 1.043)	0.983 (± 1.007)	0 (± 0)	

Notes:

[16] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for FEV1 percent predicted

End point title	Absolute change from treatment baseline to time windows for FEV1 percent predicted

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline values for enrolled, paediatric and adult subjects were 82.0 (19.3)%, 74.8 (18.0)% and 92.8 (18.0)%, respectively. Paired t-test and linear mixed model analyses were performed.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. At 12 years, data were available for only 1 subject.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[17]	
Units: percentage				
arithmetic mean (standard deviation)				
0-6 months	11.0 (± 2.8)	11.0 (± 2.8)	0 (± 0)	
1 year	11.4 (± 12.2)	14.7 (± 12.5)	6.4 (± 11.7)	
2 years	12.6 (± 18.2)	14.1 (± 11.8)	9.5 (± 34.6)	
4 years	7.1 (± 9.1)	10.8 (± 3.9)	4.7 (± 11.6)	
6 years	8.3 (± 16.4)	12.8 (± 17.3)	3.7 (± 17.7)	
8 years	5.6 (± 19.5)	15.2 (± 20.3)	-4.1 (± 16.2)	
10 years	3.4 (± 16.9)	7.8 (± 17.6)	0 (± 0)	

Notes:

[17] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for peak expiratory flow (PEF)

End point title	Absolute change from treatment baseline to time windows for peak expiratory flow (PEF)

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if there was >1 time point in the same window for a subject. Mean (SD) treatment baseline results for enrolled, paediatric and adult subjects were 4.918 (2.390), 3.967 (1.841) and 6.345 (2.638) litres per second, respectively. Paired t-test and linear mixed model analyses were done.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. Data were only available for 1 subject at 12 years.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[18]	
Units: litres per second				
arithmetic mean (standard deviation)				
0-6 months	1.335 (± 0.346)	1.335 (± 0.346)	0 (± 0)	
1 year	1.136 (± 1.345)	0.895 (± 0.741)	1.497 (± 2.055)	
2 years	1.178 (± 2.178)	1.320 (± 1.010)	0.895 (± 4.518)	

4 years	1.083 (± 0.813)	1.223 (± 0.883)	0.943 (± 0.903)	
6 years	1.168 (± 1.367)	1.237 (± 1.546)	1.100 (± 1.507)	
8 years	0.785 (± 2.587)	2.550 (± 1.886)	-0.980 (± 1.957)	
10 years	1.278 (± 2.073)	1.787 (± 2.211)	0 (± 0)	

Notes:

[18] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ Disability Index

End point title	Absolute change from treatment baseline to time windows for CHAQ Disability Index

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 1.365 (0.743), 1.484 (0.836) and 1.125 (0.530), respectively. The CHAQ-DI can range from 0 to 3; higher score indicates worsening.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. At 12 years, data were available for only 1 subject.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[19]	
Units: score				
arithmetic mean (standard deviation)				
0-6 months	0.313 (± 0.795)	0.313 (± 0.795)	0 (± 0)	
1 year	-0.078 (± 0.398)	-0.086 (± 0.459)	-0.063 (± 0.298)	
2 years	-0.125 (± 0.634)	-0.125 (± 0.680)	-0.125 (± 0.707)	
4 years	0.156 (± 0.462)	0.083 (± 0.674)	0.229 (± 0.253)	
6 years	-0.094 (± 0.675)	-0.271 (± 0.989)	0.083 (± 0.260)	
8 years	0.240 (± 0.325)	0.139 (± 0.446)	0.340 (± 0.187)	
10 years	0.688 (± 0.971)	0.458 (± 1.048)	0 (± 0)	

Notes:

[19] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ Visual Analogue Scale (VAS) Pain

End point title	Absolute change from treatment baseline to time windows for CHAQ Visual Analogue Scale (VAS) Pain

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline results for enrolled, paediatric and adult subjects were 0.583 (0.698), 0.799 (0.764) and 0.150 (0.227), respectively. Scores range from 0 (no pain) to 3 (very severe pain).

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. At 12 years, data were only available for 1 subject.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[20]	
Units: score				
arithmetic mean (standard deviation)				
0-6 months	0.330 (± 0.297)	0.330 (± 0.297)	0 (± 0)	
1 year	-0.041 (± 1.032)	-0.259 (± 1.183)	0.394 (± 0.508)	
2 years	-0.195 (± 0.398)	-0.230 (± 0.393)	-0.090 (± 0.552)	
4 years	-0.013 (± 0.344)	-0.145 (± 0.403)	0.120 (± 0.286)	
6 years	-0.020 (± 0.381)	-0.150 (± 0.556)	0.110 (± 0.062)	
8 years	0.293 (± 0.597)	0.047 (± 0.631)	0.538 (± 0.558)	
10 years	0.548 (± 0.908)	0.190 (± 0.686)	0 (± 0)	

Notes:

[20] - No adults had data available at 0-6 months. Data available for 1 adult at 10 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from treatment baseline to time windows for CHAQ VAS General

End point title	Absolute change from treatment baseline to time windows for CHAQ VAS General

End point description:

Treatment baseline: last non-missing value before first ever dose of velmanase alfa (in previous trials if subjects enrolled and treated; in rhLAMAN-07 for those not enrolled in earlier trials and placebo group, rhLAMAN-05). Assessments during treatment were assigned to a time point (calculation: (date of assessment - date of first ever dose of velmanase alfa)+1); windowing was performed using the calculated day and a window built around a target day. Six months (183 days) to 365 days were accepted between yearly evaluation visits (rhLAMAN-07); dates >365 days+183 days after a visit belonged to the next visit and dates <183 days from a visit belonged to that visit. Average values were used for analysis if >1 time point was reported in the same window for a subject. Mean (SD) treatment baseline scores for enrolled, paediatric and adult subjects were 1.365 (0.797), 1.286 (0.914) and 1.523 (0.573), respectively. Scores range from 0 to 3; higher scores indicate lower quality of life.

End point type	Secondary

End point timeframe:

Treatment baseline to 0-6, 6-18, 18-36, 36-60, 60-84, 84-108, 108-132 and 132-156 months (i.e. post-treatment baseline and 1, 2, 4, 6, 8, 10 and 12 years, respectively) from start of treatment. At 12 years, data were available for only 1 subject.

End point values	Enrolled subjects	Paediatric subjects	Adult subjects	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	9	4[21]	
Units: score				
arithmetic mean (standard deviation)				
0-6 months	0.030 (± 0.636)	0.030 (± 0.636)	0 (± 0)	
1 year	-0.211 (± 1.286)	-0.242 (± 1.569)	-0.150 (± 0.559)	
2 years	0.008 (± 1.012)	-0.195 (± 1.094)	0.615 (± 0.445)	
4 years	0.485 (± 0.561)	0.750 (± 0.455)	0.220 (± 0.608)	
6 years	-0.318 (± 1.107)	-0.410 (± 1.115)	-0.225 (± 1.339)	
8 years	0.454 (± 0.816)	0.863 (± 1.065)	0.045 (± 0.169)	
10 years	0.649 (± 0.381)	0.465 (± 0.123)	0 (± 0)	

Notes:

[21] - No adults had data available at 0-6 months. Data available for 1 subject at 10 years.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Detection of ADAs

End point title	Detection of ADAs

End point description:

Detection of ADAs was a secondary objective and safety endpoint. Blood samples were collected for ADA assessments prior to first dose of velmanase alfa for subjects not previously enrolled in a velmanase alfa trial, every 12 weeks during rhLAMAN-07 for all patients and during the CEV for patients who had enrolled in rhLAMAN-02 and rhLAMAN-05 (who performed the visit). For subjects who had received placebo during rhLAMAN-05, the first ADA assessment was considered as treatment baseline but only if captured not more than 7 days after the first study treatment administration. Subjects were considered to be ADA-positive if they were positive at treatment baseline or had an ADA-positive test at least once during rhLAMAN-07. Subjects were considered to be ADA-negative if they had no ADA-positive tests. At treatment baseline, 10 subjects were ADA-negative and 3 subjects were ADA-positive. The number of subjects who were ADA-positive/negative as defined above, is presented.

End point type	Other pre-specified

End point timeframe:

At treatment baseline (i.e. prior to first ever dose of velmanase alfa including in previous trials) and during rhLAMAN-07.

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Subject				
Positive	11			
Negative	2			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Absolute change from treatment baseline to time windows for serum IgG

End point title	Absolute change from treatment baseline to time windows for serum IgG

End point description:

Serum IgG was a safety laboratory parameter which can also be considered a pharmacodynamic marker. Treatment baseline values were only available for 4 subjects who were not previously enrolled in a velmanase alfa trial. The assessments during the trial were allocated to 6-month intervals based on the duration since the first dose of velmanase alfa in rhLAMAN-07. If there was >1 assessment per interval for the same subject, the average was used in the analysis. Mean (SD) treatment baseline value overall was 5.983 (1.414) grams/litre. Paired t-test analysis was performed.

End point type	Other pre-specified

End point timeframe:

Trial (also treatment) baseline to 6-monthly intervals until the end of trial (i.e. 0-6, 6-12, 12-18, 18-24 and 24-30 months).

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	4[22]			
Units: gram(s)/litre				
arithmetic mean (standard deviation)				
0-6 months	2.610 (± 0.833)			
6-12 months	2.779 (± 0.491)			
12-18 months	3.157 (± 0.539)			
18-24 months	3.360 (± 0.000)			
24-30 months	4.370 (± 0.042)			

Notes:

[22] - Four subjects not previously enrolled in a velmanase alfa trial with treatment baseline values.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected from the time of informed consent in rhLAMAN-07, for the duration of the trial.

Adverse event reporting additional description:

All TEAEs were collected from spontaneous, unsolicited reports of subjects, by observation and by routine open questioning.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Enrolled subjects

Reporting group description:

This was an open-label trial where all enrolled subjects received once weekly i.v. administration of the investigational medicinal product (IMP) velmanase alfa (recombinant human alpha-mannosidase). All enrolled subjects were included in the full analysis set and the safety analysis set.

Reporting group title	Paediatric subjects

Reporting group description:

Subjects aged <18 years at the time of first ever dose of velmanase alfa

Reporting group title	Adult subjects

Reporting group description:

Subjects aged ≥18 years at the time of first ever dose of velmanase alfa.

Serious adverse events	Enrolled subjects	Paediatric subjects	Adult subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	4 / 9 (44.44%)	2 / 4 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Somnolence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			

subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Enrolled subjects	Paediatric subjects	Adult subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	9 / 9 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 13 (15.38%)	2 / 9 (22.22%)	0 / 4 (0.00%)
occurrences (all)	3	3	0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1

Hypertension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Poor venous access			
subjects affected / exposed	2 / 13 (15.38%)	0 / 9 (0.00%)	2 / 4 (50.00%)
occurrences (all)	4	0	4
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Wisdom teeth removal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Catheter site erythema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Catheter site oedema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Chills			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	7	7	0
Complication associated with device			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Crying			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Extravasation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Fatigue			

subjects affected / exposed	3 / 13 (23.08%)	2 / 9 (22.22%)	1 / 4 (25.00%)
occurrences (all)	5	3	2
Hyperthermia			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	4	3	1
Malaise			
subjects affected / exposed	2 / 13 (15.38%)	0 / 9 (0.00%)	2 / 4 (50.00%)
occurrences (all)	4	0	4
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	3	3	0
Pyrexia			
subjects affected / exposed	6 / 13 (46.15%)	5 / 9 (55.56%)	1 / 4 (25.00%)
occurrences (all)	12	8	4
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Testicular pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
COVID-19			
subjects affected / exposed	4 / 13 (30.77%)	3 / 9 (33.33%)	1 / 4 (25.00%)
occurrences (all)	4	3	1
Cough			
subjects affected / exposed	6 / 13 (46.15%)	4 / 9 (44.44%)	2 / 4 (50.00%)
occurrences (all)	16	13	3
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Rhinitis allergic			

subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Behaviour disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Encopresis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Enuresis			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Hallucination			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	0	4
Sleep disorder			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Somnambulism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Product issues			
Device occlusion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Investigations			

Aspiration bone marrow			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hand fracture			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Product administration error			
subjects affected / exposed	3 / 13 (23.08%)	2 / 9 (22.22%)	1 / 4 (25.00%)
occurrences (all)	8	7	1
Road traffic accident			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Scar			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Scratch			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Skin wound			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Traumatic arthrosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Traumatic haemorrhage			

subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Upper limb fracture			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Wound			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Congenital, familial and genetic disorders			
Familial mediterranean fever			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hereditary retinal dystrophy			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Bradycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Cervical radiculopathy			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	5 / 13 (38.46%)	2 / 9 (22.22%)	3 / 4 (75.00%)
occurrences (all)	8	2	6
Paraesthesia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Seizure			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Speech disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	4	4	0
Otorrhoea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Vertigo			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Lacrimation increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	7 / 13 (53.85%)	4 / 9 (44.44%)	3 / 4 (75.00%)
occurrences (all)	12	8	4
Abdominal pain lower			

subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Anal incontinence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	4	1	3
Defaecation urgency			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Dental caries			
subjects affected / exposed	3 / 13 (23.08%)	3 / 9 (33.33%)	0 / 4 (0.00%)
occurrences (all)	3	3	0
Diarrhoea			
subjects affected / exposed	5 / 13 (38.46%)	3 / 9 (33.33%)	2 / 4 (50.00%)
occurrences (all)	13	5	8
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Inguinal hernia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	3
Toothache			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	7 / 13 (53.85%)	6 / 9 (66.67%)	1 / 4 (25.00%)
occurrences (all)	11	8	3
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	3	1	2
Hyperkeratosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Intertrigo			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Purpura			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Scar pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Skin lesion			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Urinary incontinence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 13 (30.77%)	2 / 9 (22.22%)	2 / 4 (50.00%)
occurrences (all)	10	4	6

Arthritis			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	3	2	1
Back pain			
subjects affected / exposed	4 / 13 (30.77%)	2 / 9 (22.22%)	2 / 4 (50.00%)
occurrences (all)	6	2	4
Bone pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Foot deformity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Kyphosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	2 / 13 (15.38%)	0 / 9 (0.00%)	2 / 4 (50.00%)
occurrences (all)	2	0	2
Pain in extremity			
subjects affected / exposed	4 / 13 (30.77%)	2 / 9 (22.22%)	2 / 4 (50.00%)
occurrences (all)	11	7	4
Pseudarthrosis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 9 (0.00%)	2 / 4 (50.00%)
occurrences (all)	2	0	2
COVID-19			

subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Cystitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Device related infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Ear infection			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Fungal infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Furuncle			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Nasopharyngitis			
subjects affected / exposed	6 / 13 (46.15%)	4 / 9 (44.44%)	2 / 4 (50.00%)
occurrences (all)	12	8	4
Oral herpes			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Otitis media			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Rhinitis			

subjects affected / exposed	5 / 13 (38.46%)	4 / 9 (44.44%)	1 / 4 (25.00%)
occurrences (all)	9	7	2
Tonsillitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Tracheitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	2 / 13 (15.38%)	1 / 9 (11.11%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Metabolism and nutrition disorders			
Calcium deficiency			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hyperkalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Increased appetite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Iron deficiency			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Overweight			
subjects affected / exposed	1 / 13 (7.69%)	0 / 9 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Vitamin B12 deficiency			
subjects affected / exposed	1 / 13 (7.69%)	1 / 9 (11.11%)	0 / 4 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2015	In Amendment number 1 to Protocol Version 2.0 dated 07 July 2013, Poland was included as a centre and the number of sites was increased to 12 (in France and Poland) with an increase in the number of subjects who could be enrolled to 12. Dose visits could be performed in hospitals in both countries and only for subjects in France at Lyon. In Amendment number 2 to Protocol Version 2.0 dated 07 April 2013, The trial objective was updated to include evaluation of efficacy of repeated i.v. administration of velmanase alfa and a CEV was added to evaluate additional efficacy parameters. The secondary efficacy objectives added were: evaluation of impact of long-term treatment with velmanase alfa upon serum oligosaccharides, endurance (as measured by the 3MSCT and 6MWT), pulmonary function, motor proficiency (Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition), hearing, cognitive development (Leiter International Performance Scale - Revised), central nervous system involvement (only in subjects who had participated in rhLAMAN-02 and had baseline assessments for the imaging studies), biomarkers and oligosaccharides in CSF and oligosaccharide clearance in urine (only at the CEV) and quality of life (questionnaires). Assessment of in vivo biological activity in plasma and pharmacokinetic analysis were added to secondary objectives. A safety objective of monitoring immunogenicity (ADAs) throughout the trial was added. Additional safety assessments were added at the CEV including haematology, coagulation tests, biochemistry, anti-nuclear antibodies, urinalysis, serum IgG/IgA/IgM, 12-lead electrocardiogram and echocardiogram. Assessment of changes in social and leisure skills was also planned during the CEV. Interim analysis of data from the CEV was planned. A new protocol version was not produced after these amendments and both were submitted together and approved.
17 May 2016	In Amendment number 3 dated 11 March 2016 to Protocol Version 2.0 dated 07 June 2013, the duration of the study was prolonged to 6 years. Implantation of an i.v. catheter to ease delivery of velmanase alfa and other i.v. procedures was permitted at the Investigator's discretion. Assessment of pulmonary function and collection of concomitant medication/therapy at yearly evaluation visits was added to the trial flow chart. The Protocol Version 3.0 dated 31 March 2016 and updated table of changes between Protocol Amendments 2 and 3 to Protocol Version 2.0 were submitted to the Regulatory Authority and approved.
28 December 2016	Protocol Version 4.0 dated 09 November 2016 reflected change in Sponsor from Zymenex to Chiesi and name of study treatment was changed from Lamazyn to velmanase alfa.
10 December 2019	The main changes from Protocol Versions 4.0 to 6.0 (of note, Version 5.0 was not distributed and superseded by Version 6.0) included increase in number to subjects who could be enrolled to 13 including 7 who had been enrolled in rhLAMAN-02 and rhLAMAN-05, 1 who had been enrolled in rhLAMAN-08 and 5 who had not previously been enrolled in a velmanase alfa trial, with consequent update in title and inclusion criteria; extension of trial duration to third quarter of 2022; planned evaluation of serum oligosaccharides and Ig (for safety) every 24 weeks; planned collection of baseline data for efficacy assessments and safety assessments at Visit 1 and yearly evaluations in Lyon, France for subjects not previously enrolled in a velmanase alfa trial and the subject from rhLAMAN-08 (as applicable).
02 June 2020	This was Substantial General Amendment number 1 to Protocol Version 6.0 dated 18 October 2019. It was specified that the trial was extended up to the third quarter of 2022 to support collection of long-term efficacy and safety data of velmanase alfa and allow further collection of data in an interventional trial setting during a prolonged observation period considering the slow progression of alpha-mannosidosis and to leverage the fact that this allows increased knowledge of an ultra-rare pathology in a specific and well-studied cohort of subjects.

21 July 2020	This was Substantial General Amendment number 2 to Protocol Version 6.0 dated 18 October 2019. The home infusion setting was implemented for eligible subjects. Applicable sections of the protocol were updated as a result and a new section (Section 8.4.6) was inserted specifying details of the programme. The operating manual (Version 1.0 dated 16 June 2020) was also developed. With subject consent, data collected in the electronic Case Report Form during the trial was permitted to be transferred to the French retrospective Registry (Etoile alpha). A new section in the protocol included details of the Registry.
26 November 2020	This was Substantial General Amendment number 3 to the Protocol Version 6.0 dated 18 October 2019 (as amended by Substantial General Amendments numbers 1 and 2). Additional blood samples were to be collected to further investigate the immunological response of subjects, with testing of the vaccination response to poliovirus, diphtheria toxin, tetanus toxin, Pneumococcal polysaccharide and Haemophilus influenzae type b. It was specified that remnants of samples already analysed for the trial could be used for external research purposes. Changes to trial database and Contract Research Organisations were specified and typographical errors were corrected. Sections of the protocol were updated to reflect the changes, an additional safety endpoint of immunological response to vaccines was added, the study flow chart was updated and a new section was added to the protocol including details about additional sample collection for immunological response to vaccines. It was specified that the yearly evaluation visits would be shifted from the Copenhagen University Hospital in Denmark to the Hôpital Femme Mère Enfant in Lyon, France to avoid foreign travel for subjects/relatives during the COVID-19 pandemic and ensure that the visits would be performed. It was also specified that the interval between successive yearly visits could not be more than 7 months. The laboratories for ADA, neutralising antibody and oligosaccharide testing were specified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported