Clinical trial results:
A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Trial, Investigating the Efficacy and Safety of Repeated Lamazym Treatment of Subjects with alpha-Mannosidosis

Summary

EudraCT number	2012-000979-17
Trial protocol	DE DK BE ES SE
Global end of trial date	02 May 2014

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	rhLAMAN-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01681953
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2012-000979-17

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici SpA
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency Manager, Chiesi Farmaceutici SpA, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency Manager, Chiesi Farmaceutici SpA, 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	02 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 May 2014
Global end of trial reached?	Yes
Global end of trial date	02 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective of this trial is to evaluate the efficacy and safety of repeated Lamazym i.v. treatment, compared with placebo, in subjects 5-35 years of age with alpha-Mannosidosis

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	10 September 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	Spain: 3
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	25
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	6
Adolescents (12-17 years)	6

Adults (18-64 years)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-five (25) patients were randomized to Lamazym (n=15) or Placebo (n=10). No patients withdrew from the rhLAMAN-05 trial

Pre-assignment

Screening details:

A total of 26 patients were screened in the rhLAMAN-05 trial. There was one screening failure due to level of IgE not compatible with exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

A double-blind, randomized, parallel group trial design has been chosen. The randomization (in a 3:2 ratio) into active or Placebo group was stratified on age and was used to allocate the patients into blocks. Within the blocks, a standard randomization into active and Placebo was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lamazym

Arm description:

Intravenous (i.v.) dosing of Lamazym at a dose level of 1 mg/kg body weight.

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:

Intravenous (i.v.) dosing of Lamazym at a dose level of 1 mg/kg body weight. Weekly i.v.dosing of Lamazym through 12 months was planned; a minimum of 49 infusions and a maximum of 55 infusions were administered to each patient.

Arm title	Placebo

Arm description:

Intravenous (i.v.) dosing of Placebo at a dose level of 1 mg/kg body weight

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous (i.v.) dosing of Placebo at a dose level of 1 mg/kg body weight. Weekly i.v.dosing of placebo through 12 months was planned; a minimum of 49 infusions and a maximum of 55 infusions were administered to each patient.

Number of subjects in period 1	Lamazym	Placebo
Started	15	10
Completed	15	10

Baseline characteristics

Reporting groups	
Reporting group title	Lamazym
Reporting group description:	
Intravenous (i.v.) dosing of Lamazym at a dose level of 1 mg/kg body weight.	
Reporting group title	Placebo
Reporting group description:	
Intravenous (i.v.) dosing of Placebo at a dose level of 1 mg/kg body weight	

Reporting group values	Lamazym	Placebo	Total
Number of subjects	15	10	25
Age categorical Units: Subjects			
Children (2-11 years)	4	2	6
Adolescents (12-17 years)	3	3	6
Adults (18-64 years)	8	5	13
Age continuous Units: years			
arithmetic mean	18.5	19.7	
standard deviation	± 9	± 8.9	-
Gender categorical Units: Subjects			
Female	6	5	11
Male	9	5	14

Subject analysis sets	
Subject analysis set title	Lamazym - Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) included 25 patients, i.e all randomized subjects who received at least one dose of the study treatment and with at least one post-baseline efficacy measurement	
Subject analysis set title	Lamazym - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included 25 patients, i.e. all randomised patients who received at least one dose of the study treatment	
Subject analysis set title	Lamazym - Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per-Protocol analysis Set (PP) included 25 patients, i.e all all patients from the FAS who did not have substantial deviations to the protocol	
Subject analysis set title	Lamazym - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PK analysis set (PK) included 25 patients, i.e. all patients from the safety population and treated with Lamazym excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK. During the blinded data review, all patients were included in the PK analysis set, but only the 15 patients treated with Lamazym were then analyzed.	

Subject analysis set title	Placebo - Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included 25 patients, i.e all randomized subjects who received at least one dose of the study treatment and with at least one post-baseline efficacy measurement

Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set included 25 patients, i.e. all randomised patients who received at least one dose of the study treatment

Subject analysis set title	Placebo - Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol analysis Set (PP) included 25 patients, i.e all all patients from the FAS who did not have substantial deviations to the protocol

Subject analysis set title	Placebo - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK analysis set (PK) included 25 patients, i.e. all patients from the safety population and treated with Lamazym excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK. During the blinded data review, all patients were included in the PK analysis set, but only the 15 patients treated with Lamazym were then analyzed.

Reporting group values	Lamazym - Full Analysis Set (FAS)	Lamazym - Safety	Lamazym - Per protocol
Number of subjects	15	15	15
Age categorical Units: Subjects			
Children (2-11 years)	4	4	4
Adolescents (12-17 years)	3	3	3
Adults (18-64 years)	8	8	8
Age continuous Units: years			
arithmetic mean	18.5	18.5	18.5
standard deviation	± 9	± 9	± 9
Gender categorical Units: Subjects			
Female	6	6	6
Male	9	9	9

Reporting group values	Lamazym - PK	Placebo - Full Analysis Set (FAS)	Placebo - Safety
Number of subjects	15	10	10
Age categorical Units: Subjects			
Children (2-11 years)	4	2	2
Adolescents (12-17 years)	3	3	3
Adults (18-64 years)	8	5	5
Age continuous Units: years			
arithmetic mean	18.5	19.7	19.7
standard deviation	± 9	± 8.9	± 8.9

Gender categorical Units: Subjects			
Female	6	5	5
Male	9	5	5

Reporting group values	Placebo - Per protocol	Placebo - PK	
Number of subjects	10	10	
Age categorical Units: Subjects			
Children (2-11 years)	2		
Adolescents (12-17 years)	3		
Adults (18-64 years)	5		
Age continuous Units: years			
arithmetic mean	19.7		
standard deviation	± 8.9	±	
Gender categorical Units: Subjects			
Female	5		
Male	5		

End points

End points reporting groups

Reporting group title	Lamazym
Reporting group description:	
Intravenous (i.v.) dosing of Lamazym at a dose level of 1 mg/kg body weight.	
Reporting group title	Placebo
Reporting group description:	
Intravenous (i.v.) dosing of Placebo at a dose level of 1 mg/kg body weight	
Subject analysis set title	Lamazym - Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) included 25 patients, i.e all randomized subjects who received at least one dose of the study treatment and with at least one post-baseline efficacy measurement	
Subject analysis set title	Lamazym - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included 25 patients, i.e. all randomised patients who received at least one dose of the study treatment	
Subject analysis set title	Lamazym - Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per-Protocol analysis Set (PP) included 25 patients, i.e all all patients from the FAS who did not have substantial deviations to the protocol	
Subject analysis set title	Lamazym - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PK analysis set (PK) included 25 patients, i.e. all patients from the safety population and treated with Lamazym excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK. During the blinded data review, all patients were included in the PK analysis set, but only the 15 patients treated with Lamazym were then analyzed.	
Subject analysis set title	Placebo - Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) included 25 patients, i.e all randomized subjects who received at least one dose of the study treatment and with at least one post-baseline efficacy measurement	
Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set included 25 patients, i.e. all randomised patients who received at least one dose of the study treatment	
Subject analysis set title	Placebo - Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per-Protocol analysis Set (PP) included 25 patients, i.e all all patients from the FAS who did not have substantial deviations to the protocol	
Subject analysis set title	Placebo - PK
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PK analysis set (PK) included 25 patients, i.e. all patients from the safety population and treated with Lamazym excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK. During the blinded data review, all patients were included in the PK analysis set, but only the 15 patients treated with Lamazym were then analyzed.	

Primary: Change from baseline to week 52 in serum oligosaccharides

End point title	Change from baseline to week 52 in serum oligosaccharides

End point description:

End point type	Primary

End point timeframe:

Serum oligosaccharides concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: µmol/L				
arithmetic mean (standard deviation)	-5.1 (± 1.2)	-1.6 (± 1.7)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.37
upper limit	-2.62

Primary: Change from baseline to week 52 in the 3-minute stair climb test (3MSCT)

End point title	Change from baseline to week 52 in the 3-minute stair climb test (3MSCT)

End point description:

The 3MSCT measures the number of steps climbed up in 3 minutes and it was performed in accordance with the guidelines.
The test was performed twice, and the better result of the 2 tests was used.

End point type	Primary

End point timeframe:

The 3MSCT was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: steps/min				
arithmetic mean (standard deviation)	0.6 (± 8.6)	-2.4 (± 5.5)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.406
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.81
upper limit	9.05

Secondary: Change from baseline to week 52 in 6 minute walk test (6MWT)

End point title	Change from baseline to week 52 in 6 minute walk test (6MWT)

End point description:

Change from baseline to week 52 in 6MWT was included as a prioritized secondary endpoint

End point type	Secondary

End point timeframe:

The 6MWT was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: meters				
arithmetic mean (standard deviation)	4.4 (± 46.12)	-4.6 (± 40.79)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.692
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	7.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.76
upper limit	45.46

Secondary: Change from baseline to week 52 in FVC percent of predicted normal value (FVC %)

End point title	Change from baseline to week 52 in FVC percent of predicted normal value (FVC %)

End point description:

Change from baseline to week 52 in FVC% was included as a prioritized secondary endpoint

End point type	Secondary

End point timeframe:

FVC% was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	9		
Units: percent				
arithmetic mean (standard deviation)	8.17 (± 9.85)	2 (± 12.61)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.278
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.78
upper limit	16.6

Secondary: Change from baseline to week 26 in the BOT2 test - Running Speed and Agility

End point title	Change from baseline to week 26 in the BOT2 test - Running Speed and Agility

End point description:

End point type	Secondary

End point timeframe:

The Bruininks-Oseretsky (BOT2) test of motor proficiency was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: points				
arithmetic mean (standard deviation)	-0.93 (± 2.22)	-0.3 (± 2.67)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.434
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.08
upper limit	1.37

Secondary: Change from baseline to week 52 in the BOT2 test - Running Speed and Agility

End point title	Change from baseline to week 52 in the BOT2 test - Running Speed and Agility

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: points				
arithmetic mean (standard deviation)	-0.07 (± 3.03)	-0.78 (± 1.48)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.998
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	2.16

Secondary: Change from baseline to week 26 in the BOT2 test - Body coordination

End point title	Change from baseline to week 26 in the BOT2 test - Body coordination

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: points				
arithmetic mean (standard deviation)	-0.27 (± 4.93)	0.8 (± 4.32)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.451
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-1.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.64
upper limit	2.59

Secondary: Change from baseline to week 52 in the BOT2 test - Body coordination

End point title	Change from baseline to week 52 in the BOT2 test - Body coordination

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: points				
arithmetic mean (standard deviation)	0.93 (± 5.18)	0.8 (± 5.24)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Placebo - Full Analysis Set (FAS) v Lamazym - Full Analysis Set (FAS)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	2.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	7.22

Secondary: Change from baseline to week 26 in the BOT2 test - Fine Manual Control	
End point title	Change from baseline to week 26 in the BOT2 test - Fine Manual Control

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: Points				
arithmetic mean (standard deviation)	-0.07 (± 6.51)	-0.9 (± 5.78)		

Statistical analyses

Statistical analysis title	Lamzym vs Placebo
Comparison groups	Placebo - Full Analysis Set (FAS) v Lamazym - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.937
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.43
upper limit	4.78

Secondary: Change from baseline to week 52 in the BOT2 test - Fine Manual Control	
End point title	Change from baseline to week 52 in the BOT2 test - Fine Manual Control

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: points				
arithmetic mean (standard deviation)	2.73 (± 6.39)	1.33 (± 5.59)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.381
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	7.48

Secondary: Change from baseline to week 26 in the BOT2 test - Manual Coordination

End point title	Change from baseline to week 26 in the BOT2 test - Manual Coordination

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: points				
arithmetic mean (standard deviation)	1.47 (± 7.69)	-0.1 (± 3.38)		

Statistical analyses

Statistical analysis title	Lamzym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.688
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.25
upper limit	6.33

Secondary: Change from baseline to week 52 in the BOT2 test - Manual Coordination

End point title	Change from baseline to week 52 in the BOT2 test - Manual Coordination

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: points				
arithmetic mean (standard deviation)	2.8 (± 6.46)	-0.1 (± 3.38)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.787
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.33
upper limit	4.04

Secondary: Change from baseline to week 26 in the BOT2 test - Total	
End point title	Change from baseline to week 26 in the BOT2 test - Total
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to week 52 in the BOT2 test - Manual Coordination	

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: points				
arithmetic mean (standard deviation)	0.2 (± 12.8)	-0.5 (± 12.26)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.875
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.02
upper limit	9.45

Secondary: Change from baseline to week 52 in the BOT2 test - Total

End point title	Change from baseline to week 52 in the BOT2 test - Total

End point description:

End point type	Secondary

End point timeframe:

The BOT2 test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: points				
arithmetic mean (standard deviation)	6.4 (± 13.38)	-0.33 (± 9.59)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.344
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	4.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.86
upper limit	13.94

Secondary: Change from baseline to week 26 in the Leiter R – Design Analogies

End point title	Change from baseline to week 26 in the Leiter R – Design Analogies

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.16 (± 1.11)	0.4 (± 1.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Design Analogies

End point title	Change from baseline to week 52 in the Leiter R – Design Analogies

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: years				
arithmetic mean (standard deviation)	0.81 (± 1.47)	0.64 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Figure Ground

End point title	Change from baseline to week 26 in the Leiter R – Figure Ground

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.07 (± 1.15)	0.11 (± 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Figure Ground

End point title	Change from baseline to week 52 in the Leiter R – Figure Ground

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.37 (± 1.15)	0 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Form Completion

End point title	Change from baseline to week 26 in the Leiter R – Form Completion

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.26 (± 1.38)	-0.22 (± 1.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Form Completion

End point title	Change from baseline to week 52 in the Leiter R – Form Completion

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.63 (± 1.52)	0.22 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Paper Folding

End point title	Change from baseline to week 26 in the Leiter R – Paper Folding

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: years				
arithmetic mean (standard deviation)	-0.87 (± 2.19)	-0.25 (± 2.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Paper Folding

End point title	Change from baseline to week 52 in the Leiter R – Paper Folding

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: years				
arithmetic mean (standard deviation)	0.21 (± 2.26)	-0.31 (± 2.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Repeated Pattern

End point title	Change from baseline to week 26 in the Leiter R – Repeated Pattern

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: years				
arithmetic mean (standard deviation)	0.39 (± 0.78)	-0.44 (± 1.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Repeated Pattern

End point title	Change from baseline to week 52 in the Leiter R – Repeated Pattern

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: years				
arithmetic mean (standard deviation)	0.09 (± 0.64)	-0.69 (± 1.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Sequential Order

End point title	Change from baseline to week 26 in the Leiter R – Sequential Order

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: years				
arithmetic mean (standard deviation)	-0.26 (± 1.95)	0.57 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Sequential Order

End point title	Change from baseline to week 52 in the Leiter R – Sequential Order

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	9		
Units: years				
arithmetic mean (standard deviation)	-0.34 (± 1.79)	0.27 (± 1.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Associated Pairs

End point title	Change from baseline to week 26 in the Leiter R – Associated Pairs

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.13 (± 1.89)	0.59 (± 1.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Associated Pairs

End point title	Change from baseline to week 52 in the Leiter R – Associated Pairs

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
least squares mean (standard deviation)	0.18 (± 2.54)	-0.14 (± 1.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Forward Memory

End point title	Change from baseline to week 26 in the Leiter R – Forward Memory

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	-0.46 (± 2.76)	0.52 (± 1.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 52 in the Leiter R – Forward Memory

End point title	Change from baseline to week 52 in the Leiter R – Forward Memory

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.91 (± 2.34)	0.32 (± 1.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 26 in the Leiter R – Total Equivalence Age AM

End point title	Change from baseline to week 26 in the Leiter R – Total Equivalence Age AM

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.1 (± 1.33)	0.27 (± 0.62)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.702
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.73

Secondary: Change from baseline to week 52 in the Leiter R – Total Equivalence Age AM

End point title	Change from baseline to week 52 in the Leiter R – Total Equivalence Age AM

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.02 (± 1.41)	0.11 (± 1.02)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.681
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.73

Secondary: Change from baseline to week 26 in the Leiter R – Total Equivalence Age VR

End point title	Change from baseline to week 26 in the Leiter R – Total Equivalence Age VR

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	-0.01 (± 0.67)	0.1 (± 0.52)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.454
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.29

Secondary: Change from baseline to week 52 in the Leiter R – Total Equivalence Age VR

End point title	Change from baseline to week 52 in the Leiter R – Total Equivalence Age VR

End point description:

End point type	Secondary

End point timeframe:

The Leiter R cognitive function test was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: years				
arithmetic mean (standard deviation)	0.17 (± 0.71)	0.16 (± 0.65)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.864
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.48

Secondary: Change from baseline to week 26 in CSF oligosaccharides

End point title	Change from baseline to week 26 in CSF oligosaccharides

End point description:

End point type	Secondary

End point timeframe:

CSF oligosaccharides concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: µmol/L				
arithmetic mean (standard deviation)	1.4 (± 2.1)	0.4 (± 1.7)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.327
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	2.56

Secondary: Change from baseline to week 52 in CSF oligosaccharides

End point title	Change from baseline to week 52 in CSF oligosaccharides

End point description:

End point type	Secondary

End point timeframe:

CSF oligosaccharides concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: µmol/L				
arithmetic mean (standard deviation)	-0.4 (± 1.2)	-0.5 (± 0.9)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.897
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.93

Secondary: Change from baseline to week 26 in CSF Tau Protein concentration

End point title	Change from baseline to week 26 in CSF Tau Protein concentration

End point description:

End point type	Secondary

End point timeframe:

CSF biomarkers (Tau Protein, Neurofilament Protein and Glial Fibrillary Acidic Protein) concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: ng/L				
arithmetic mean (standard deviation)	13.8 (± 80.6)	-69.1 (± 80.1)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	95.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.96
upper limit	165.69

Secondary: Change from baseline to week 52 in CSF Tau Protein concentration

End point title	Change from baseline to week 52 in CSF Tau Protein concentration

End point description:

End point type	Secondary

End point timeframe:

CSF biomarkers (Tau Protein, Neurofilament Protein and Glial Fibrillary Acidic Protein) concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: ng/L				
arithmetic mean (standard deviation)	-61 (± 117.5)	-60.1 (± 70.2)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.356
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	32.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.01
upper limit	103.96

Secondary: Change from baseline to week 26 in CSF Neurofilament Protein concentration

End point title	Change from baseline to week 26 in CSF Neurofilament Protein concentration

End point description:

End point type	Secondary

End point timeframe:

CSF biomarkers (Tau Protein, Neurofilament Protein and Glial Fibrillary Acidic Protein) concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: ng/L				
arithmetic mean (standard deviation)	26 (± 173.6)	-224 (± 608.3)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	101.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.94
upper limit	239

Secondary: Change from baseline to week 52 in CSF Neurofilament Protein concentration

End point title	Change from baseline to week 52 in CSF Neurofilament Protein concentration

End point description:

End point type	Secondary

End point timeframe:

CSF biomarkers (Tau Protein, Neurofilament Protein and Glial Fibrillary Acidic Protein) concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: ng/L				
arithmetic mean (standard deviation)	-15.3 (± 87.2)	-112 (± 598)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Placebo - Full Analysis Set (FAS) v Lamazym - Full Analysis Set (FAS)

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.639
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-35.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-188.3
upper limit	118.09

Secondary: Change from baseline to week 26 in CSF Glial Fibrillary Acidic Protein concentration

End point title	Change from baseline to week 26 in CSF Glial Fibrillary Acidic Protein concentration

End point description:

End point type	Secondary

End point timeframe:

CSF biomarkers (Tau Protein, Neurofilament Protein and Glial Fibrillary Acidic Protein) concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: ng/L				
arithmetic mean (standard deviation)	42 (± 188.4)	-8 (± 106.5)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.573
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	37.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-99.18
upper limit	174.43

Secondary: Change from baseline to week 52 in CSF Glial Fibrillary Acidic Protein concentration

End point title	Change from baseline to week 52 in CSF Glial Fibrillary Acidic Protein concentration

End point description:

End point type	Secondary

End point timeframe:

CSF biomarkers (Tau Protein, Neurofilament Protein and Glial Fibrillary Acidic Protein) concentration was measured at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: ng/L				
arithmetic mean (standard deviation)	107.3 (± 187.6)	141 (± 231.9)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.575
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-46.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-218.1
upper limit	124.38

Secondary: Change from baseline to week 26 in FEV1

End point title	Change from baseline to week 26 in FEV1

End point description:

End point type	Secondary

End point timeframe:

Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	8		
Units: liters				
arithmetic mean (standard deviation)	0.23 (± 0.28)	-0.04 (± 0.24)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.52

Secondary: Change from baseline to week 52 in FEV1

End point title	Change from baseline to week 52 in FEV1

End point description:

End point type	Secondary

End point timeframe:

Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	9		
Units: liters				
arithmetic mean (standard deviation)	0.32 (± 0.34)	0.2 (± 0.12)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Placebo - Full Analysis Set (FAS) v Lamazym - Full Analysis Set (FAS)
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.608
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.31

Secondary: Change from baseline to Visit 26 in FEV1 Percent of predicted normal value

End point title	Change from baseline to Visit 26 in FEV1 Percent of predicted normal value

End point description:

End point type	Secondary

End point timeframe:

Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	8		
Units: percent				
arithmetic mean (standard deviation)	6.1 (± 9.54)	-1.38 (± 6.91)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	10.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	19.16

Secondary: Change from baseline to Visit 52 in FEV1 Percent of predicted normal value

End point title	Change from baseline to Visit 52 in FEV1 Percent of predicted normal value

End point description:

End point type	Secondary

End point timeframe:

Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	9		
Units: percent				
arithmetic mean (standard deviation)	6.5 (± 8.66)	4.44 (± 4.69)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.618
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	8.74

Secondary: Change from baseline to Visit 26 in FVC

End point title	Change from baseline to Visit 26 in FVC

End point description:

End point type	Secondary

End point timeframe:

Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	8		
Units: liters				
arithmetic mean (standard deviation)	0.24 (± 0.32)	-0.03 (± 0.17)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.64

Secondary: Change from baseline to Visit 52 in FVC	
End point title	Change from baseline to Visit 52 in FVC
End point description:	
End point type	Secondary
End point timeframe:	
Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)	

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	9		
Units: liters				
arithmetic mean (standard deviation)	0.4 (± 0.41)	0.11 (± 0.5)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.202
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.68

Secondary: Change from baseline to Visit 26 in PEF

End point title	Change from baseline to Visit 26 in PEF

End point description:

End point type	Secondary

End point timeframe:

Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	8		
Units: L/s				
arithmetic mean (standard deviation)	0.92 (± 0.73)	0.04 (± 0.62)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Placebo - Full Analysis Set (FAS) v Lamazym - Full Analysis Set (FAS)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.66

Secondary: Change from baseline to Visit 52 in PEF

End point title	Change from baseline to Visit 52 in PEF

End point description:

End point type	Secondary

End point timeframe:

Pulmonary function test were performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	9		
Units: L/s				
arithmetic mean (standard deviation)	1 (± 0.9)	0.68 (± 0.87)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.837
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.9

Secondary: Change from baseline to Visit 26 in Pure tone audiometry (PTA) - air conduction left ear

End point title	Change from baseline to Visit 26 in Pure tone audiometry (PTA) - air conduction left ear

End point description:

End point type	Secondary

End point timeframe:

PTA (pure tone audiometry) was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: dbHL				
arithmetic mean (standard deviation)	0.59 (± 7.08)	-1.09 (± 10.74)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.419
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	2.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.24
upper limit	9.82

Secondary: Change from baseline to Visit 52 in Pure tone audiometry (PTA) - air conduction left ear

End point title	Change from baseline to Visit 52 in Pure tone audiometry (PTA) - air conduction left ear

End point description:

End point type	Secondary

End point timeframe:

Pure tone audiometry was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: dbHL				
arithmetic mean (standard deviation)	0.95 (± 8.03)	0.76 (± 7.83)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.626
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.62
upper limit	7.5

Secondary: Change from baseline to Visit 26 in Pure tone audiometry (PTA) - air conduction right ear

End point title	Change from baseline to Visit 26 in Pure tone audiometry (PTA) - air conduction right ear

End point description:

End point type	Secondary

End point timeframe:

Pure tone audiometry was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: dbHL				
arithmetic mean (standard deviation)	1.08 (± 9.05)	-1.44 (± 10.61)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.467
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.54
upper limit	11.67

Secondary: Change from baseline to Visit 52 in Pure tone audiometry (PTA) - air conduction right ear

End point title	Change from baseline to Visit 52 in Pure tone audiometry (PTA) - air conduction right ear

End point description:

End point type	Secondary

End point timeframe:

Pure tone audiometry was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: dbHL				
arithmetic mean (standard deviation)	1.94 (± 11.34)	-1.89 (± 8.99)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	4.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.64
upper limit	13.81

Secondary: Change from baseline to Visit 26 in Pure tone audiometry (PTA) - bone conduction best ear

End point title	Change from baseline to Visit 26 in Pure tone audiometry (PTA) - bone conduction best ear

End point description:

End point type	Secondary

End point timeframe:

Pure tone audiometry was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: dbHL				
arithmetic mean (standard deviation)	3.21 (± 3.49)	-0.71 (± 5.46)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	4.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	7.94

Secondary: Change from baseline to Visit 52 in Pure tone audiometry (PTA) - bone conduction best ear

End point title	Change from baseline to Visit 52 in Pure tone audiometry (PTA) - bone conduction best ear

End point description:

End point type	Secondary

End point timeframe:

Pure tone audiometry was performed at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: dbHL				
arithmetic mean (standard deviation)	2.36 (± 5.21)	0.13 (± 5.89)		

Statistical analyses

Statistical analysis title	Lamazym vs Placebo
Comparison groups	Lamazym - Full Analysis Set (FAS) v Placebo - Full Analysis Set (FAS)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.217
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	2.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	7.42

Secondary: Change from baseline to Visit 26 in CHAQ score - Disability Index

End point title	Change from baseline to Visit 26 in CHAQ score - Disability Index

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: digit				
arithmetic mean (standard deviation)	-0.06 (± 0.38)	0.16 (± 0.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 52 in CHAQ score - Disability Index

End point title	Change from baseline to Visit 52 in CHAQ score - Disability Index

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: digit				
arithmetic mean (standard deviation)	-0.01 (± 0.32)	0.18 (± 0.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 26 in CHAQ score - VAS pain

End point title	Change from baseline to Visit 26 in CHAQ score - VAS pain

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	9		
Units: digit				
arithmetic mean (standard deviation)	0.2 (± 0.79)	0.3 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 52 in CHAQ score - VAS pain

End point title	Change from baseline to Visit 52 in CHAQ score - VAS pain

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	9		
Units: digit				
arithmetic mean (standard deviation)	0.19 (± 0.69)	0.15 (± 0.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 26 in CHAQ score - VAS general

End point title	Change from baseline to Visit 26 in CHAQ score - VAS general

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: digit				
arithmetic mean (standard deviation)	0.03 (± 0.63)	0.41 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 52 in CHAQ score - VAS general

End point title	Change from baseline to Visit 52 in CHAQ score - VAS general

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: digit				
arithmetic mean (standard deviation)	0.51 (± 0.93)	0.44 (± 0.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 26 in EQ-5D-5L VAS

End point title	Change from baseline to Visit 26 in EQ-5D-5L VAS

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: digit				
arithmetic mean (standard deviation)	5.71 (± 16.94)	3 (± 15.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 52 in EQ-5D-5L VAS

End point title	Change from baseline to Visit 52 in EQ-5D-5L VAS

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: digit				
arithmetic mean (standard deviation)	2 (± 17.95)	3.7 (± 15.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 26 in EQ-5D-5L Index

End point title	Change from baseline to Visit 26 in EQ-5D-5L Index

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	8		
Units: digit				
arithmetic mean (standard deviation)	0.06 (± 0.12)	0.04 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 52 in EQ-5D-5L Index

End point title	Change from baseline to Visit 52 in EQ-5D-5L Index

End point description:

End point type	Secondary

End point timeframe:

Health Questionnaires were administered at baseline (Visit 0), at Midterm evaluation (Visit 26a) and at End evaluation (Visit 52a)

End point values	Lamazym - Full Analysis Set (FAS)	Placebo - Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	8		
Units: digit				
arithmetic mean (standard deviation)	0.04 (± 0.09)	0.03 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed at baseline, at midterm evaluation (visit 26a) and at end evaluation (visit 52a)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Lamazym - Safety

Reporting group description:

Intravenous (i.v.) dosing of Lamazym at a dose level of 1 mg/kg body weight.

Reporting group title	Placebo - Safety

Reporting group description:

Intravenous (i.v.) dosing of Placebo at a dose level of 1 mg/kg body weight

Serious adverse events	Lamazym - Safety	Placebo - Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee deformity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sjogren's syndrome			

subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lamazym - Safety	Placebo - Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	9 / 10 (90.00%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 15 (40.00%)	5 / 10 (50.00%)	
occurrences (all)	11	11	
Chills			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	4	
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Catheter site pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Infusion site oedema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Seasonal allergy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Food allergy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	4	3	
Nasal congestion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Asthma			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Stress			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychotic behaviour			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Insomnia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Investigations			
Cardiac murmur			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood bilirubin decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Amylase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Fall			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Contusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Head injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Arthropod sting			

subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Wrist fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 15 (33.33%)	3 / 10 (30.00%)	
occurrences (all)	7	9	
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Syncope			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Loss of consciousness			

subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Aphonia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 15 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Ear congestion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Conjunctival hyperaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 15 (20.00%)	4 / 10 (40.00%)	
occurrences (all)	5	6	
Diarrhoea			

subjects affected / exposed	2 / 15 (13.33%)	3 / 10 (30.00%)	
occurrences (all)	2	3	
Toothache			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Dental caries			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Oral mucosal blistering			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Lip blister			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Mouth ulceration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Tongue injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Inguinal hernia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			

subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gingival swelling			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Mouth cyst			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Food poisoning			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cold sweat			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Acne			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Scar pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Vitiligo			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 15 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	4	6	
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	4	
Back pain			
subjects affected / exposed	2 / 15 (13.33%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Pain in jaw			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Spondylolisthesis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	10 / 15 (66.67%)	7 / 10 (70.00%)	
occurrences (all)	30	16	
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	3	
Ear infection			
subjects affected / exposed	2 / 15 (13.33%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Acute tonsillitis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Wound infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pharyngotonsillitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Tinea versicolour			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Otitis externa			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

Herpes simplex			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Parotitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2012	The Amendment 1 concerns the following points: - Exclusion criteria; - Safety laboratory assessments; - Recording of data; - End of trial recordings; - Monitoring and data quality assurance; - Data Management; - Case report forms; - Record retention.
26 July 2012	The Amendment 2 concerns the Exclusion criteria.
26 October 2012	The Amendment 3 concerns the following points: - Synopsis; -Trial design; - Patient population and selection; - Recruitment; - Packaging and labelling; - Table 9.1; - Baseline (Visit 0); - Power and sample size.
19 March 2013	The Amendment 4 concerns the following points: - Synopsis; - Trial design.

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 limitations or caveats are applicable to this summary

Notes: