Clinical trial results:
A single center, randomized, open-label, multiple-dose study of the efficacy and long-term safety of rhLAMAN (recombinant human alpha-mannosidase or Lamazym) for the treatment of patients with alpha-mannosidosis

Summary

EudraCT number	2010-022085-26
Trial protocol	DK
Global end of trial date	26 January 2012

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	09 August 2015
Version creation reason	• Correction of full data set Correction of Sponsor organisation name and address.

Trial information

Trial identification

Sponsor protocol code	rhLAMAN-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01285700
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 Spa, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, 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	Interim
Date of interim/final analysis	26 January 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2012
Global end of trial reached?	Yes
Global end of trial date	26 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Define effective dose based on evaluation of efficacy of rhLAMAN (Lamazym) from baseline on: The biochemical markers , The clinical parameters
- To evaluate the long-term safety profile of rhLAMAN (Lamazym)

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	24 January 2011
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:

After written approval from the IEC was obtained, the investigator asked the participants in the phase 1 (rhLAMAN-02) trial whether they wanted to continue in this subsequent trial. All participating patients were recruited at Copenhagen University Hospital, Denmark.

Pre-assignment

Screening details:

All 10 patients from the previous trial (rhLAMAN-02) continued into this trial. They were screened, and subsequently randomized. No patients failed screening. One patient (25 U/kg) was withdrawn from treatment and subsequently withdrawn from the trial.

Period 1

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

Blinding implementation details:

This was an open-label trial and remained open-label to all staff involved both at the sponsor and Larix.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lamazym 25 U/kg

Arm description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients con-tinued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

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:

Lamazym at dose levels of 25 U/kg or 50 U/kg administered as intravenous (i.v.) infusions.
The patients received i. v. infusions every week, for a total of 55 infusions (Visits 2-56).

Arm title	Lamazym 50 U/kg

Arm description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients continued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

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:

Lamazym at dose levels of 25 U/kg or 50 U/kg administered as intravenous (i.v.) infusions.
The patients received i. v. infusions every week, for a total of 55 infusions (Visits 2-56).

Number of subjects in period 1	Lamazym 25 U/kg	Lamazym 50 U/kg
Started	5	5
Completed	4	5
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Lamazym 25 U/kg

Reporting group description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients con-tinued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

Reporting group title	Lamazym 50 U/kg

Reporting group description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients continued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

Reporting group values	Lamazym 25 U/kg	Lamazym 50 U/kg	Total
Number of subjects	5	5	10
Age categorical Units: Subjects			
Children (2-11 years)	2	2	4
Adolescents (12-17 years)	3	3	6
Age continuous Units: years			
arithmetic mean	12.7	12.5	
standard deviation	± 3.6	± 4.4	-
Gender categorical Units: Subjects			
Female	1	2	3
Male	4	3	7

End points

End points reporting groups

Reporting group title	Lamazym 25 U/kg

Reporting group description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients con-tinued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

Reporting group title	Lamazym 50 U/kg

Reporting group description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients continued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

Primary: Change from baseline in serum oligasaccharide concentration

End point title	Change from baseline in serum oligasaccharide concentration

End point description:

For oligosaccharides in serum, urine and CSF a decrease in concentration was considered as an improvement for the patients and a biomarker for biochemical efficacy of Lamazym.

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: µmol/L				
arithmetic mean (full range (min-max))	3.5 (3 to 5)	2.4 (2 to 3)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.085
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.47
upper limit	0.21

Notes:

[1] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in urine oligasaccharide concentration

End point title	Change from baseline in urine oligasaccharide concentration

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: µmol/L				
arithmetic mean (full range (min-max))	402.25 (245 to 716)	297.6 (185 to 427)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/Kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.426
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-103.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-399.41
upper limit	192.87

Notes:

[2] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF oligosaccharides

End point title	Change from baseline in CSF oligosaccharides

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: µmol/L				
arithmetic mean (full range (min-max))	6.25 (5 to 7)	10.8 (7 to 14)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/Kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.033
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	9.45

Notes:

[3] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF albumin

End point title	Change from baseline in CSF albumin

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: 10E-3				
arithmetic mean (full range (min-max))	14.35 (4 to 39)	5.42 (2 to 10)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.296
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-9.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.39
upper limit	10.3

Notes:

[4] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF-GFAp

End point title	Change from baseline in CSF-GFAp

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: ng/L				
arithmetic mean (full range (min-max))	850 (420 to 11130)	854 (600 to 1260)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.282
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-109.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-335.24
upper limit	116.78

Notes:

[5] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF-glucose	
End point title	Change from baseline in CSF-glucose

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mmol/L				
arithmetic mean (full range (min-max))	3 (3 to 3)	3 (3 to 3)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.741
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.47

Notes:

[6] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF immunoglobulin G-index

End point title	Change from baseline in CSF immunoglobulin G-index

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.re.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: digit				
arithmetic mean (full range (min-max))	1 (1 to 1)	0.522 (0 to 1)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.187
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.1

Notes:

[7] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF immunoglobulin G

End point title	Change from baseline in CSF immunoglobulin G

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: g/L				
arithmetic mean (full range (min-max))	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.291
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.11

Notes:

[8] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF NFL

End point title	Change from baseline in CSF NFL

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: ng/L				
arithmetic mean (full range (min-max))	690 (410 to 1180)	616 (340 to 820)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.692
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	29.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-142.2
upper limit	200.31

Notes:

[9] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF protein

End point title	Change from baseline in CSF protein

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: g/L				
arithmetic mean (full range (min-max))	1.13 (0 to 3)	0.388 (0 to 1)		

Statistical analyses

Statistical analysis title	Lamzym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.302
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	0.89

Notes:

[10] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF erythrocytes

End point title	Change from baseline in CSF erythrocytes

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: 10E6/L				
arithmetic mean (full range (min-max))	358.5 (0 to 749)	28.6 (0 to 143)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.275
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-202.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-614.86
upper limit	209.95

Notes:

[11] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF tau

End point title	Change from baseline in CSF tau

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: ng/L				
arithmetic mean (full range (min-max))	283.25 (103 to 404)	505.8 (384 to 613)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.158
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	110.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.54
upper limit	279.13

Notes:

[12] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Primary: Change from baseline in CSF leukocytes

End point title	Change from baseline in CSF leukocytes

End point description:

End point type	Primary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: 10E6/L				
arithmetic mean (full range (min-max))	0 (0 to 0)	1.2 (0 to 6)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.405
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	4.96

Notes:

[13] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change frm baseline in MRI ADC grey matter

End point title	Change frm baseline in MRI ADC grey matter

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mm2/sec				
arithmetic mean (full range (min-max))	764 (742 to 812)	823.6 (735 to 1031)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.364
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	65.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-98.46
upper limit	230.26

Notes:

[14] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in MRI ADC standard

End point title	Change from baseline in MRI ADC standard

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mm2/sec				
arithmetic mean (full range (min-max))	851 (808 to 893)	866.6 (752 to 1055)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.246
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-21.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.21
upper limit	19.35

Notes:

[15] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in MRI ADC white matter

End point title	Change from baseline in MRI ADC white matter

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: mm2/sec				
arithmetic mean (full range (min-max))	973.25 (896 to 1056)	981.6 (840 to 1085)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.487
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-40.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-173.99
upper limit	93.14

Notes:

[16] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: ppm				
arithmetic mean (full range (min-max))	1 (1 to 1)	2 (1 to 3)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.777
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	1.3

Notes:

[17] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: ppm				
arithmetic mean (full range (min-max))	1 (0 to 3)	2 (1 to 3)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.787
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.01

Notes:

[18] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: digit				
arithmetic mean (full range (min-max))	1 (1 to 1)	1.106 (1 to 2)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.8
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.26

Notes:

[19] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: digit				
arithmetic mean (full range (min-max))	1 (1 to 1)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazyn 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.876
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.37

Notes:

[20] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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

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

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: digit				
arithmetic mean (full range (min-max))	1 (1 to 1)	1 (1 to 2)		

Statistical analyses

Statistical analysis title	lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.66
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.57

Notes:

[21] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: ppm				
arithmetic mean (full range (min-max))	1 (0 to 2)	1.8 (0 to 3)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg

Statistical analysis description:

The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg

Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.451
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.54

Secondary: Change from baseline in gait step lenghth

End point title	Change from baseline in gait step lenghth

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: cm				
arithmetic mean (full range (min-max))	1 (1 to 1)	0.523 (0 to 1)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	-0.04

Notes:

[22] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in gait step width

End point title	Change from baseline in gait step width

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: cm				
arithmetic mean (full range (min-max))	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.285
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.02

Notes:

[23] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in gait cadence

End point title	Change from baseline in gait cadence

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: rpm				
arithmetic mean (full range (min-max))	116 (104 to 125)	126.4 (106 to 169)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.742
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.56
upper limit	20.66

Notes:

[24] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in gait velocity

End point title	Change from baseline in gait velocity

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: m/sec				
arithmetic mean (full range (min-max))	1 (1 to 1)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.542
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.18

Notes:

[25] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from basline in BOT2

End point title	Change from basline in BOT2

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	31.25 (25 to 40)	20.4 (0 to 35)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.793
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.13
upper limit	11.43

Notes:

[26] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in BOT2 fine motor integration

End point title	Change from baseline in BOT2 fine motor integration

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	25.5 (17 to 33)	16.2 (0 to 28)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.135
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.47
upper limit	1.12

Notes:

[27] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in BOT2 manual dexterity

End point title	Change from baseline in BOT2 manual dexterity

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	20 (18 to 24)	15.6 (2 to 26)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.498
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.09
upper limit	2.77

Notes:

[28] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in BOT2 upper limb coordination

End point title	Change from baseline in BOT2 upper limb coordination

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	30.75 (26 to 36)	15.2 (2 to 28)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.155
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	3.22

Notes:

[29] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in BOT2 bilateral coordination

End point title	Change from baseline in BOT2 bilateral coordination

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	15.5 (9 to 20)	13 (2 to 20)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.999
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.36
upper limit	4.35

Secondary: Change from baseline in BOT2 balance

End point title	Change from baseline in BOT2 balance

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	16.5 (10 to 24)	12.8 (1 to 20)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.661
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.24
upper limit	4.94

Notes:

[30] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	19 (12 to 23)	15.2 (0 to 24)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.749
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.07
upper limit	3.85

Notes:

[31] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	7.167 (7 to 8)	6.133 (4 to 8)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.088
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	0.17

Notes:

[32] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	7.458 (7 to 9)	5.367 (3 to 8)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.261
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.81
upper limit	1.25

Notes:

[33] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	6.625 (6 to 8)	6.367 (5 to 9)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.962
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	1.12

Notes:

[34] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	5.729 (5 to 7)	4.983 (3 to 8)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.614
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.59

Notes:

[35] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	5.979 (5 to 7)	5.667 (5 to 7)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.294
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	0.63

Notes:

[36] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: integer				
arithmetic mean (full range (min-max))	8.813 (7 to 11)	7.188 (7 to 8)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.263
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.18
upper limit	1.43

Notes:

[37] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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

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

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: integer				
arithmetic mean (full range (min-max))	6.583 (6 to 7)	5.6 (3 to 8)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	-0.16

Notes:

[38] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in pulmonary FVC

End point title	Change from baseline in pulmonary FVC

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: liters				
arithmetic mean (full range (min-max))	2.95 (2 to 4)	2.302 (1 to 3)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.901
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	1.36

Notes:

[39] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in pulmonary FVC - percent

End point title	Change from baseline in pulmonary FVC - percent

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: percent				
arithmetic mean (full range (min-max))	93.667 (88 to 98)	81.4 (51 to 111)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	= 0.532
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-11.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.91
upper limit	31.6

Notes:

[40] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in FEV

End point title	Change from baseline in FEV

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: liters				
arithmetic mean (full range (min-max))	2.697 (2 to 4)	2.188 (1 to 3)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.847
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	1.24

Secondary: Change from baseline in pulmonary FEV - percent

End point title	Change from baseline in pulmonary FEV - percent

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: percent				
arithmetic mean (full range (min-max))	92.333 (86 to 102)	83.4 (55 to 115)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamzym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.639
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-8.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.64
upper limit	35.55

Notes:

[41] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in pulmonary peak expiratory flow rate

End point title	Change from baseline in pulmonary peak expiratory flow rate

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: L/sec				
arithmetic mean (full range (min-max))	5.277 (4 to 6)	4.116 (1 to 6)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	= 0.967
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	2.15

Notes:

[42] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: Change from baseline in pulmonary maximal inspiratory pressure

End point title	Change from baseline in pulmonary maximal inspiratory pressure

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: cm H20				
arithmetic mean (full range (min-max))	35.867 (21 to 45)	20.425 (20 to 21)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.037
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.37
upper limit	-2.03

Secondary: Change from baseline in pulmonary total lung capacity

End point title	Change from baseline in pulmonary total lung capacity

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: liters				
arithmetic mean (full range (min-max))	3.36 (3 to 4)	5 (5 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pulmonary total lung capacity - percent	
End point title	Change from baseline in pulmonary total lung capacity - percent

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: percent				
arithmetic mean (full range (min-max))	29 (25 to 33)	38 (38 to 38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pulmonary diffusion capacity	
End point title	Change from baseline in pulmonary diffusion capacity

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: mmmol/L/kPa				
arithmetic mean (full range (min-max))	5.995 (5 to 7)	6 (6 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pulmonary S Raw

End point title	Change from baseline in pulmonary S Raw

End point description:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: kPa				
arithmetic mean (full range (min-max))	1 (1 to 1)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.126
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.92

Notes:

[43] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: dB				
arithmetic mean (full range (min-max))	50.7 (14 to 73)	63.52 (51 to 73)		

Statistical analyses

Statistical analysis title	lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	= 0.105
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	10.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.01
upper limit	24.32

Notes:

[44] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: dB				
arithmetic mean (full range (min-max))	51.525 (21 to 70)	59.02 (45 to 71)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 50 U/kg v Lamazym 25 U/kg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.14
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	7.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.18
upper limit	17.62

Notes:

[45] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

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:

End point type	Secondary

End point timeframe:

This parameter was measured at baseline and at Visit 13a and Visit 26a. Only data on "end evaluation" (26th week) are reported here.

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: dB				
arithmetic mean (full range (min-max))	52.2 (35 to 65)	50.275 (41 to 65)		

Statistical analyses

Statistical analysis title	Lamazym 50 U/kg vs Lamazym 25 U/kg
Comparison groups	Lamazym 25 U/kg v Lamazym 50 U/kg

Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.287
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.81
upper limit	5.07

Notes:

[46] - The study aims to define effective dose (dose ranging) based on evaluation of efficacy of Lamazym from baseline, so it has an explorative nature.

Secondary: AUCcorr

End point title	AUCcorr

End point description:

End point type	Secondary

End point timeframe:

At Visit 13a (interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: h*µg/L				
arithmetic mean (standard deviation)	216284 (± 48875)	401086 (± 113064)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC

End point title	AUC

End point description:

End point type	Secondary

End point timeframe:

At Visit 13 a(interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: h*µg/L				
arithmetic mean (standard deviation)	159120 (± 106004)	444046 (± 139984)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUCt

End point title	AUCt

End point description:

End point type	Secondary

End point timeframe:

At Visit 13a (interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: h*µg/L				
arithmetic mean (standard deviation)	143925 (± 99419)	407623 (± 140646)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUCextrap

End point title	AUCextrap

End point description:

End point type	Secondary

End point timeframe:

At Visit 13a (interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: percent				
arithmetic mean (standard deviation)	11.7 (± 5.4)	9 (± 4.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax

End point title	Cmax

End point description:

End point type	Secondary

End point timeframe:

At Visit 13a (interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: µg/L				
arithmetic mean (standard deviation)	8858 (± 2700)	17260 (± 2051)		

Statistical analyses

No statistical analyses for this end point

Secondary: CL

End point title	CL

End point description:

End point type	Secondary

End point timeframe:

At Visit 13a (interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: L/h/kg				
arithmetic mean (standard deviation)	0.0136 (± 0.0189)	0.004 (± 0.0014)		

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2

End point title	t1/2

End point description:

End point type	Secondary

End point timeframe:

At Visit 13a (interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: hours				
arithmetic mean (standard deviation)	24.4 (± 18.3)	43.7 (± 16.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vz

End point title	Vz

End point description:

End point type	Secondary

End point timeframe:

At Visit 13a (interim data).

End point values	Lamazym 25 U/kg	Lamazym 50 U/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: L/kg				
arithmetic mean (standard deviation)	0.172 (± 0.023)	0.232 (± 0.059)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Visit 2 to Visit 57 (last visit)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Lamazym 25 U/kg

Reporting group description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients con-tinued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

Reporting group title	Lamazym 50 U/kg

Reporting group description:

The patients were allocated to study treatment by randomization. In the previous trial (rhLAMAN-02) patients were stratified to 5 different dose levels. The patients continued from the rhLAMAN-02 trial into the rhLAMAN-03 trial. The dose levels were handled as blocks in the rhLAMAN-03 randomization. I.e. one patient from each dose level in this trial was randomized to 25 U/kg and 50 U/kg, respectively.

Serious adverse events	Lamazym 25 U/kg	Lamazym 50 U/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lamazym 25 U/kg	Lamazym 50 U/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Skin papilloma			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	
occurrences (all)	1	3	
Ear tube insertion			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Wisdom teeth removal			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Catheter site pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Chills			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Feeling hot			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Medical device pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Hypersensitivity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Seasonal allergy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Sneezing			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Tracheitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Investigations			
Weight increased			
subjects affected / exposed	3 / 5 (60.00%)	3 / 5 (60.00%)	
occurrences (all)	4	3	

White blood cells urine positive			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	
occurrences (all)	4	7	
Post lumbar puncture syndrome			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Contusion			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Arthropod bite			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Infected bites			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Joint sprain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Tooth injury			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Wound			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	
occurrences (all)	2	7	
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Inner ear inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Eye disorders			
Eye infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Ear infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	3 / 5 (60.00%)	
occurrences (all)	0	3	
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Nausea			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Reflux gastritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Pain of skin			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	
occurrences (all)	4	2	
Arthralgia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 5 (100.00%)	4 / 5 (80.00%)	
occurrences (all)	11	7	
Gastroenteritis			

subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2010	• Addition of a pregnancy test in the post-menarche adolescent women at inclusion and throughout the trial • Reduction of the infusion rate from 1.5 mg/min to 0.5 mg/min protein • A time-interval was added for timing of PK measurements Changes were not expected to affect the objectives of the trial.
01 March 2011	• Due to patient convenience, the time point for PK sampling was moved from Visit 11 to 13a. This change was not expected to affect the outcome of the tests, as both original and change visits were performed after steady state was reached.
26 April 2011	• Due to a medication pause during the trial, a need for definition of procedures for terminating the trial before time ("early termination") was needed and additions to Section 7.4 (Patient withdrawal) was added. Furthermore additional sections were added: Sections 7.4.1 (Pause with medication), 7.4.2 (Withdrawal of medication) and 7.4.3 (Withdrawal of all trial related procedures). The changes were not expected to affect the secondary objective (long-term safety) as the intention was to keep the patient in the trial and collect safety data from the subsequent visits.
22 June 2011	To avoid the patients should terminate their treatment between the present protocol and inclusion in the following phase 2b protocol, a continuation phase was added. The continuation phase extended the trial up to 12 months, with continuation of weekly dosing. Additionally the end evaluation at Visit 26a was moved one week, from Week 28 ± 2 to Week 29 ± 2 due to logistic reasons. The changes were not expected to affect the objectives of the trial.
20 December 2011	To avoid the patients should terminate their treatment between the present protocol and inclusion in the following phase 2b protocol, Amendment 5 introduced the possibility of, if necessary, extending the continuation phase introduced in Amendment 4 with additional 4 weeks (Visit 56). Further, the possibility of using a freeze dried batch of drug was introduced in case of shortage of drug supply.

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: