Clinical trial results:
A 24-month Multicenter, Open-label Phase II Trial Investigating the Safety and Efficacy of Repeated velmanase alfa (recombinant human alpha-mannosidase) Treatment in Pediatric Patients below 6 years of age with Alpha-Mannosidosis

Summary

EudraCT number	2016-001988-36
Trial protocol	DK DE AT FR IT
Global end of trial date	03 July 2020

Results information

Result version number	v1 (current)
This version publication date	02 April 2021
First version publication date	02 April 2021

Trial information

Trial identification

Sponsor protocol code	CCD-LMZYMAA1-08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, 43122, Parma, Italy,
Public contact	Chiara Franke, Clinical Project Manager, Chiesi Farmaceutici S.p.A., 0039 3451247439, c.franke.consultant@chiesi.com
Scientific contact	Chiara Franke, Clinical Project Manager, Chiesi Farmaceutici S.p.A., 0039 3451247439, c.franke.consultant@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001056-PIP02-12
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2020
Global end of trial reached?	Yes
Global end of trial date	03 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were to evaluate safety and efficacy of repeated velmanase alfa intravenous (i.v.) infusions in paediatric subjects aged less than 6 years with alpha-mannosidosis.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines, and following all other requirements of local laws. Safety was assessed at every visit in terms of physical examinations, vital signs, adverse events (AEs), laboratory evaluations (haematology, biochemistry, coagulation, urinalysis) and monitoring of immunoglobulin (Ig)G immunogenicity. Adverse events and serious AEs were assessed at the baseline visit, all dose visits and in connection with the dosing performed at evaluation visits. Electrocardiograms and echocardiograms were recorded at the baseline visit, monitored during and after infusions at dose visits and recorded at the 12 and 24 months evaluation visits, and for the subject enrolled in France, also at the 40 months evaluation visit. Weight was recorded at baseline and every 4 weeks and used for dosage calculation. Head circumference and height were recorded at baseline and evaluation visits and growth velocity was assessed throughout the study. Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate and temperature) were monitored and the subject was observed for AEs during infusions of velmanase alfa, and during the observation period after dosing. At the discretion of the Investigator, a central venous catheter could be implanted to ease administration of velmanase alfa and facilitate other i.v. procedures during the study, and anaesthesia could be used during lumbar punctures, with prothrombin time or International Normalized Ratio being assessed prior to anaesthesia. Prior medications and medical/surgical history was recorded at baseline, concomitant medications and illnesses were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2016
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	Austria: 1
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	5
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 6 subjects were screened according to inclusion/exclusion criteria, of these 5 subjects were enrolled in the study. Included subjects had to have a confirmed diagnosis of alpha-mannosidosis as defined by alpha-mannosidase activity in leukocytes or fibroblasts <10% of normal activity (historical data) and be aged <6 years at screening.

Pre-assignment

Screening details:

At the screening visit, eligible consenting subjects were identified, informed consent was obtained. The subject's ability to fulfil inclusion/exclusion criteria was evaluated, screening assessments were performed and the Investigator reviewed the results against the criteria. One subject (in Denmark) was a screen failure (exclusion criterion met).

Period 1

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

Arms

Arm title	Enrolled subjects

Arm description:

This was an open-label trial where all enrolled subjects received once weekly administration of i.v. velmanase alfa (recombinant human alpha-mannosidase).

Arm type	Experimental
Investigational medicinal product name	Velmanase alfa
Investigational medicinal product code	CHFLMZYMAA1
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 and every 4 weeks). Velmanase alfa is supplied as a freeze-dried sterile product in single use vials containing 10 mg of investigational medicinal product (IMP); each vial is to be reconstituted with 5.0 mL water for injection. Stability of the reconstituted product is 24 hours at 2-8°C and 10 hours at a maximum of 25°C. The solution should have reached room temperature prior to infusion. Vials were prepared as per the volume required for the dose of IMP and swirled with slow rotations for 10-15 seconds after reconstitution. The required volume was withdrawn into one or more large-dose syringes and an infusion set with a mounted filter was filled. The maximum infusion rate was 22.5 mL/hour. The last empty syringe was replaced with a syringe filled with 20 mL isotonic sodium chloride to infuse IMP left in the set. An i.v. catheter could be implanted to ease delivery.

Number of subjects in period 1	Enrolled subjects
Started	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	5	5	
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)	5	5	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	4.30		
inter-quartile range (Q1-Q3)	4.10 to 4.60	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	3	3	

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 administration of i.v. velmanase alfa (recombinant human alpha-mannosidase).

Primary: Number of subjects with infusion-related reactions

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

End point description:

An AE was defined as any untoward medical occurrence in a subject administered a medicinal product and which did not necessarily have a causal relationship with this treatment. An infusion-related reaction (IRR) was defined as an AE which occurred during or after 2 hours of infusion of velmanase alfa and which was assessed by the Investigator as being infusion-related. Reported terms for AEs were coded using the Medical Dictionary for Regulatory Activities version 19.0. Absolute counts, percentages and number of events were presented for the number of subjects with at least one IRR, tabulated by System Organ Class and Preferred Term (PT). The number of subjects experiencing events by PT is presented. A subject who experienced multiple occurrences of an AE is presented only once in the respective subject count.

End point type	Primary

End point timeframe:

Data for IRRs were collected from the first infusion, for the duration of the 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: Due to the small sample size, as per protocol, data have been presented mainly through listings and when applicable only summarised, with no inferential statistics implemented.

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	5[2]			
Units: subjects				
Urticaria	1			
Chills	1			
Hyperthermia	1			
Anal pruritus	1			
Cyanosis	1			

Notes:

[2] - Three subjects - 15 events: cyanosis-2, chills-3, hyperthermia-2, urticaria-5, anal pruritus-3.

Statistical analyses

No statistical analyses for this end point

Primary: Detection of anti-velmanase alfa IgG antibodies

End point title	Detection of anti-velmanase alfa IgG antibodies[3]

End point description:

Samples were collected for detection of anti-velmanase alfa IgG antibodies (ADAs) at baseline and every 4 weeks post-treatment for the first 3 months, then every 8 weeks. Additional samples could be collected at the Investigator's discretion when an IRR was suspected or as per clinical judgement. All

IgG seropositive patients were tested for the presence of IgG neutralising antibodies to velmanase alfa. All subjects were ADA negative at study entry. The number of subjects who tested positive for ADAs during the study or remained negative throughout the study is presented. Of the subjects who seroconverted during the study, 2 subjects tested positive, then negative and then positive again during treatment; 2 subjects remained ADA positive from first detection until the end of the study.

End point type	Primary

End point timeframe:

From baseline to the 24 months evaluation visit for 2 subjects, to 26 and a half months from baseline for 1 subject, to approximately 25 months from baseline for 1 subject, and to the 40 months evaluation visit for 1 subject.

Notes:

[3] - 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: Due to the small sample size, as per protocol, data have been presented mainly through listings and when applicable only summarised, with no inferential statistics implemented.

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	5[4]			
Units: subjects				
Positive	4			
Negative	1			

Notes:

[4] - For ADA+ subjects, ADA concentrations ranged from below lower limit of quantification to 174 U/mL

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in serum oligosaccharide concentration (GlcNac[Man]2)

End point title	Change from baseline in serum oligosaccharide concentration (GlcNac[Man]2)

End point description:

Serum oligosaccharide concentration before and after treatment with velmanase alfa was an important biomarker used to assess the efficacy of velmanase alfa. Change from baseline in serum concentrations of serum oligosaccharides was analysed at the 6 months, 12 months, 18 months and 24 months evaluation visits, and for 1 patient, also at the 40 months evaluation visit. Change from baseline in serum concentration of GlcNac(Man)2 at the 24 months evaluation visit is reported.

End point type	Secondary

End point timeframe:

Change from baseline to the 24 months evaluation visit

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: micromole(s)/litre				
median (inter-quartile range (Q1-Q3))	-7.10 (-10.40 to -5.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in serum oligosaccharide concentrations (GlcNac[Man]3)

End point title	Change from baseline in serum oligosaccharide concentrations (GlcNac[Man]3)

End point description:

Serum oligosaccharide concentration before and after treatment with velmanase alfa was an important biomarker used to assess the efficacy of velmanase alfa. Change from baseline in concentration of serum oligosaccharides was analysed at 6 months, 12 months, 18 months, 24 months, and for 1 patient, also at 40 months. Change from baseline in serum concentration of GlcNac(Man)3 at 24 months is reported.

End point type	Secondary

End point timeframe:

Change from baseline to the 24 months evaluation visit

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: micromole(s)/litre				
median (inter-quartile range (Q1-Q3))	-0.50 (-1.00 to -0.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of stairs climbed during the 3-Minute Stair Climb Test

End point title	Number of stairs climbed during the 3-Minute Stair Climb Test

End point description:

The number of steps climbed in 3 minutes was measured at baseline and at evaluation visits at 6 months, 12 months, 18 months, 24 months and for 1 patient, at 40 months, to evaluate endurance. The 3-Minute Stair Climb Test is an indicator of functional exercise capacity. The test was administered by a certified physiotherapist in subjects from 4 years of age or when applicable according to the judgement of the Investigator. At each time point, 2 assessments were carried out on different days and the best value was evaluated for efficacy. The number of steps climbed in 3 minutes at baseline and 24 months is presented.

End point type	Secondary

End point timeframe:

Baseline to 24 months evaluation visit.

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: steps				
median (inter-quartile range (Q1-Q3))				
Baseline	143.5 (115.5 to 162.0)			
24 months evaluation visit	119.5 (64.0 to 164.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Distance covered during the 6-Minute Walk Test

End point title	Distance covered during the 6-Minute Walk Test

End point description:

The 6-Minute Walk Test is an indicator of functional exercise capacity measuring the distance walked (in metres) on a flat, hard, surface in a period of 6 minutes. The test evaluates the global and integrated responses of all the systems involved during exercise including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units and muscle metabolism. The test was administered by a certified physiotherapist in subjects from 4 years of age, or when applicable as per the Judgement of the Investigator, and performed in accordance with the American Thoracic Society standards. In order to evaluate endurance, the test was administered on two different days at each assessment, with best value evaluated for efficacy. Assessments were performed at baseline, 6 months, 12 months, 18 months, 24 months and for 1 patient, at 40 months. The distances walked in 6 minutes at baseline and 24 months are presented.

End point type	Secondary

End point timeframe:

Baseline to the 24 months evaluation visit

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	4[5]			
Units: Steps				
median (inter-quartile range (Q1-Q3))				
Baseline	278.5 (247.5 to 344.0)			
24 months evaluation visit	265.0 (248.0 to 438.0)			

Notes:

[5] - 4 at baseline, 3 at 24 months

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in V Wave threshold (automatic auditory brainstem response audiometry)

End point title	Change from baseline in V Wave threshold (automatic auditory brainstem response audiometry)

End point description:

Automatic auditory brainstem response (A-ABR) audiometry is a neurologic test of auditory brainstem function in response to auditory stimuli (click or tone pip) transmitted from an acoustic transducer (insert earphone or headphone), which generate an evoked potential. Administration and interpretation are typically performed by an audiologist. The elicited waveform response is measured by surface electrodes typically placed at the vertex of the scalp and ear lobes. The amplitude (microvoltage) of the signal is averaged and charted against time (in milliseconds). The waveform peaks are labelled I-VII. These waveforms normally occur within a 10 millisecond time period after a click stimulus presented at high intensities (70-90 decibels above normal adult hearing level [dB nHL]). The V Wave threshold was measured for each ear at baseline and evaluation visits at 12 months, 24 months and for 1 patient, at 40 months. Change from baseline in V Wave threshold at 12 months is presented.

End point type	Secondary

End point timeframe:

Baseline to 12 months evaluation visit.

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: dB nHL				
median (inter-quartile range (Q1-Q3))				
Right ear	-10.0 (-17.5 to -2.5)			
Left ear	-2.5 (-7.5 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in serum immunoglobulin concentrations

End point title	Change from baseline in serum immunoglobulin concentrations

End point description:

Change from baseline in serum IgG, IgA and IgM concentrations were assessed at evaluation visits at 6 months, 12 months, 18 months, 24 months, and for 1 patient, at 40 months, for evaluation of subjects' immunological profiles. The change from baseline in serum Ig concentrations at 24 months is presented.

End point type	Secondary

End point timeframe:

Baseline to the 24 months evaluation visit.

End point values	Enrolled subjects			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: gram(s)/litre				
median (inter-quartile range (Q1-Q3))				
IgG	3.510 (1.985 to 5.195)			
IgA	0.285 (0.110 to 0.795)			
IgM	-0.160 (-0.195 to 0.265)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data for AEs were collected from the time of informed consent, for the duration of the trial.

Adverse event reporting additional description:

The Investigator collected all AEs from spontaneous reports of subjects, and by observation and routine open questioning. Only the treatment-emergent adverse events are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Enrolled subjects

Reporting group description:

This was an open-label trial where all enrolled subjects received once weekly administration of i.v. velmanase alfa (recombinant human alpha-mannosidase).

Serious adverse events	Enrolled subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Vascular fragility			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Chills			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cat scratch disease			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Enrolled subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 5 (80.00%)		
occurrences (all)	20		
Chills			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Hyperthermia			

subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 7 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all) Breast swelling subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 4 / 5 (80.00%) 10 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Investigations Blood iron decreased subjects affected / exposed occurrences (all) Cardiac murmur subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2 1 / 5 (20.00%) 1		
Injury, poisoning and procedural complications Fall			

subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2		
Ligament sprain subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2		
Arthropod bite subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Eye injury subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Joint injury subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Limb injury subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Post lumbar puncture syndrome subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Cardiac disorders			
Cyanosis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Poor quality sleep subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Ear and labyrinth disorders Ear haemorrhage subjects affected / exposed occurrences (all) Ear pain subjects affected / exposed occurrences (all) Hypoacusis subjects affected / exposed occurrences (all) Middle ear disorder subjects affected / exposed occurrences (all) Otorrhoea subjects affected / exposed occurrences (all) Tympanic membrane disorder subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Eye disorders Hypermetropia subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dental caries subjects affected / exposed occurrences (all) Anal pruritus	 5 / 5 (100.00%) 10 3 / 5 (60.00%) 4 2 / 5 (40.00%) 2		

subjects affected / exposed occurrences (all) Dental cyst subjects affected / exposed occurrences (all) Gastrointestinal disorder subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Tooth disorder subjects affected / exposed occurrences (all) Tooth loss subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Skin and subcutaneous tissue disorders Swelling face subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 5		
Musculoskeletal and connective tissue disorders Jaw disorder subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Infections and infestations			

Otitis media				
subjects affected / exposed	4 / 5 (80.00%)			
occurrences (all)	9			
Rhinitis				
subjects affected / exposed	3 / 5 (60.00%)			
occurrences (all)	10			
Conjunctivitis				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	4			
Ear infection				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	5			
Gastroenteritis				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	6			
Nasopharyngitis				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	9			
Upper respiratory tract infection				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	5			
Bronchitis				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	2			
Dental fistula				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Febrile infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Gastrointestinal infection				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	3			

Pharyngitis streptococcal subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Tooth infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Viral infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2017	Rationale was to update final selected laboratories and harmonise safety and pharmacokinetic timepoints. Details of new Clinical Project Manager, sites/countries, safety contacts, human blood bank and finalised central laboratories were updated. Time points for safety and pharmacokinetic assessments were harmonised; theoretical time point '22-hour post-infusion stop' was substituted with '24-hour post-infusion stop' for pharmacokinetic analysis. The following were specified in Sections: 1.2.5, 14 and Appendix (App) 1: the trial would be conducted in compliance with current ICH E6 GCP; 2.0: primary endpoints amended to delete detection of neutralising/inhibitory antibodies, Childhood Health Assessment Questionnaire deleted as assessment of quality of life via questionnaire to parents (secondary efficacy endpoints efficacy); other sections updated as required; 3.0: magnetic resonance spectroscopy, magnetic resonance imaging (MRI) and diffusion-MRI of the brain would be performed at baseline only if historical data in the previous 3 months were not available, allowing for retrospective MRI data to be used; other sections of the protocol updated and further details on these assessments also included in Section 8.8; 7: time points for pharmacokinetic assessments and the amount of blood/cerebrospinal fluid (CSF) to be collected for various analyses specified in text/trial flow chart; 7.1.2.1: assessments at baseline would be performed over 2 weeks (instead of 1 week) and alpha-mannosidase activity in leukocytes would be evaluated only if historical data were not available; 8.1: heading updated to specify that CSF oligosaccharides would also be assessed; 9.1.3.1: blood samples for clinical laboratory evaluations would be drawn 24 hours after infusion-stop (not after start of dosing); 10.1.5: requirement for the Investigator to consult with allergic reaction expert in case of severe IRR removed; 16.1, 16.2 added, 19 modified, App II included.
21 January 2019	New Section 8.10.2 was inserted, specifying details of planned additional blood sampling for bioanalytical assay development. The rationale was to develop a bioanalytical assay for the evaluation of the oligosaccharides content in the mononuclear cells aiming at following treatment response in a clinically relevant tissue. The Contract Research Organisation and Sponsor safety contact details were updated in Section 10.9.
11 April 2019	Details of the new Clinical Program Leader were provided. The laboratories involved in the additional blood sampling measurement mentioned in the previous version of the protocol were specified and details were updated in relevant sections of the protocol. Section 10.7 was updated regarding follow-up of AEs. Details on recording of AEs and reporting of SAEs to Sponsor were updated in Sections 10.8 and 10.9, respectively.

27 April 2019	Amendment number 1.0 (France) dated 12 February 2019 to Protocol Version 6.0 (dated 15 January 2019) was approved by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) on 27 April 2019. The rationale for the amendment was to extend the treatment for a further 12 months to cover the treatment for the subject enrolled in France until the availability of the drug on the French market. The IMP achieved reimbursement in France in December 2018 but was still not available on the market. Modification was required to the informed consent and the Case Report Form. Changes were made to sections of the protocol as appropriate to extend the duration of treatment for the French subject to 36 months, with addition of a final 36 months evaluation visit for performing efficacy assessments. For secondary endpoints it was specified that these included changes from baseline to 36 months for the French subject. The trial flow chart was updated to include additional dose visits, details of the evaluation visit and assessments at 36 months and specification of an end of trial visit for the French subject.
24 June 2020	Amendment number 2.0 (France) dated 17 April 2020 to Protocol Version 7.0 (dated 30 January 2020) was approved by the Comités de Protection des Personnes on 24 June 2020. The rationale for the amendment was to extend the treatment for a further 4 months to cover the treatment for the subject enrolled in France until the coronavirus-19 (COVID-19) emergency was over. Due to the pandemic the subject could not complete the 36 months evaluation visit, and the treatment was stopped from 16 March to 20 April 2020. The sponsor assumed that the COVID-19 restrictions would be over by August 2020 and thought to extend the treatment for the French subject for a further 4 months, and add a final evaluation visit at 40 months (Week 166 +/- 5 weeks) after at least 4 weeks of treatment resumption. Modification was required to the informed consent and the Case Report Form. Changes were made to sections of the protocol as appropriate to extend the duration of treatment for the French subject to 40 months, with addition of the final evaluation visit for performing efficacy assessments. For secondary endpoints it was specified that these included changes from baseline to 40 months for the French subject. The trial flow chart was updated to include additional dose visits, details of the evaluation visit and assessments at 40 months and specification of an end of trial visit for the French subject.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	Only the subject enrolled in France was affected. Due to the COVID-19 pandemic the treatment was stopped for the subject from 16 March to 20 April 2020. The treatment was extended for a further 4 months for this subject, and a final evaluation visit was planned after 40 months of treatment (after at least 4 weeks of treatment resumption).	20 April 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the COVID-19 pandemic, 1 patient missed 4 dose visits and performed 2 out of visit window, and the post-infusion observational period was reduced for some visits for 1 patient. Other patients had completed the study before.

Notes: