



## Clinical trial results:

### A Single Center, Open-Label, Non-Randomized, Uncontrolled, Multiple-Dose, Dose Escalation Study of the Safety, Pharmacokinetics, Efficacy and Long Term Safety of HGT-1111 (Recombinant Human Arylsulfatase A [rhASA, Metazym]) for the Treatment of Patients with Late Infantile Metachromatic Leukodystrophy (MLD)

#### Summary

EudraCT number	2007-006345-40
Trial protocol	DK
Global end of trial date	25 September 2008

#### Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	13 May 2015

#### Trial information

##### Trial identification

Sponsor protocol code	HGT-MLD-048/rhASA-03
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00633139
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?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	25 September 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 September 2008
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The overall objective was to evaluate the long-term safety, efficacy and pharmacokinetics (PK) of recombinant human arylsulfatase A (rhASA) (HGT-1111) treatment in subjects with late infantile Metachromatic Leukodystrophy (MLD) and to determine the minimum effective dose.

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 (ICH) guidelines for good clinical practices (GCP) was followed.

After written approval from the Independent Ethics Committee (IEC) and competent authority has been obtained, the Investigator obtained informed consent from the subject's legally acceptable representative.

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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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

Notes:

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**Subjects enrolled per age group**

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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
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## Subject disposition

### Recruitment

Recruitment details:

Children with an established diagnosis of late infantile metachromatic leukodystrophy (MLD) due to arylsulfatase A (ASA) deficiency were recruited.

### Pre-assignment

Screening details:

All subjects that completed study rhASA-01 (2006-005341-11) except 1 subject who did not complete (at week 18) the rhASA-01 (2006-005341-11) participated in rhASA-03 (2007-006345-40).

### 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
<b>Arm title</b>	Cohort 1

Arm description:

Subjects received a single dose of rhASA at 25 units per kilogram (U/kg) intravenous (IV) infusion in rhASA-01 (2006-005341-11) study. Thereafter a repeated dose of rhASA at 50 U/kg, over 30 minutes was administered every other week up to Week 52.

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:

Subjects received a single dose of rhASA at 25 U/kg IV infusion in rhASA-01 (2006-005341-11) study. Thereafter a repeated dose of rhASA at 50 U/kg, over 30 minutes was administered every other week up to Week 52.

<b>Arm title</b>	Cohort 2
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Arm description:

Subjects received a repeated dose of rhASA at 100 U/kg IV infusion over 30 minutes was administered every other week up to Week 52.

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:

Subjects received a repeated dose of rhASA at 100 U/kg IV infusion over 30 minutes was administered every other week up to Week 52.

<b>Arm title</b>	Cohort 3
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Arm description:

Subjects received a repeated dose of rhASA at 200 U/kg IV infusion over 60 minutes was administered every other week up to Week 52.

Arm type	Experimental
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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:

Subjects received a repeated dose of rhASA at 200 U/kg IV infusion over 60 minutes was administered every other week up to Week 52.

<b>Number of subjects in period 1</b>	Cohort 1	Cohort 2	Cohort 3
Started	4	5	4
Completed	4	4	3
Not completed	0	1	1
Consent withdrawn by subject	-	1	-
Non compliance	-	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1
Reporting group description: Subjects received a single dose of rhASA at 25 units per kilogram (U/kg) intravenous (IV) infusion in rhASA-01 (2006-005341-11) study. Thereafter a repeated dose of rhASA at 50 U/kg, over 30 minutes was administered every other week up to Week 52.	
Reporting group title	Cohort 2
Reporting group description: Subjects received a repeated dose of rhASA at 100 U/kg IV infusion over 30 minutes was administered every other week up to Week 52.	
Reporting group title	Cohort 3
Reporting group description: Subjects received a repeated dose of rhASA at 200 U/kg IV infusion over 60 minutes was administered every other week up to Week 52.	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	4	5	4
Age categorical Units: Subjects			
<=18 years	4	5	4
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age continuous Units: months			
arithmetic mean	36.25	41.8	30.75
standard deviation	± 9.32	± 10.13	± 7.27
Gender categorical Units: Subjects			
Female	2	3	3
Male	2	2	1
Region of Enrollment Units: Subjects			
Denmark	4	5	4

Reporting group values	Total		
Number of subjects	13		
Age categorical Units: Subjects			
<=18 years	13		
Between 18 and 65 years	0		
>=65 years	0		
Age continuous Units: months			
arithmetic mean	-		
standard deviation	-		
Gender categorical Units: Subjects			
Female	8		

Male	5		
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Region of Enrollment Units: Subjects			
Denmark	13		

## End points

### End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Subjects received a single dose of rhASA at 25 units per kilogram (U/kg) intravenous (IV) infusion in rhASA-01 (2006-005341-11) study. Thereafter a repeated dose of rhASA at 50 U/kg, over 30 minutes was administered every other week up to Week 52.	
Reporting group title	Cohort 2
Reporting group description: Subjects received a repeated dose of rhASA at 100 U/kg IV infusion over 30 minutes was administered every other week up to Week 52.	
Reporting group title	Cohort 3
Reporting group description: Subjects received a repeated dose of rhASA at 200 U/kg IV infusion over 60 minutes was administered every other week up to Week 52.	

### Primary: Relative Changes (%) in Gross Motor Function Measurement (GMFM)

End point title	Relative Changes (%) in Gross Motor Function Measurement (GMFM)
End point description: Change (percent change) in GMFM is measured from baseline to end of study (Week 52). GMFM is measured using GMFM-88. The GMFM-88 item scores can be summed to calculate a total GMFM-88 score. For each GMFM-88 item, the score is between 0 (minimal) to 3 (maximum). The total GMFM-88 score is between 0 (minimal) to 264 (maximum). Relative changes in GMFM are calculated as percentage change from baseline divided by the age difference in months between first and last visit. The GMFM score decreases over time, which, indicates that the disease worsened over time.  Score over time (SOT), data mentioned over arithmetic mean represents the adjusted mean.  Intent to Treat (ITT) population included all the subjects in the study.	
End point type	Primary
End point timeframe: Baseline to 52 Weeks	

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: Relative % change in total GMFM-88 SOT				
arithmetic mean (confidence interval 95%)	-2.98 (-6.08 to 0.12)	-5.42 (-8.5 to -2.34)	-5.28 (-8.91 to -1.65)	

### Statistical analyses

Statistical analysis title	Relative Changes (%) in GMFM
Comparison groups	Cohort 1 v Cohort 2 v Cohort 3



Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4013
Method	ANCOVA

### Primary: Relative Change in Mullen's Scales of Early Learning

End point title	Relative Change in Mullen's Scales of Early Learning
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End point description:

Changes in Mullen's Scales of Early Learning are measured from baseline to end of study (Week 52) using Mullen's Scales of Early Learning. T scores, percentile ranks, and age equivalents can be computed for the four scales separately (visual reception, fine motor, expressive language, and receptive language). Relative change is calculated as percentage change from baseline divided by the age-difference in months between first and last visit. When Mullen's score decreases over time, it indicates the disease worsened over time.

Data mentioned over arithmetic mean represents the adjusted mean.

ITT Population.

End point type	Primary
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End point timeframe:

52 weeks

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: Relative % change in Mullen's SOT				
arithmetic mean (confidence interval 95%)	-2.82 (-6.31 to 0.66)	-2.97 (-6.47 to 0.54)	-6.98 (-11.95 to -2.01)	

### Statistical analyses

Statistical analysis title	Mullen's Scales of Early Learning
Comparison groups	Cohort 1 v Cohort 2 v Cohort 3
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.275
Method	ANCOVA

### Secondary: Change in Cerebrospinal Fluid (CSF) Sulfatide

End point title	Change in Cerebrospinal Fluid (CSF) Sulfatide
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End point description:

Changes in CSF sulfatide from baseline to end of study (Week 52).

Data mentioned over arithmetic mean represents the adjusted mean.

ITT Population.

End point type	Secondary
End point timeframe:	
52 weeks	

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: %change in CSF sulfatide				
arithmetic mean (confidence interval 95%)	8.6 (-0.77 to 17.97)	-1.53 (-8.63 to 5.56)	-2.77 (-14.35 to 8.81)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in Cerebrospinal Fluid (CSF) Sulfatide
Comparison groups	Cohort 1 v Cohort 2 v Cohort 3
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1363
Method	ANCOVA

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

52 weeks of treatment

Adverse event reporting additional description:

All other Adverse Events (AEs) (>5% reporting frequency) reported here are either PRB (probable) or DEF (definitely) related to drug administration.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	8.2
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### Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Cohort 1: Subjects received a single dose of rhASA at 25 U/kg IV infusion in rhASA-01 (2006-005341-11) study. Thereafter a repeated dose of rhASA at 50 U/kg, over 30 minutes was administered every other week up to Week 52.

Reporting group title	Cohort 2
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Reporting group description:

Cohort 2: Subjects received a repeated dose of rhASA at 100 U/kg IV infusion over 30 minutes was administered every other week up to Week 52.

Reporting group title	Cohort 3
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Reporting group description:

Cohort 3: Subjects received a repeated dose of rhASA at 200 U/kg IV infusion over 60 minutes was administered every other week up to Week 52.

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	3 / 4 (75.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Peritonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
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
Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	3 / 4 (75.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

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			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Blood iron decreased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0
Blood iron increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Drug specific antibody present subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0
General physical condition abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 4 (25.00%) 1
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 4 (25.00%) 2
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Injury, poisoning and procedural complications			
Feeding tube complication subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Medical device complication subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 4 (25.00%) 1
Procedural pain			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 4 (25.00%) 1
Congenital, familial and genetic disorders Leukodystrophy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Nervous system disorders Cognitive disorder subjects affected / exposed occurrences (all)  Convulsion subjects affected / exposed occurrences (all)  Hypotonia subjects affected / exposed occurrences (all)  Muscle spasticity subjects affected / exposed occurrences (all)  Mutism subjects affected / exposed occurrences (all)  Speech disorder developmental subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 5  0 / 4 (0.00%) 0  2 / 4 (50.00%) 5  4 / 4 (100.00%) 6  0 / 4 (0.00%) 0  1 / 4 (25.00%) 2	2 / 5 (40.00%) 3  0 / 5 (0.00%) 0  4 / 5 (80.00%) 5  4 / 5 (80.00%) 7  0 / 5 (0.00%) 0  2 / 5 (40.00%) 2	1 / 4 (25.00%) 1  2 / 4 (50.00%) 2  3 / 4 (75.00%) 4  1 / 4 (25.00%) 1  1 / 4 (25.00%) 1  0 / 4 (0.00%) 0
General disorders and administration site conditions Discomfort subjects affected / exposed occurrences (all)  Infusion related reaction subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0  2 / 4 (50.00%) 15  3 / 4 (75.00%) 6	1 / 5 (20.00%) 1  2 / 5 (40.00%) 16  3 / 5 (60.00%) 4	0 / 4 (0.00%) 0  3 / 4 (75.00%) 11  3 / 4 (75.00%) 5
Gastrointestinal disorders			

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

Muscle spasms subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	3 / 5 (60.00%) 3	1 / 4 (25.00%) 1
Infections and infestations			
Acute tonsillitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 4 (25.00%) 1
Bronchitis acute subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0
Enterobiasis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 3	2 / 5 (40.00%) 2	1 / 4 (25.00%) 1
Herpangina subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1	1 / 4 (25.00%) 1
Otitis media subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 4 (25.00%) 1
Postoperative infection			



subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Urinary tract 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
Viral infection			
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
21 February 2008	<p>- For the first infusion within each cohort, it will be required not to dose the 4 subjects within each cohort simultaneously. A minimum interval of 60 minutes between each subject will be allowed.</p> <p>-Subjects experiencing a mild infusion-related reaction may be pre-medicated with antihistamine for subsequent infusions. If fever is a component of the reaction, pre-medication with ibuprofen or acetaminophen may be considered. If infusions continue without incidents, then tapering of medications can be considered</p> <p>-Dose Reduction: The subject will discontinue if he/she experiences severe or intolerable reactions defined as: 1) liver (or other) toxicity attributed to rhASA; 2) symptoms suggestive of immune complex disease attributable to rhASA; or 3) unmanageable infusion-associated reaction (IAR), defined as an IAR that does not respond to pretreatment, rate reduction or treatment during the reaction. The final decision to discontinue treatment will be made by Investigator in consultation with Zymenex, and upon recommendation by the data monitoring committee (DMC) /allergic reaction review board (ARRB).</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported