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

## Summary

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

### Results information

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

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | rhLAMAN-05 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Zymenex A/S |
| Sponsor organisation address | Roskildevej 12C, Hilleroed, Denmark, 3400 |
| Public contact | Clinical Trial Transparency, Chiesi Farmaceutici SpA, clinicaltrials_info@chiesi.com |
| Scientific contact | Clinical Trial Transparency, Chiesi Farmaceutici SpA, clinicaltrials_info@chiesi.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-001056-PIP02-12 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 02 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 May 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 May 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 10 September 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

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

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

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Lamazym |

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

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

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

Dosage and administration details:

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

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

## Baseline characteristics

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

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

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

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

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 5 | 5 |
| Male | 9 | 5 | 5 |

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

## End points

### End points reporting groups

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

## Primary: Change from baseline to week 52 in serum oligosaccharides

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

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

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

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

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

End point description:

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

| End point type | Primary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

**Statistical analyses**

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

**Statistical analyses**

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

| Secondary: Change from baseline to week 26 in CSF oligosaccharides | |
|---|---|
| End point title | Change from baseline to week 26 in CSF oligosaccharides |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

**Statistical analyses**

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

| Secondary: Change from baseline to week 52 in CSF oligosaccharides | |
|---|---|
| End point title | Change from baseline to week 52 in CSF oligosaccharides |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

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

## Secondary: Change from baseline to week 26 in FEV1

| End point title | Change from baseline to week 26 in FEV1 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

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

## Secondary: Change from baseline to week 52 in FEV1

| End point title | Change from baseline to week 52 in FEV1 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

**Secondary: Change from baseline to Visit 26 in FVC**

| End point title | Change from baseline to Visit 26 in FVC |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

## Secondary: Change from baseline to Visit 52 in FVC

| End point title | Change from baseline to Visit 52 in FVC |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

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

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

## Secondary: Change from baseline to Visit 26 in PEF

| | |
|---|---|
| End point title | Change from baseline to Visit 26 in PEF |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

## Secondary: Change from baseline to Visit 52 in PEF

| End point title | Change from baseline to Visit 52 in PEF |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

**Statistical analyses**

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

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

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

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

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

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

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

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

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo - Safety |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Lamazym - Safety |

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

| |
|---|
| No limitations or caveats are applicable to this summary |

Notes: