# Clinical trial results:
# A Single Center, Open-label, Non-randomized, Uncontrolled, Multiple-dose, Dose Escalation Study of the Safety, Pharmacokinetics and Efficacy of Metazym for the Treatment of Patients With Late Infantile Metachromatic Leukodystrophy (MLD)

## Summary

| | |
|---|---|
| EudraCT number | 2006-005341-11 |
| Trial protocol | DK |
| Global end of trial date | 27 March 2008 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 September 2018 |
| First version publication date | 01 August 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | rhASA-01 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00418561 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Shire |
| Sponsor organisation address | 300 Shire Way, Lexington, Massachusetts, United States, 02421 |
| Public contact | Norman Barton, Shire, +1 781-482-9297, nbarton@shire.com |
| Scientific contact | Norman Barton, Shire, +1 781-482-9297, nbarton@shire.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 27 March 2008 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 March 2008 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety profile of Metazym and to determine the pharmacokinetic (PK) profile of Metazym in subjects with late infantile metachromatic leukodystrophy (MLD) as measured by recombinant human Arylsulphatase A (rhASA) levels in plasma and Arylsulfatase A (ASA) activity in leukocytes.

Protection of trial subjects:

This study conformed to the standards of conduct for clinical studies as set forth in the Declaration of Helsinki and the legal regulations in Denmark. International Conference on Harmonization/Good Clinical Practice (ICH/GCP) guidelines for clinical studies were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 22 January 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Denmark: 13 |
| Worldwide total number of subjects | 13 |
| EEA total number of subjects | 13 |

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) | 13 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Thirteen subjects participated in the study.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1 |

Arm description:

Single dose of 25 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), thereafter, received repeated doses of 50 U/kg recombinant human Arylsulphatase A, once in every 2 weeks for a period of 26 weeks, as an intravenous (IV) infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant human Arylsulfatase A (rhASA) |
| Investigational medicinal product code | HGT-1111 |
| Other name | Metazym |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose of 25 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), thereafter, received repeated doses of 50 U/kg recombinant human Arylsulphatase A, once in every 2 weeks for a period of 26 weeks, as an IV infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| | |
|---|---|
| **Arm title** | Cohort 2 |

Arm description:

Repeated doses of 100 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant human Arylsulfatase A (rhASA) |
| Investigational medicinal product code | HGT-1111 |
| Other name | Metazym |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Repeated doses of 100 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| | |
|---|---|
| **Arm title** | Cohort 3 |

Arm description:

Repeated doses of 200 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 60 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant human Arylsulfatase A (rhASA) |
| Investigational medicinal product code | HGT-1111 |
| Other name | Metazym |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Repeated doses of 200 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 60 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| **Number of subjects in period 1** | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Started | 4 | 5 | 4 |
| Completed | 4 | 4 | 4 |
| Not completed | 0 | 1 | 0 |
| Subject's (guardian's) decision | - | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1 |
| Reporting group description: | |
| Single dose of 25 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), thereafter, received repeated doses of 50 U/kg recombinant human Arylsulphatase A, once in every 2 weeks for a period of 26 weeks, as an intravenous (IV) infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight. | |
| Reporting group title | Cohort 2 |
| Reporting group description: | |
| Repeated doses of 100 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight. | |
| Reporting group title | Cohort 3 |
| Reporting group description: | |
| Repeated doses of 200 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 60 minutes. Dosage adjustment was done monthly to account for changes in body weight. | |

| Reporting group values | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Number of subjects | 4 | 5 | 4 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: months<br>arithmetic mean<br>standard deviation | <br><br>36.25<br>± 9.32 | <br><br>41.8<br>± 10.13 | <br><br>30.75<br>± 7.27 |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 2 | 3 | 3 |
| Male | 2 | 2 | 1 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 13 | | |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: months<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 8 | | |
| Male | 5 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1 |
| Reporting group description: | |
| Single dose of 25 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), thereafter, received repeated doses of 50 U/kg recombinant human Arylsulphatase A, once in every 2 weeks for a period of 26 weeks, as an intravenous (IV) infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight. | |
| Reporting group title | Cohort 2 |
| Reporting group description: | |
| Repeated doses of 100 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight. | |
| Reporting group title | Cohort 3 |
| Reporting group description: | |
| Repeated doses of 200 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 60 minutes. Dosage adjustment was done monthly to account for changes in body weight. | |

### Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

| | |
|---|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs)[1] |
| End point description: | |
| An adverse event (AE) is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a subject participating in a clinical study with study drug, regardless of causal relationship. TEAEs were AEs occurred after study drug administration that were absent before treatment or that worsened relative to pre-treatment state, up to Week 28 until evaluation (when last cohort had 26-week evaluation and data management performed within 4 weeks) completed.<br>Intent-to-treat (ITT) population included all subjects who received at least 1 dose of study drug. | |
| End point type | Primary |
| End point timeframe: | |
| From study drug administration up to Week 28 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | 4 | 5 | 4 | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Gross Motor Function Measure (GMFM) at Week

**26**

| End point title | Change From Baseline in Gross Motor Function Measure (GMFM) at Week 26 |
|---|---|

End point description:

GMFM was measured using GMFM-88 item scores and summed to calculate a total GMFM-88 score. For each GMFM-88 item, the score was between 0 (minimal) to 3 (maximum). The total GMFM-88 score was between 0 (minimal) and 264 (maximum). The decrease in GMFM score over time indicates worsening of disease over time. Relative change from baseline at Week 26 was calculated as percentage change from baseline divided by the age-difference in months between first and last visit. Adjusted mean and 95 percent (%) confidence intervals were reported.
ITT population.

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

End point timeframe:

Baseline, Week 26

| **End point values** | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: percent (%) change | | | | |
| arithmetic mean (confidence interval 95%) | -2.36 (-7.62 to 2.91) | -8.29 (-13.55 to -3.02) | -10.9 (-16.17 to -5.64) | |

**Statistical analyses**

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

The comparisons of the three doses were done using analysis of variance (ANOVA) model including the baseline measurement as a covariate.

| Comparison groups | Cohort 1 v Cohort 2 v Cohort 3 |
|---|---|
| Number of subjects included in analysis | 13 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0737 [2] |
| Method | ANOVA |

Notes:

[2] - Test for no difference between cohorts.

**Primary: Change From Baseline in Cerebrospinal Fluid (CSF) Sulfatide at Week 26**

| End point title | Change From Baseline in Cerebrospinal Fluid (CSF) Sulfatide at Week 26 |
|---|---|

End point description:

Relative change from baseline at Week 26 was calculated as percentage change from baseline divided by the age-difference in months between first and last visit. Adjusted mean and 95 percent (%) confidence intervals were reported.
ITT population.

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

End point timeframe:

Baseline, Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: percent (%) change | | | | |
| arithmetic mean (confidence interval 95%) | 24.55 (0.44 to 48.66) | -3.77 (-22.33 to 14.8) | -4.32 (-28.17 to 19.53) | |

### Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|

Statistical analysis description:

The comparisons of the three doses were done using ANOVA model including the baseline measurement as a covariate.

| | |
|---|---|
| Comparison groups | Cohort 1 v Cohort 2 v Cohort 3 |
| Number of subjects included in analysis | 13 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1115 [3] |
| Method | ANOVA |

Notes:

[3] - Test for no difference between cohorts.

### Primary: Number of Subjects With Shift From Baseline to Week 26 in Sulfatide Levels in Urine

| End point title | Number of Subjects With Shift From Baseline to Week 26 in Sulfatide Levels in Urine[4] |
|---|---|

End point description:

Number of subjects with shifts between negative (value=0) and positive (value=1) values in urine sulfatide levels from baseline at Week 26 is reported.
ITT population. Here, the number of subjects analyzed are the subjects evaluable for this endpoint.

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

End point timeframe:

Baseline up to Week 26

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 2 | 2 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Negative(0) to negative(0) | 0 | 0 | 0 | |
| Negative(0) to positive(1) | 0 | 0 | 0 | |
| Positive(1) to negative(0) | 0 | 0 | 0 | |

| | | | | |
|---|---|---|---|---|
| Positive(1) to positive(1) | 3 | 2 | 2 | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline in Mullen’s Scales of Early Learning at Week 26

| | |
|---|---|
| End point title | Change From Baseline in Mullen’s Scales of Early Learning at Week 26 |

End point description:

Mullen's Scales of Early Learning is used to assess performance and learning ability in young children. The scale consisted of 144 items that had specific scoring criteria for each item. The scores were converted to T-scores with a decrease in score indicating worsening of disease. Relative change from baseline at Week 26 was calculated as percentage change from baseline divided by the age-difference in months between first and last visit. Adjusted mean and 95 percent (%) confidence intervals were reported.
ITT population.

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

End point timeframe:

Baseline, Week 26

| **End point values** | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: percent (%) change | | | | |
| arithmetic mean (confidence interval 95%) | 16.28 (0.72 to 31.84) | 0.26 (-15.49 to 16.02) | -4.92 (-20.26 to 10.41) | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|

Statistical analysis description:

The comparisons of the three doses were done using ANOVA model including the baseline measurement as a covariate.

| | |
|---|---|
| Comparison groups | Cohort 1 v Cohort 2 v Cohort 3 |
| Number of subjects included in analysis | 13 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1268 [5] |
| Method | ANOVA |

Notes:

[5] - Test for no difference between cohorts.

## Primary: Maximum Plasma Drug Concentration (Cmax) of Recombinant Human Arylsulphatase A (rhASA)

| End point title | Maximum Plasma Drug Concentration (Cmax) of Recombinant Human Arylsulphatase A (rhASA)[6] |
|---|---|

End point description:

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

End point timeframe:

Pre-dose and post-dose at 20, 40, 90 minutes, 3, 6 and 8 hours on Day 0, 40 minutes post-dose at Week 4, Pre-dose and post-dose at 20, 40, 90 minutes, 3, 6 and 8 hours at Week 8

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to quick disappearance of rhASA from plasma, rHASA levels were not possible to report.

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[7] | 0[8] | 0[9] | |
| Units: microgram per liter | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | |

Notes:

[7] - Due to quick disappearance of rhASA from plasma, rhASA levels were not possible to report.

[8] - Due to quick disappearance of rhASA from plasma, rhASA levels were not possible to report.

[9] - Due to quick disappearance of rhASA from plasma, rhASA levels were not possible to report.

### Statistical analyses

No statistical analyses for this end point

## Primary: Arylsulfatase A (ASA) Activity in Leukocytes

| End point title | Arylsulfatase A (ASA) Activity in Leukocytes[10] |
|---|---|

End point description:

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

End point timeframe:

Pre-dose and post-dose at 24 hours on Day 0 and at Weeks 8 and 26

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data could not be reported as the results were presented graphically, as planned.

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[11] | 0[12] | 0[13] | |
| Units: Not applicable | | | | |

Notes:

[11] - Data could not be reported as the results were presented graphically, as planned.

[12] - Data could not be reported as the results were presented graphically, as planned.

[13] - Data could not be reported as the results were presented graphically, as planned.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Nerve Conduction Velocity at Week 26

| End point title | Change From Baseline in Nerve Conduction Velocity at Week 26 |
|---|---|

End point description:

An electrophysiological evaluation using standard electrophysiological and electromyography to measure the speed and extent of nerve conduction and units are expressed in meters per second. '99999' indicate that the data could not be reported since there were no subjects evaluable for SN, Sensory R LM - MC category at Week 26.
Abbreviations: MN=Median Nerve; PN=Peroneal Nerve; SN=Sural Nerve; Dig.=Digit; FH=fibular hemimelia; L LM=left lateral medial; R LM=right lateral medial; MC=medial collateral.
ITT population. Here, "N" signifies the number of subjects who were evaluable for the respective category.

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

End point timeframe:

Baseline, Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: meters per second | | | | |
| arithmetic mean (standard deviation) | | | | |
| MN, Elbow Wrist: Baseline (N=4,5,4) | 20.38 (± 6.99) | 25.78 (± 17.72) | 15.95 (± 5.68) | |
| MN, Elbow Wrist: Change at Week 26 (N=4,4,4) | -4 (± 1.1) | 2.62 (± 4.42) | -3.65 (± 3.33) | |
| MN, Dig. II Wrist: Baseline (N=3,5,4) | 39.83 (± 7.22) | 36.82 (± 16.64) | 23.3 (± 11.99) | |
| MN, Dig. II Wrist: Change at Week 26 (N=3,4,4) | -11.7 (± 5.78) | -0.25 (± 4.39) | -1.33 (± 4.72) | |
| PN, Dig. Ankle FH: Baseline (N=4,4,4) | 20.7 (± 9.08) | 32.23 (± 21.41) | 14.13 (± 5.92) | |
| PN, Dig. Ankle FH: Change at Week 26 (N=4,3,4) | -7.85 (± 3.92) | -2.43 (± 1.59) | -2.65 (± 3.61) | |
| SN, Sensory L LM - MC: Baseline (N=4,4,4) | 26.88 (± 9.29) | 36.13 (± 20.61) | 29.18 (± 15.93) | |
| SN, Sensory L LM - MC: Change at Week 26 (N=3,3,4) | -5.57 (± 4.18) | 3.7 (± 9.79) | -9.33 (± 10.64) | |
| SN, Sensory R LM - MC: Baseline (N=4,4,4) | 31.35 (± 6.46) | 34.58 (± 17.74) | 27.48 (± 13.91) | |
| SN, Sensory R LM - MC: Change at Week 26 (N=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects who had Undergone Nerve Biopsy and had a Normal Nerve at Both Baseline and Week 26

| End point title | Number of Subjects who had Undergone Nerve Biopsy and had a Normal Nerve at Both Baseline and Week 26 |
|---|---|

End point description:

ITT population.

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

End point timeframe:

Baseline, Week 26

| **End point values** | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Baseline | 0 | 2 | 0 | |
| Week 26 | 0 | 2 | 0 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Shift From Baseline to Week 26 in Magnetic Resonance Imaging (MRI)-Loes scores

| End point title | Number of Subjects With Shift From Baseline to Week 26 in Magnetic Resonance Imaging (MRI)-Loes scores |
|---|---|

End point description:

Loes scoring system is used to grade the demyelinating abnormalities on brain MRI. A total of 17 locations of the brain were scored from 0 (normal appearance) to 2 (dense appearance). The total score ranged from 0 to 34 with a score of 14 or greater being considered severe. Number of participants with any shift of score between 0 to 2 for each of the 17 locations (Parieto Occipital [PO]-Periventricular [P], Central [C], Subcortical [Sc]; Anterior Temporal [AT]-P, C, Sc; Frontal [F]-P, C, Sc; Corpus Callosum [CC]-Splenium [S], Genus [G]; Projection Fibers [PF]-Capsular interna [CI] ant, CI post, Brainstem [B]; Cerebellum [Cb]-Cortex, Atrophy; Basal Ganglia [BG]-BG, Thalamus [T]; Cerebral Atrophy [CA]-CA), are only reported.
ITT population. Here, number of subjects analyzed in the Cohort 2 are the subjects evaluable for this endpoint.

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

End point timeframe:

Baseline up to Week 26

| **End point values** | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 4 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| PO, P: 1 to 2 | 1 | 0 | 1 | |
| PO, P: 2 to 2 | 3 | 4 | 3 | |
| PO, C: 2 to 2 | 4 | 4 | 4 | |
| PO, Sc: 0 to 0 | 1 | 0 | 1 | |

| | | | | |
|---|---|---|---|---|
| PO, Sc: 0 to 1 | 0 | 1 | 0 | |
| PO, Sc: 0 to 2 | 0 | 0 | 1 | |
| PO, Sc: 1 to 1 | 0 | 1 | 0 | |
| PO, Sc: 1 to 2 | 0 | 0 | 1 | |
| PO, Sc: 2 to 2 | 3 | 2 | 1 | |
| AT, P: 0 to 2 | 1 | 0 | 0 | |
| AT, P: 1 to 2 | 0 | 1 | 2 | |
| AT, P: 2 to 2 | 3 | 3 | 2 | |
| AT, C: 0 to 2 | 1 | 0 | 0 | |
| AT, C: 1 to 2 | 0 | 0 | 1 | |
| AT, C: 2 to 2 | 3 | 4 | 3 | |
| AT, Sc: 0 to 0 | 1 | 0 | 1 | |
| AT, Sc: 0 to 1 | 0 | 1 | 0 | |
| AT, Sc: 0 to 2 | 0 | 2 | 2 | |
| AT, Sc: 1 to 1 | 0 | 1 | 0 | |
| AT, Sc: 1 to 2 | 1 | 0 | 0 | |
| AT, Sc: 2 to 2 | 2 | 0 | 1 | |
| F, P: 0 to 2 | 1 | 0 | 1 | |
| F, P: 1 to 2 | 0 | 1 | 1 | |
| F, P: 2 to 2 | 3 | 3 | 2 | |
| F, C: 1 to 2 | 1 | 0 | 2 | |
| F, C: 2 to 2 | 3 | 4 | 2 | |
| F, Sc: 0 to 0 | 1 | 0 | 1 | |
| F, Sc: 0 to 2 | 0 | 2 | 2 | |
| F, Sc: 1 to 2 | 1 | 1 | 0 | |
| F, Sc: 2 to 2 | 2 | 1 | 1 | |
| CC, S: 1 to 0 | 0 | 1 | 1 | |
| CC, S: 1 to 2 | 1 | 0 | 0 | |
| CC, S: 2 to 0 | 1 | 1 | 1 | |
| CC, S: 2 to 1 | 2 | 1 | 0 | |
| CC, S: 2 to 2 | 0 | 1 | 2 | |
| CC, G: 0 to 2 | 1 | 1 | 0 | |
| CC, G: 1 to 1 | 0 | 1 | 0 | |
| CC, G: 1 to 2 | 0 | 0 | 2 | |
| CC, G: 2 to 1 | 1 | 0 | 1 | |
| CC, G: 2 to 2 | 2 | 2 | 1 | |
| PF, CI ant: 0 to 0 | 2 | 3 | 4 | |
| PF, CI ant: 0 to 1 | 1 | 1 | 0 | |
| PF, CI ant: 1 to 1 | 1 | 0 | 0 | |
| PF, CI post: 0 to 0 | 0 | 1 | 0 | |
| PF, CI post: 0 to 1 | 1 | 0 | 2 | |
| PF, CI post: 1 to 1 | 0 | 2 | 0 | |
| PF, CI post: 1 to 2 | 1 | 0 | 1 | |
| PF, CI post: 2 to 1 | 0 | 1 | 0 | |
| PF, CI post: 2 to 2 | 2 | 0 | 1 | |
| PF, B: 0 to 0 | 1 | 0 | 1 | |
| PF, B: 0 to 1 | 0 | 1 | 1 | |
| PF, B: 0 to 2 | 0 | 0 | 1 | |
| PF, B: 1 to 0 | 0 | 1 | 0 | |
| PF, B: 1 to 1 | 1 | 0 | 0 | |
| PF, B: 1 to 2 | 1 | 1 | 1 | |
| PF, B: 2 to 2 | 1 | 1 | 0 | |

| | | | | |
|---|---|---|---|---|
| Cb, Cortex: 0 to 0 | 2 | 1 | 1 | |
| Cb, Cortex: 0 to 1 | 0 | 2 | 2 | |
| Cb, Cortex: 1 to 1 | 2 | 1 | 1 | |
| Cb, Atrophy: 0 to 0 | 1 | 1 | 3 | |
| Cb, Atrophy: 0 to 1 | 1 | 1 | 0 | |
| Cb, Atrophy: 1 to 1 | 2 | 2 | 1 | |
| Bg, Bg: 0 to 0 | 2 | 3 | 2 | |
| Bg, Bg: 0 to 1 | 0 | 0 | 2 | |
| Bg, Bg: 1 to 0 | 0 | 1 | 0 | |
| Bg, Bg: 1 to 1 | 2 | 0 | 0 | |
| Bg, T: 0 to 0 | 2 | 3 | 3 | |
| Bg, T: 1 to 0 | 0 | 1 | 1 | |
| Bg, T: 1 to 1 | 2 | 0 | 0 | |
| CA, CA: 0 to 0 | 1 | 0 | 2 | |
| CA, CA: 0 to 1 | 0 | 2 | 1 | |
| CA, CA: 1 to 1 | 1 | 1 | 1 | |
| CA, CA: 1 to 2 | 2 | 1 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Paediatric Evaluation of Disability Inventory (PEDI) Scores at Week 26

| | |
|---|---|
| End point title | Change From Baseline in Paediatric Evaluation of Disability Inventory (PEDI) Scores at Week 26 |

End point description:

PEDI is used for the clinical evaluation of functional capabilities, performance and changes in functional skills in children with disabilities. It consisted of 20 items scored on a scale from 0 (total assistance) to 5 (independent). Total score ranged from 0-100 with higher scores indicating better functioning. None, child, rehab, extensive are items in 3 domains (self-care, mobility and social functioning).
ITT population. Here, "N" signifies the number of subjects who were evaluable for the respective category.

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

End point timeframe:

Baseline, Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Self-care, None: Baseline (N=4,5,4) | 6.25 (± 0.96) | 6 (± 1.41) | 4.75 (± 2.06) | |
| Self-care, None: Change at Week 26 (N=4,4,4) | -0.75 (± 1.5) | -1.5 (± 1.73) | -1.5 (± 1.91) | |
| Self-care, Child: Baseline (N=4,5,4) | 1.75 (± 0.96) | 2 (± 1.41) | 3.25 (± 2.06) | |
| Self-care, Child: Change at Week 26 (N=4,4,4) | 0.75 (± 1.5) | 1.25 (± 1.5) | 0.75 (± 2.22) | |
| Self-care, Rehab: Baseline (N=4,5,4) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |

| | | | | |
|---|---|---|---|---|
| Self-care, Rehab: Change at Week 26 (N=4,4,4) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |
| Self-care, Extensive: Baseline (N=4,5,4) | 0 (± 0) | 0.2 (± 0.45) | 0 (± 0) | |
| Self-care, Extensive: Change at Week 26 (N=4,4,4) | 0 (± 0) | 0.25 (± 0.5) | 0.5 (± 0.58) | |
| Mobility, None: Baseline (N=4,5,4) | 4.25 (± 1.89) | 3.6 (± 1.14) | 5 (± 0.82) | |
| Mobility, None: Change at Week 26 (N=4,4,4) | -0.75 (± 1.71) | -0.5 (± 1.29) | -1.25 (± 1.71) | |
| Mobility, Child: Baseline (N=4,5,4) | 2.5 (± 1.91) | 2.4 (± 1.67) | 1.25 (± 1.26) | |
| Mobility, Child: Change at Week 26 (N=4,4,4) | 0 (± 1.41) | 0.25 (± 1.26) | -0.5 (± 0.58) | |
| Mobility, Rehab: Baseline (N=4,5,4) | 0 (± 0) | 1 (± 1.41) | 0.75 (± 0.96) | |
| Mobility, Rehab: Change at Week 26 (N=4,4,4) | 1 (± 0.82) | 0.25 (± 0.5) | 0.5 (± 1.73) | |
| Mobility, Extensive: Baseline (N=4,5,4) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |
| Mobility, Extensive: Change at Week 26 (N=4,4,4) | 0 (± 0) | 0 (± 0) | 1.25 (± 1.5) | |
| Social, None: Baseline (N=4,5,4) | 4.25 (± 0.96) | 4.6 (± 0.55) | 4.75 (± 0.5) | |
| Social, None: Change at Week 26 (N=4,4,4) | 0.75 (± 0.96) | -0.25 (± 0.5) | 0.25 (± 0.5) | |
| Social, Child: Baseline (N=4,5,4) | 1.5 (± 2.38) | 0 (± 0) | 0.25 (± 0.5) | |
| Social, Child: Change at Week 26 (N=4,4,4) | -1.5 (± 2.38) | 0 (± 0) | -0.25 (± 0.5) | |
| Social, Rehab: Baseline (N=4,5,4) | 0 (± 0) | 0.4 (± 0.55) | 0 (± 0) | |
| Social, Rehab: Change at Week 26 (N=4,4,4) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |
| Social, Extensive: Baseline (N=4,5,4) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |
| Social, Extensive: Change at Week 26 (N=4,4,4) | 0 (± 0) | 0.25 (± 0.5) | 0 (± 0) | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Biochemistry

| End point title | Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Biochemistry |
|---|---|

End point description:

Number of subjects with at least 1 shift from baseline to Week 26, are reported.
Abbreviations: ALT=Alanine transaminase; CK=Creatine kinase; AP=Amyloid P component; LDH=Lactate dehydrogenase.
ITT population. Here, number of subjects analyzed in the Cohort 2 are the subjects evaluable for this endpoint.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline up to Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 4 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| ALT-Serum: Low to low | 2 | 0 | 1 | |
| ALT-Serum: Low to normal | 1 | 1 | 0 | |
| ALT-Serum: Normal to low | 0 | 1 | 2 | |
| ALT-Serum: Normal to normal | 0 | 1 | 1 | |
| ALT-Serum: High to low | 1 | 0 | 0 | |
| ALT-Serum: High to normal | 0 | 1 | 0 | |
| Amylase-Serum: Normal to normal | 4 | 4 | 4 | |
| AP-Serum: Normal to normal | 4 | 4 | 4 | |
| Calcium-Serum: Normal to normal | 4 | 3 | 4 | |
| CK-Serum: Normal to normal | 4 | 3 | 2 | |
| CK-Serum: Normal to high | 0 | 1 | 0 | |
| CK-Serum: High to normal | 0 | 0 | 1 | |
| CK-Serum: High to high | 0 | 0 | 1 | |
| Creatinine-Serum: Normal to normal | 4 | 4 | 4 | |
| Iron-Serum: Low to normal | 0 | 1 | 0 | |
| Iron-Serum: Normal to low | 0 | 0 | 1 | |
| Iron-Serum: Normal to normal | 3 | 3 | 3 | |
| Iron-Serum: Normal to high | 1 | 0 | 0 | |
| LDH-Serum: Normal to normal | 3 | 4 | 4 | |
| LDH-Serum: High to normal | 1 | 0 | 0 | |
| Magnesium-Serum: Normal to normal | 4 | 4 | 4 | |
| Phosphate-Serum: Normal to normal | 2 | 3 | 3 | |
| Phosphate-Serum: Normal to high | 1 | 0 | 0 | |
| Phosphate-Serum: High to normal | 1 | 1 | 1 | |
| Potassium-Serum: Normal to normal | 4 | 4 | 4 | |
| Sodium-Serum: Normal to normal | 4 | 3 | 4 | |
| Sodium-Serum: High to normal | 0 | 1 | 0 | |
| T Bilirubin-Serum: Normal to normal | 4 | 3 | 4 | |
| T Bilirubin-Serum: High to normal | 0 | 1 | 0 | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Coagulation

| End point title | Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Coagulation |
|---|---|

End point description:

Number of subjects with at least 1 shift from baseline to Week 26 are reported. The shift reported below for Cohort 1 was from low level at baseline to low level at Week 26.
ITT population.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline up to Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 0[14] | 0[15] | |
| Units: Subjects | | | | |
| number (not applicable) | 4 | | | |

Notes:

[14] - No subjects with shift from baseline to Week 26 in coagulation evaluations.

[15] - No subjects with shift from baseline to Week 26 in coagulation evaluations.

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Genotyping

| End point title | Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Genotyping |
|---|---|

End point description:

Number of subjects with at least 1 shift from baseline to Week 26 are reported.
Abbreviations: CSF=Cerebrospinal fluid; NFP=Neurofilament proteins.
ITT population. The number of subjects analyzed in the Cohort 2 are the subjects evaluable for this outcome. Here, "N" signifies the number of subjects who were evaluable for the respective category.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline up to Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 4 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Albumin CSF: Normal to normal (N=3,4,4) | 0 | 2 | 0 | |
| Albumin CSF: Normal to high (N=3,4,4) | 1 | 0 | 0 | |
| Albumin CSF: High to high (N=3,4,4) | 2 | 2 | 4 | |
| Albumin index: Normal to normal (N=3,4,4) | 0 | 1 | 0 | |
| Albumin index: High to high (N=3,4,4) | 3 | 3 | 4 | |
| Albumin Serum: Low to low (N=3,4,4) | 2 | 2 | 2 | |
| Albumin Serum: Low to normal (N=3,4,4) | 0 | 1 | 0 | |
| Albumin Serum: Normal to low (N=3,4,4) | 0 | 0 | 1 | |
| Albumin Serum: Normal to normal (N=3,4,4) | 1 | 1 | 1 | |
| Chitotriosidase CSF: Low to low (N=4,4,4) | 1 | 0 | 0 | |

| | | | | |
|---|---|---|---|---|
| Chitotriosidase CSF: High to high (N=4,4,4) | 3 | 4 | 4 | |
| NFP CSF: Normal to high (N=4,4,4) | 1 | 0 | 0 | |
| NFP CSF: High to high (N=4,4,4) | 3 | 4 | 4 | |
| Sulfatide CSF: High to high (N=3,4,4) | 3 | 4 | 4 | |
| Tauprotein CSF: High to low (N=4,4,4) | 0 | 1 | 0 | |
| Tauprotein CSF: High to high (N=4,4,4) | 4 | 3 | 4 | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Hematology

| End point title | Number of Subjects With Shift From Baseline to Week 26 in Clinical Laboratory Evaluations: Hematology |
|---|---|

End point description:

Number of subjects with at least 1 shift from baseline to Week 26 are reported.
Abbreviations: Abs=Absolute count; ERCS=Erythrocytes; MCHC=Mean corpuscular hemoglobin concentration; MCH=Mean cell hemoglobin.
ITT population. The number of subjects analyzed in the Cohort 2 are the subjects evaluable for this outcome. Here, "N" signifies the number of subjects who were evaluable for the respective category.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline up to Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 4 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Basophils Abs - Blood: Normal to normal (N=4,4,4) | 4 | 4 | 4 | |
| Eosinophil Abs - Blood: Normal to normal (N=4,4,4) | 4 | 4 | 4 | |
| ERCS - Blood: Low to low (N=4,4,4) | 1 | 0 | 0 | |
| ERCS - Blood: Normal to normal (N=4,4,4) | 3 | 4 | 4 | |
| Haemoglobin - Blood: Low to low (N=4,4,4) | 1 | 1 | 1 | |
| Haemoglobin - Blood: Low to normal (N=4,4,4) | 1 | 0 | 1 | |
| Haemoglobin - Blood: Normal to low (N=4,4,4) | 1 | 0 | 1 | |
| Haemoglobin - Blood: Normal to normal (N=4,4,4) | 1 | 3 | 1 | |
| Lymphocyte Abs - Blood: Low to low (N=4,4,4) | 0 | 1 | 0 | |
| Lymphocyte Abs - Blood: Normal to low (N=4,4,4) | 2 | 2 | 2 | |

| | | | | |
|---|---|---|---|---|
| Lymphocyte Abs - Blood: Normal to normal (N=4,4,4) | 2 | 1 | 2 | |
| MCHC - Blood: Normal to normal (N=4,4,4) | 3 | 3 | 4 | |
| MCHC - Blood: High to normal (N=4,4,4) | 1 | 1 | 0 | |
| MCH - Blood: Low to low (N=4,4,4) | 0 | 0 | 1 | |
| MCH - Blood: Normal to normal (N=4,4,4) | 4 | 4 | 3 | |
| Monocytes Abs - Blood: Normal to normal (N=4,4,4) | 4 | 4 | 3 | |
| Monocytes Abs - Blood: High to normal (N=4,4,4) | 0 | 0 | 1 | |
| Neutropil Abs - Blood: Normal to normal (N=4,4,4) | 4 | 4 | 3 | |
| Neutropil Abs - Blood: Normal to high (N=4,4,4) | 0 | 0 | 1 | |
| Thrombocytes - Blood: Normal to low (N=4,3,4) | 1 | 0 | 1 | |
| Thrombocytes - Blood: Normal to normal (N=4,3,4) | 2 | 0 | 2 | |
| Thrombocytes - Blood: High to normal (N=4,3,4) | 1 | 3 | 1 | |
| T Leucocytes - Blood: Low to normal (N=4,4,4) | 0 | 0 | 1 | |
| T Leucocytes - Blood: Normal to low (N=4,4,4) | 2 | 2 | 0 | |
| T Leucocytes - Blood: Normal to normal (N=4,4,4) | 2 | 2 | 3 | |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Abnormal Findings in Urine Analysis

| End point title | Number of Subjects With Abnormal Findings in Urine Analysis |
|---|---|

End point description:

The parameters analyzed in urine were albumin/protein, glucose, leucocytes, acetoacetate/ketones, nitrite and pH. Urine analysis findings were considered abnormal as judged by the investigator.
ITT population.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline up to Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of Subjects With Clinically Significant Abnormal Electrocardiogram (ECG) Findings

| End point title | Number of Subjects With Clinically Significant Abnormal Electrocardiogram (ECG) Findings |
|---|---|

End point description:

Abnormal ECG findings were considered as clinically significant at the discretion of investigator.
ITT population.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline up to Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Change From Baseline in Chitotriosidase at Week 26

| End point title | Change From Baseline in Chitotriosidase at Week 26 |
|---|---|

End point description:

ITT population. Here, "N" signifies the number of subjects who were evaluable for the respective category.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: nanomole/hour/milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N=4, 5, 4) | 924 (± 1431) | 1481 (± 1165) | 367 (± 179) | |
| Change at Week 26 (N=4, 4, 4) | -76 (± 393.9) | -228 (± 692.7) | 94.75 (± 103.6) | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline in Neurofilament Proteins (NFP), Glial Fibrillary Acidic Protein (GFAP) and Tauprotein in Cerebrospinal Fluid (CSF) at Week 26

| End point title | Change From Baseline in Neurofilament Proteins (NFP), Glial Fibrillary Acidic Protein (GFAP) and Tauprotein in Cerebrospinal Fluid (CSF) at Week 26 |
|---|---|

End point description:

ITT population. Here, "N" signifies the number of subjects who were evaluable for the respective category.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: nanogram/milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| NFP: Baseline (N=4, 5, 4) | 5436 (± 3698) | 7848 (± 4510) | 12558 (± 3529) | |
| NFP: Change at Week 26 (N=4, 4, 4) | 1134 (± 8098) | -3505 (± 2553) | -4020 (± 9061) | |
| GFAP: Baseline (N=4, 5, 4) | 1758 (± 397.4) | 1014 (± 524.3) | 1415 (± 625.7) | |
| GFAP: Change at Week 26 (N=4, 4, 4) | 330 (± 380.3) | 402.5 (± 460.5) | 502.5 (± 285.4) | |
| Tauprotein: Baseline (N=4, 5, 4) | 1148 (± 143.4) | 1014 (± 530.9) | 1610 (± 543.4) | |
| Tauprotein: Change at Week 26 (N=4, 4, 4) | -288 (± 692.3) | -273 (± 228.7) | -118 (± 907.6) | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline in Amplitude at Week 26

| End point title | Change From Baseline in Amplitude at Week 26 |
|---|---|

End point description:

'99999' indicate that the data could not be reported since there were no subjects evaluable for SN, Sensory R LM - MC category at Week 26.
Abbreviations: MN=Median Nerve; PN=Peroneal Nerve; SN=Sural Nerve; Dig.=Digit; APB=abductor pollicis brevis; EDB=extensor digitorum brevis.
ITT population. Here, "N" signifies the number of subjects who were evaluable for the respective category.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline, Week 26

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 5 | 4 | |
| Units: millivolts | | | | |
| arithmetic mean (standard deviation) | | | | |
| MN, Wrist-APB: Baseline (N=4,5,4) | 5.63 (± 1.73) | 7.88 (± 2.2) | 4.3 (± 1.05) | |
| MN, Wrist-APB: Change at Week 26 (N=4,4,4) | 0 (± 2.84) | 0.65 (± 0.74) | -0.35 (± 1.66) | |
| MN, Elbow-APB: Baseline (N=4,5,4) | 3.85 (± 1.23) | 6.34 (± 2.71) | 2.65 (± 0.6) | |
| MN, Elbow-APB: Change at Week 26 (N=4,4,4) | 0.15 (± 2.05) | 0.33 (± 0.57) | -0.55 (± 0.65) | |
| MN, Dig. II Wrist: Baseline (N=4,5,4) | 2.68 (± 1.3) | 11.64 (± 14.89) | 1.78 (± 0.83) | |
| MN, Dig. II Wrist: Change at Week 26 (N=4,4,4) | -0.32 (± 1) | 3.53 (± 6.6) | -0.93 (± 0.85) | |
| PN, Ankle EDB: Baseline (N=4,4,4) | 1.85 (± 0.91) | 5.4 (± 2.55) | 1.3 (± 0.68) | |
| PN, Ankle EDB: Change at Week 26 (N=4,3,4) | -0.72 (± 1.66) | -0.43 (± 1.56) | 0.08 (± 0.96) | |
| PN, FH EDB: Baseline (N=4,4,4) | 2.43 (± 1.8) | 4.98 (± 2.95) | 0.95 (± 0.74) | |
| PN, FH EDB: Change at Week 26 (N=4,3,4) | -1.68 (± 2.06) | -0.63 (± 1.46) | 0.16 (± 0.75) | |
| SN, Sensory L LM - MC: Baseline (N=4,4,4) | 5.25 (± 6.31) | 41.18 (± 51.5) | 1.65 (± 2.28) | |
| SN, Sensory L LM - MC: Change at Week 26 (N=4,3,4) | -2.45 (± 4.18) | 0.53 (± 21.75) | -0.78 (± 2.34) | |
| SN, Sensory R LM - MC: Baseline (N=4,4,4) | 5.35 (± 5.45) | 50.05 (± 56.13) | 1.73 (± 2.01) | |
| SN, Sensory R LM - MC: Change at Week 26 (N=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Physical Examination Results

| End point title | Physical Examination Results |
|---|---|

End point description:

Physical examination included general appearance, skin, head, ears, eyes, nose and throat, lymph nodes, heart, lungs, abdomen, extremities/joints, hip, neurological, mental status and, if appropriate, breasts, external genitalia, pelvic and rectal, and in addition weight, height and head circumference were recorded.
ITT population.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline up to Week 26

| **End point values** | Cohort 1 | Cohort 2 | Cohort 3 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[16] | 0[17] | 0[18] | |
| Units: Not applicable | | | | |

Notes:

[16] - Results could not be reported since data were collected in subject's listing only as planned.

[17] - Results could not be reported since data were collected in subject's listing only as planned.

[18] - Results could not be reported since data were collected in subject's listing only as planned.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From study drug administration up to Week 28 until evaluation (when last cohort had 26-week evaluation and data management performed within 4 weeks)

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 8.2 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1 |

Reporting group description:

Single dose of 25 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), thereafter, received repeated doses of 50 U/kg recombinant human Arylsulphatase A, once in every 2 weeks for a period of 26 weeks, as an intravenous (IV) infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| | |
|---|---|
| Reporting group title | Cohort 2 |

Reporting group description:

Repeated doses of 100 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 30 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| | |
|---|---|
| Reporting group title | Cohort 3 |

Reporting group description:

Repeated doses of 200 U/kg recombinant human Arylsulphatase A (Metazym, rhASA), once in every 2 weeks for a period of 26 weeks, as an IV infusion over 60 minutes. Dosage adjustment was done monthly to account for changes in body weight.

| Serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 5 (40.00%) | 2 / 4 (50.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis acute | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 5 (40.00%) | 2 / 4 (50.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 5 / 5 (100.00%) | 4 / 4 (100.00%) |
| Investigations | | | |
| Drug specific antibody present | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood iron decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Feeding tube complication | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Pallor | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |
| Muscle spasticity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Convulsion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Speech disorder developmental | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mutism | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 3 / 5 (60.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 1 | 6 | 3 |
| Discomfort | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Immune system disorders | | | |
| Type III immune complex mediated reaction | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 1 / 5 (20.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 12 | 2 | 2 |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 5 (40.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 4 | 3 |
| Nausea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngolaryngeal pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 3 / 5 (60.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 3 | 1 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Bronchitis acute | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Herpangina | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Acute tonsillitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Varicella | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 5 (20.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Postoperative infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 5 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Otitis media | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 5 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 13 April 2007 | The study was extended to last from 8 weeks to 26 weeks. |

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.

ASA activity in leukocytes could not be included in EudraCT results format as the results were presented graphically. Due to quick disappearance of rhASA from plasma, rhASA levels were not possible to report.

Notes: