Clinical trial results:
A multi-center, open-label trial of the long-term efficacy and safety of Lamazym for the treatment of patients with alpha-Mannosidosis.

Summary

EudraCT number	2011-004355-40
Trial protocol	DK DE BE GB ES
Global end of trial date	20 September 2013

Results information

Result version number	v1 (current)
This version publication date	11 August 2016
First version publication date	11 August 2016

Trial information

Trial identification

Sponsor protocol code	rhLAMAN-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01681940
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zymenex A/S
Sponsor organisation address	Roskildevej 12C, Hilleroed, Denmark, 3400
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., clinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., clinicalTrials_info@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2013
Global end of trial reached?	Yes
Global end of trial date	20 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective of this trial is the evaluation of long-term efficacy, safety and tolerability of Lamazym treatment in patients with alpha-Mannosidosis.

The primary objectives of the trial are:
Evaluation of long-term efficacy from baseline of Lamazym on reduction of the biomarker Oligosaccharides in blood and CSF and an improvement in the 3 minute stair climb, 6 minute walk test and pulmonary function from baseline.

Protection of trial subjects:

The study was conducted in accordance with the declaration of Helsinki, good clinical practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2012
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	Denmark: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	5

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 10 patients were enrolled in the rhLAMAN-02 and rhLAMAN-03 trials. One (1) patient (Patient 03) was withdrawn from treatment in the rhLAMAN-03 trial after approximately 2.5 months of treatment and was subsequently withdrawn from the trial. All 9 patients who completed the rhLAMAN-03 trial continued into the rhLAMAN-04 trial.

Pre-assignment

Screening details:

No patients failed screening or withdrew from the rhLAMAN-04 trial

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	Lamazym

Arm description:

In the Laman04 study, all patients were treated with the same dose: 1 mg/kg body weight, and each patient received weekly i.v. infusions of Lamazym with 7 days ± 2 days required between each infusion

Arm type	Experimental
Investigational medicinal product name	Lamazym
Investigational medicinal product code	
Other name	recombinant human alpha-mannosidase
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

In the Laman04 all patients were treated with the same dose: 1 mg/kg body weight, and each patient received weekly i.v. infusions of Lamazym with 7 days ± 2 days required between each infusion

Number of subjects in period 1	Lamazym
Started	10
Completed	9
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	11.8		
standard deviation	± 3.7	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	7	7	

Subject analysis sets

Subject analysis set title	Baseline
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all 10 patients receiving the investigational medicinal product in at least one of the rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04. The FAS corresponds to the efficacy analysis set.

Subject analysis set title	End evaluation
Subject analysis set type	Full analysis

Subject analysis set description:

End evaluation is made at Visit 26a of the rhLAMAN04 study

Reporting group values	Baseline	End evaluation	
Number of subjects	10	9	
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	11.8	11.8	
standard deviation	± 3.7	± 3.7	
Gender categorical Units: Subjects			
Female	3	2	
Male	7	7	

End points

End points reporting groups

Reporting group title	Lamazym
Reporting group description:	
In the Laman04 study, all patients were treated with the same dose: 1 mg/kg body weight, and each patient received weekly i.v. infusions of Lamazym with 7 days ± 2 days required between each infusion	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) includes all 10 patients receiving the investigational medicinal product in at least one of the rhLAMAN-02, rhLAMAN-03 and rhLAMAN-04. The FAS corresponds to the efficacy analysis set.	
Subject analysis set title	End evaluation
Subject analysis set type	Full analysis
Subject analysis set description:	
End evaluation is made at Visit 26a of the rhLAMAN04 study	

Primary: Change from baseline in blood serum oligosaccharides

End point title	Change from baseline in blood serum oligosaccharides
End point description:	
Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.1 of the CSR	
End point type	Primary
End point timeframe:	
Serum oligosaccharides were measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: umol/L				
arithmetic mean (standard deviation)	9.4 (± 2.88)	-8.11 (± 3.1)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Primary: Change from baseline in CSF oligosaccharides

End point title	Change from baseline in CSF oligosaccharides

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.3 of the CSR

End point type	Primary

End point timeframe:

CSF oligosaccharides were measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: umol/L				
arithmetic mean (standard deviation)	10.7 (± 4.55)	-1.67 (± 2.55)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.086
Method	ANCOVA

Primary: Change from baseline in 3-min stair climb

End point title	Change from baseline in 3-min stair climb

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.4 of the CSR

End point type	Primary

End point timeframe:

Stair climbing was assessed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: steps				
arithmetic mean (standard deviation)	156.7 (± 40.48)	39.33 (± 29.59)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	ANCOVA

Primary: Change from baseline in 6-min walk test

End point title	Change from baseline in 6-min walk test

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.5 of the CSR

End point type	Primary

End point timeframe:

6-minute walk test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: min				
arithmetic mean (standard deviation)	444.45 (± 104.03)	71.17 (± 62.8)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description: End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	ANCOVA

Primary: Change from baseline in pulmonary FVC

End point title	Change from baseline in pulmonary FVC
End point description: Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.6 of the CSR	
End point type	Primary
End point timeframe: FVC was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: liters				
arithmetic mean (standard deviation)	2.07 (± 0.91)	0.6 (± 0.44)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description: End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	ANCOVA

Primary: Change from baseline of pulmonary FVC as percent of predicted normal value

End point title	Change from baseline of pulmonary FVC as percent of predicted normal value

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.7 of the CSR

End point type	Primary

End point timeframe:

FVC was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 12), and at rhLAMAN-04 evaluation (Visit 26a, month 18).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: percent				
arithmetic mean (standard deviation)	79.05 (± 15.78)	9.17 (± 17.63)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.157
Method	ANCOVA

Primary: Change from baseline in pulmonary FEV1

End point title	Change from baseline in pulmonary FEV1

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available

before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.8 of the CSR

End point type	Primary

End point timeframe:

FEV1 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 12), and at rhLAMAN-04 evaluation (Visit 26a, month 18).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Liters				
arithmetic mean (standard deviation)	1.93 (± 0.85)	0.28 (± 0.33)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.035
Method	ANCOVA

Primary: Change from baseline in pulmonary FEV1 as percent of predicted normal value

End point title	Change from baseline in pulmonary FEV1 as percent of predicted normal value

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.9 of the CSR

End point type	Primary

End point timeframe:

FEV1 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: percent				
arithmetic mean (standard deviation)	79.1 (± 15.62)	-0.11 (± 16.86)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.985
Method	ANCOVA

Primary: Change from baseline in pulmonary peak expiratory flow rate

End point title	Change from baseline in pulmonary peak expiratory flow rate
End point description:	
Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.10 of the CSR	
End point type	Primary
End point timeframe:	
PEF rate was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: L/sec				
arithmetic mean (standard deviation)	3.71 (± 1.52)	0.4 (± 0.92)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23
Method	ANCOVA

Secondary: Change from baseline in BOT2 balance

End point title	Change from baseline in BOT2 balance

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.11 of the CSR

End point type	Secondary

End point timeframe:

BOT2 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 12), and at rhLAMAN-04 evaluation (Visit 26a, month 18).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	14.7 (± 7.13)	0.11 (± 4.78)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.946
Method	ANCOVA

Secondary: Change from baseline in BOT2 bilateral coordination

End point title	Change from baseline in BOT2 bilateral coordination

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.12 of the CSR

End point type	Secondary

End point timeframe:

BOT2 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 12), and at rhLAMAN-04 evaluation (Visit 26a, month 18).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	11.4 (± 5.1)	3.11 (± 2.57)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	ANCOVA

Secondary: Change from baseline in BOT2 running speed and agility

End point title	Change from baseline in BOT2 running speed and agility

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.13 of the CSR

End point type	Secondary

End point timeframe:

BOT2 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	13.7 (± 7.2)	2.11 (± 2.71)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.048
Method	ANCOVA

Secondary: Change from baseline in BOT2 upper limb coordination

End point title	Change from baseline in BOT2 upper limb coordination

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.14 of the CSR

End point type	Secondary

End point timeframe:

BOT2 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	16.7 (± 12.6)	3.33 (± 8.14)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.254
Method	ANCOVA

Secondary: Change from baseline in BOT2 manual dexterity

End point title	Change from baseline in BOT2 manual dexterity

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.15 of the CSR

End point type	Secondary

End point timeframe:

BOT2 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 12), and at rhLAMAN-04 evaluation (Visit 26a, month 18).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	14.9 (± 6.31)	1.89 (± 2.52)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.055
Method	ANCOVA

Secondary: Change from baseline in BOT2 fine motor integration

End point title	Change from baseline in BOT2 fine motor integration

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.16 of the CSR

End point type	Secondary

End point timeframe:

BOT2 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	19.8 (± 12.04)	0.67 (± 5.74)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.737
Method	ANCOVA

Secondary: Change from baseline in BOT2 fine motor precision

End point title	Change from baseline in BOT2 fine motor precision
End point description:	
Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.17 of the CSR	
End point type	Secondary
End point timeframe:	
BOT2 was measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 12), and at rhLAMAN-04 evaluation (Visit 26a, month 18).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	23.4 (± 9.79)	3.67 (± 3.2)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	ANCOVA

Secondary: Change from baseline in CSF-GFAp

End point title	Change from baseline in CSF-GFAp

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.18 of the CSR

End point type	Secondary

End point timeframe:

CSF biomarkers were measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ng/L				
arithmetic mean (standard deviation)	807 (± 334.5)	-364.44 (± 199.07)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Secondary: Change from baseline in CSF-NFLp

End point title	Change from baseline in CSF-NFLp

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.19 of the CSR

End point type	Secondary

End point timeframe:

CSF biomarkers were measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ng/L				
arithmetic mean (standard deviation)	606 (± 228.68)	-180 (± 176.64)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.016
Method	ANCOVA

Secondary: Change from baseline in CSF-Tau

End point title	Change from baseline in CSF-Tau

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.20 of the CSR

End point type	Secondary

End point timeframe:

CSF biomarkers were measured at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ng/L				
arithmetic mean (standard deviation)	711 (± 305.34)	-58.44 (± 112.96)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description: End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.159
Method	ANCOVA

Secondary: Change from baseline in Leiter R test score - Design analogies

End point title	Change from baseline in Leiter R test score - Design analogies
End point description: Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.26 of the CSR	
End point type	Secondary
End point timeframe: Leiter R test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	5.86 (± 1.61)	0.75 (± 1.36)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description: End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.137
Method	ANCOVA

Secondary: Change from baseline in Leiter R test score - Figure ground

End point title	Change from baseline in Leiter R test score - Figure ground

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.27 of the CSR

End point type	Secondary

End point timeframe:

Leiter R test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	6.59 (± 1.18)	0.27 (± 0.85)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.372
Method	ANCOVA

Secondary: Change from baseline in Leiter R test score - Form completion

End point title	Change from baseline in Leiter R test score - Form completion

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.28 of the CSR

End point type	Secondary

End point timeframe:

Leiter R test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Integer				
arithmetic mean (standard deviation)	6.11 (± 1.43)	0.87 (± 0.92)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	ANCOVA

Secondary: Change from baseline in Leiter R test score - Paper folding

End point title	Change from baseline in Leiter R test score - Paper folding

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.29 of the CSR

End point type	Secondary

End point timeframe:

Leiter R test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	8		
Units: integer				
arithmetic mean (standard deviation)	6.82 (± 1.2)	0.94 (± 1.7)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.163
Method	ANCOVA

Secondary: Change from baseline in Leiter R test score - Repeated pattern

End point title	Change from baseline in Leiter R test score - Repeated pattern

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.30 of the CSR

End point type	Secondary

End point timeframe:

Leiter R test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	8		
Units: integer				
arithmetic mean (standard deviation)	5.35 (± 0.75)	0.22 (± 0.97)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.544
Method	ANCOVA

Secondary: Change from baseline in Leiter R test score - Sequential order

End point title	Change from baseline in Leiter R test score - Sequential order

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.31 of the CSR

End point type	Secondary

End point timeframe:

Leiter R test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	8		
Units: integer				
arithmetic mean (standard deviation)	4.85 (± 1.42)	0.63 (± 1.01)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.125
Method	ANCOVA

Secondary: Change from baseline in Leiter R test score - Total equivalence age 1

End point title	Change from baseline in Leiter R test score - Total equivalence age 1

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.32 of the CSR

End point type	Secondary

End point timeframe:

Leiter R test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: integer				
arithmetic mean (standard deviation)	5.63 (± 1.23)	0.46 (± 0.49)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	ANCOVA

Secondary: Change from baseline in audiometric best ear bone conduction

End point title	Change from baseline in audiometric best ear bone conduction

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.33 of the CSR

End point type	Secondary

End point timeframe:

Hearing test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Decibel				
arithmetic mean (standard deviation)	50.72 (± 11.91)	-3.8 (± 9.78)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.277
Method	ANCOVA

Secondary: Change from baseline in audiometric left ear air conduction

End point title	Change from baseline in audiometric left ear air conduction

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.34 of the CSR

End point type	Secondary

End point timeframe:

Hearing test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Decibel				
arithmetic mean (standard deviation)	61.1 (± 16.86)	-4.36 (± 8.42)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.159
Method	ANCOVA

Secondary: Change from baseline in audiometric right ear air conduction

End point title	Change from baseline in audiometric right ear air conduction

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.35 of the CSR

End point type	Secondary

End point timeframe:

Hearing test was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: decibel				
arithmetic mean (standard deviation)	59.35 (± 18.83)	-4.57 (± 6.16)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.057
Method	ANCOVA

Secondary: Change from baseline in CHAQ - pain on VAS

End point title	Change from baseline in CHAQ - pain on VAS

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.37 of the CSR

End point type	Secondary

End point timeframe:

CHAQ was administered at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	7		
Units: mm				
arithmetic mean (standard deviation)	14 (± 17.31)	3.57 (± 16.06)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.578
Method	ANCOVA

Secondary: Change from baseline in CHAQ - general evaluation on VAS

End point title	Change from baseline in CHAQ - general evaluation on VAS
End point description:	
Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.38 of the CSR	
End point type	Secondary
End point timeframe:	
CHAQ was administered at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	8		
Units: mm				
arithmetic mean (standard deviation)	23.44 (± 21.33)	-3.13 (± 20.07)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.673
Method	ANCOVA

Secondary: Change from baseline in MRI ADC grey matter

End point title	Change from baseline in MRI ADC grey matter

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.39 of the CSR

End point type	Secondary

End point timeframe:

MRI was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: mm2/sec				
arithmetic mean (standard deviation)	802.6 (± 39.4)	-20.44 (± 62.9)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.358
Method	ANCOVA

Secondary: Change from baseline in MRI ADC standard

End point title	Change from baseline in MRI ADC standard

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.40 of the CSR

End point type	Secondary

End point timeframe:

MRI was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: mm2/sec				
arithmetic mean (standard deviation)	864 (± 89.94)	-9.44 (± 54.04)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.614
Method	ANCOVA

Secondary: Change from baseline in MRI ADC white matter

End point title	Change from baseline in MRI ADC white matter

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.41 of the CSR

End point type	Secondary

End point timeframe:

MRI was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: mm2/sec				
arithmetic mean (standard deviation)	911.4 (± 112.77)	48.44 (± 88.58)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.139
Method	ANCOVA

Secondary: Change from baseline in MRS mannose complex visual grey matter

End point title	Change from baseline in MRS mannose complex visual grey matter
End point description:	
Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.42 of the CSR	
End point type	Secondary
End point timeframe:	
MRS was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ppm				
arithmetic mean (standard deviation)	1.9 (± 0.74)	-0.33 (± 0.5)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	Baseline v End evaluation

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.081
Method	ANCOVA

Secondary: Change from baseline in MRS mannose complex visual standard

End point title	Change from baseline in MRS mannose complex visual standard

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.43 of the CSR

End point type	Secondary

End point timeframe:

MRS was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ppm				
arithmetic mean (standard deviation)	1.67 (± 1.12)	0 (± 0.53)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	ANCOVA

Secondary: Change from baseline in MRS mannose complex visual white matter

End point title	Change from baseline in MRS mannose complex visual white matter

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).

See Table 14.2.1.44 of the CSR

End point type	Secondary

End point timeframe:

MRS was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ppm				
arithmetic mean (standard deviation)	1.8 (± 1.14)	-0.22 (± 0.67)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.347
Method	ANCOVA

Secondary: Change from baseline in MRS numerical mannose complex index grey matter

End point title	Change from baseline in MRS numerical mannose complex index grey matter

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).
See Table 14.2.1.45 of the CSR

End point type	Secondary

End point timeframe:

MRS was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ppm				
arithmetic mean (standard deviation)	1 (± 0.51)	-0.06 (± 0.28)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	
Comparison groups	End evaluation v Baseline
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.54
Method	ANCOVA

Secondary: Change from baseline in MRS numerical mannose complex index standard

End point title	Change from baseline in MRS numerical mannose complex index standard
End point description:	
Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value). See Table 14.2.1.46 of the CSR	
End point type	Secondary
End point timeframe:	
MRS was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).	

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ppm				
arithmetic mean (standard deviation)	1 (± 0.26)	-0.02 (± 0.29)		

Statistical analyses

Statistical analysis title	End of LAMAN04 vs Baseline
Statistical analysis description:	
End evaluation is made at Visit 26a of the LAMAN04 study	

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.839
Method	ANCOVA

Secondary: Change from baseline in MRS numerical mannose complex index white matter

End point title	Change from baseline in MRS numerical mannose complex index white matter

End point description:

Baseline data for efficacy endpoints was recorded in the rhLAMAN-02 trial (the last value available before first dosing in rhLAMAN-02 was always used as the baseline value).

End point type	Secondary

End point timeframe:

MRS was performed at baseline (rhLAMAN-02 Visit 2), at interim evaluation (Visit 13a, month 3), and at rhLAMAN-04 evaluation (Visit 26a, month 6).

End point values	Baseline	End evaluation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: ppm				
arithmetic mean (standard deviation)	0.99 (± 0.39)	0.04 (± 0.29)		

Statistical analyses

Statistical analysis title	End evaluation vs baseline

Statistical analysis description:

End evaluation is made at Visit 26a of the LAMAN04 study

Comparison groups	Baseline v End evaluation
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.733
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were recorded at interim evaluation (Visit 13a, month 12), at each dose visit (Visits 2-88), at rhLAMAN-04 evaluation (Visit 26a, month 18) and at Visit 89 (end of trial).

Adverse event reporting additional description:

The reporting was based on the full analysis set (FAS) and the safety analysis set (the safety analysis set was defined as all patients exposed to at least one dose of IMP) and included all 10 patients who initiated treatment with Lamazym in the rhLAMAN-02 trial, and out of which 9 patients continued into the rhLAMAN-04 trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Safety analysis set

Reporting group description:

The safety analysis set was defined as all patients exposed to at least one dose of IMP) and included all 10 patients who initiated treatment with Lamazym in the rhLAMAN-02 trial, and out of which 9 patients continued into the rhLAMAN-04 trial

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Loss of consciousness	Additional description: An SAE of loss of consciousness occurred during the rhLAMAN-04 trial 14 months after start of treatment. It was severe and assessed by the investigator to be possibly related to trial drug.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Injury, poisoning and procedural complications			

Excoriation subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3		
Contusion subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 6		
Wound subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Procedural pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 3		
Arthropod bite subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Procedural headache subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Open wound subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Ligament sprain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Joint dislocation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Application site erythema subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Foreign body in eye subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Nervous system disorders Headache			

subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Loss of consciousness subjects affected / exposed occurrences (all) Epilepsy subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 4 1 / 9 (11.11%) 2 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all)	 3 / 9 (33.33%) 4 2 / 9 (22.22%) 2 1 / 9 (11.11%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) Middle ear inflammation subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
Eye disorders Eye infection subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		

Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Tooth loss subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 2 / 9 (22.22%) 2 1 / 9 (11.11%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2 1 / 9 (11.11%) 1		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all) Aggression subjects affected / exposed occurrences (all) Initial insomnia subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
Renal and urinary disorders Haematuria			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Tendon calcification			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Osteochondrosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Joint instability			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 9 (88.89%)		
occurrences (all)	17		
Gastroenteritis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Fungal infection			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2012	The period subjects will receive one dose of enzyme every week passes from 6 months to 10 months. - Continuation of the treatment passes from a total of 30 ± 4 weeks to a total of 40 ± 6 weeks. So that the EOT is numbered Visit #47 instead of Visit #35 - The dose visits becomes numbered 2-46 instead of 2-34.
13 November 2012	- The period subjects will receive one dose of enzyme every week passes from 6 months to 16 months. - Continuation of the treatment passes from a total of 30 ± 4 weeks to a total of 72 weeks. So that the EOT is numbered Visit #73 instead of Visit #35 - The dose visits becomes numbered 2-72 instead of 2-34.
16 April 2013	The period subjects will receive one dose of enzyme every week passes from 6 months to 20 months. - Continuation of the treatment passes from a total of 30 ± 4 weeks to a total of 88 weeks. So that the EOT is numbered Visit #89 instead of Visit #35 - The dose visits becomes numbered 2-89 instead of 2-34.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No caveats or limitations are applicable to this summary of the results

Notes: