



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 | <ul style="list-style-type: none">• 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) | EMA-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 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).

| | |
|------------------|-----------------|
| 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 |
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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 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 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 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 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 oligosaccharide concentration

| | |
|---|---|
| End point title | Change from baseline in serum oligosaccharide 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 | 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 ^[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: mm ² /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 lengthth

| | |
|--|--|
| End point title | Change from baseline in gait step lengthth |
| 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 baseline in BOT2

| | |
|--|------------------------------|
| End point title | Change from baseline 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 H2O | | | | |
| 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: mmol/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 (\pm 0.0189) | 0.004 (\pm 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 (\pm 18.3) | 43.7 (\pm 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 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 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 occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 | |
| Surgical and medical procedures | | | |
| Tooth extraction subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 3 / 5 (60.00%) 3 | |
| Ear tube insertion subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 5 (40.00%) 2 | |
| Wisdom teeth removal subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| General disorders and administration site conditions | | | |
| Malaise subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 2 | 0 / 5 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 5 (40.00%) 2 | |
| Catheter site pain subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Chills subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Feeling hot subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Medical device pain subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Immune system disorders | | | |

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 05 November 2010 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 \pm 2 to Week 29 \pm 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: