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 Units: Subjects			
Age Continuous Units: months arithmetic mean standard deviation	 36.25 ± 9.32	 41.8 ± 10.13	 30.75 ± 7.27
Gender, Male/Female Units: Subjects			
Female	2	3	3
Male	2	2	1

Reporting group values	Total		
Number of subjects	13		
Age categorical Units: Subjects			
Age Continuous Units: months arithmetic mean standard deviation	 -		
Gender, Male/Female 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. 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: