



Clinical trial results:

A Multi-center, Open-Label Extension Study of HGT-1111 (Recombinant Human Arylsulfatase A or rhASA) Treatment in Patients with Late Infantile Metachromatic Leukodystrophy (MLD)

Summary

EudraCT number	2008-000084-41
Trial protocol	DK FR IT BE
Global end of trial date	22 October 2010

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	27 May 2015

Trial information

Trial identification

Sponsor protocol code	HGT-MLD-049
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00681811
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 Human Genetic Therapies, Inc., +1 781-482-9297, nbarton@shire.com
Scientific contact	Norman Barton, Shire Human Genetic Therapies, Inc., +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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 October 2010
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 October 2010
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to provide ongoing treatment of HGT-1111 to subjects who completed study HGT-MLD-048 (previously study rhASA-03) (2008-000084-41) until HGT-1111 was commercially available or the study was terminated by the Sponsor, provided no safety concerns emerged.

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 was followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	11
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:

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

Pre-assignment

Screening details:

All subjects that completed study HGT-MLD-048/rhASA-03 (2007-006345-40) participated in this study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	100 U/kg HGT-1111

Arm description:

Subjects received 100 units per kilogram (U/kg) of HGT-1111 intravenous (IV) infusion every other week.

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

Dosage and administration details:

Subjects received 100 U/kg of HGT-1111 IV infusion every other week.

Arm title	200 U/kg HGT-1111
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Arm description:

Subjects received 200 U/kg of HGT-1111 IV infusion every other week.

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

Dosage and administration details:

Subjects received 200 U/kg of HGT-1111 IV infusion every other week.

Number of subjects in period 1	100 U/kg HGT-1111	200 U/kg HGT-1111
Started	6	5
Completed	3	1
Not completed	3	4
Consent withdrawn by subject	2	2
Adverse event, non-fatal	1	1
Non-compliance	-	1

Baseline characteristics

Reporting groups

Reporting group title	100 U/kg HGT-1111
Reporting group description: Subjects received 100 units per kilogram (U/kg) of HGT-1111 intravenous (IV) infusion every other week.	
Reporting group title	200 U/kg HGT-1111
Reporting group description: Subjects received 200 U/kg of HGT-1111 IV infusion every other week.	

Reporting group values	100 U/kg HGT-1111	200 U/kg HGT-1111	Total
Number of subjects	6	5	11
Age categorical			
Units: Subjects			
Less than equal to (\leq) 18 years	6	5	11
Between 18 and 65 years	0	0	0
Greater than equal to (\geq) 65 years	0	0	0
Age continuous			
Age at week 54 or week 56 in HGT-MLD-049 (2008-000084-41)			
Units: months			
arithmetic mean	53.14	49.99	
standard deviation	± 10.526	± 8.752	-
Gender categorical			
Units: Subjects			
Female	3	3	6
Male	3	2	5

End points

End points reporting groups

Reporting group title	100 U/kg HGT-1111
Reporting group description: Subjects received 100 units per kilogram (U/kg) of HGT-1111 intravenous (IV) infusion every other week.	
Reporting group title	200 U/kg HGT-1111
Reporting group description: Subjects received 200 U/kg of HGT-1111 IV infusion every other week.	
Subject analysis set title	100 U/kg HGT-1111 (Month 6)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 100 U/kg of HGT-1111 intravenous (IV) infusion every other week up to month 6.	
Subject analysis set title	200 U/kg HGT-1111 (Month 6)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 200 U/kg of HGT-1111 IV infusion every other week up to month 6.	
Subject analysis set title	100 U/kg HGT-1111 (Month 12)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 100 U/kg of HGT-1111 IV infusion every other week up to month 12.	
Subject analysis set title	200 U/kg HGT-1111 (Month 12)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 200 U/kg of HGT-1111 IV infusion every other week up to month 12.	
Subject analysis set title	100 U/kg HGT-1111 (Month 18)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 100 U/kg of HGT-1111 IV infusion every other week up to month 18.	
Subject analysis set title	200 U/kg HGT-1111 (Month 18)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 200 U/kg of HGT-1111 IV infusion every other week up to month 18.	
Subject analysis set title	100 U/kg HGT-1111 (Month 24)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 100 U/kg of HGT-1111 IV infusion every other week up to month 24.	
Subject analysis set title	200 U/kg HGT-1111 (Month 24)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 200 U/kg of HGT-1111 IV infusion every other week up to month 24.	

Primary: Days of Exposure to HGT-1111

End point title	Days of Exposure to HGT-1111 ^[1]
End point description: End of study defined as until HGT-1111 is commercially available, the subject's participation is discontinued, or the study is terminated by the Sponsor.	
End point type	Primary
End point timeframe: Baseline until end of study	

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: Only descriptive statistics were done, no inferential statistical analyses were performed.

End point values	100 U/kg HGT-1111	200 U/kg HGT-1111		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Days				
arithmetic mean (standard deviation)	644.7 (± 276.11)	544.8 (± 397.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Level of Cerebrospinal Fluid (CSF) Sulfatide

End point title	Level of Cerebrospinal Fluid (CSF) Sulfatide
End point description:	
Level of CSF sulfatide measured at 6-month intervals in HGT-MLD-049 (2008-000084-41).	
Number of subjects analysed is for subjects who were evaluable for this outcome measure at respective arm.	
99999 signifies standard deviation not reported as there was only 1 evaluable subject.	
End point type	Secondary
End point timeframe:	
Baseline until end of study	

End point values	100 U/kg HGT-1111 (Month 6)	200 U/kg HGT-1111 (Month 6)	100 U/kg HGT-1111 (Month 12)	200 U/kg HGT-1111 (Month 12)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	4	5	3
Units: nanomole per liter (nmol/L)				
arithmetic mean (standard deviation)	685 (± 522.79)	732.5 (± 545.06)	745 (± 525.12)	1150 (± 676.39)

End point values	100 U/kg HGT-1111 (Month 18)	200 U/kg HGT-1111 (Month 18)	100 U/kg HGT-1111 (Month 24)	200 U/kg HGT-1111 (Month 24)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	2
Units: nanomole per liter (nmol/L)				
arithmetic mean (standard deviation)	700 (± 526.78)	850 (± 491.81)	900 (± 99999)	837.5 (± 441.94)

Statistical analyses

No statistical analyses for this end point

Secondary: Level of White Matter Metabolites

End point title	Level of White Matter Metabolites
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End point description:

Level of white matter metabolites [N-acetyl Aspartate (NAA)] measured at 6-month intervals in HGT-MLD-049 (2008-000084-41)

No subjects were analysed after Month 18 hence, data not available after Month 18.

Number of subjects analysed is for subjects who were evaluable for this outcome measure at respective arm.

End point type	Secondary
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End point timeframe:

Baseline until end of study

End point values	100 U/kg HGT-1111 (Month 6)	200 U/kg HGT-1111 (Month 6)	100 U/kg HGT-1111 (Month 12)	200 U/kg HGT-1111 (Month 12)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	4	5	2
Units: nmol/L				
arithmetic mean (standard deviation)	0.528 (± 0.176)	0.385 (± 0.237)	0.598 (± 0.208)	0.47 (± 0.198)

End point values	100 U/kg HGT-1111 (Month 18)	200 U/kg HGT-1111 (Month 18)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: nmol/L				
arithmetic mean (standard deviation)	0.51 (± 0.141)	0.805 (± 0.445)		

Statistical analyses

No statistical analyses for this end point

Secondary: Score of Gross Motor Function Measurement (GMFM)

End point title	Score of Gross Motor Function Measurement (GMFM)
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End point description:

Gross motor function is measured using GMFM-88 and measured at 6-month intervals in HGT-MLD-049 (2008-000084-41) study. 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). With GMFM score decreases over time, it indicates disease progression.

Number of subjects analysed is for subjects who were evaluable for this outcome measure at respective arm.

End point type	Secondary
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End point timeframe:

Baseline until end of study

End point values	100 U/kg HGT-1111 (Month 6)	200 U/kg HGT-1111 (Month 6)	100 U/kg HGT-1111 (Month 12)	200 U/kg HGT-1111 (Month 12)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	5	5	3
Units: score on the scale				
arithmetic mean (standard deviation)	16.8 (± 11.3)	9.2 (± 11.71)	15.6 (± 15.84)	8.7 (± 9.29)

End point values	100 U/kg HGT-1111 (Month 18)	200 U/kg HGT-1111 (Month 18)	100 U/kg HGT-1111 (Month 24)	200 U/kg HGT-1111 (Month 24)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	2	2	2
Units: score on the scale				
arithmetic mean (standard deviation)	16.8 (± 13.6)	9 (± 5.66)	14.5 (± 10.61)	13 (± 11.31)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to End of Study (until HGT-1111 is commercially available, the subject's participation is discontinued, or the study is terminated by the Sponsor)

Adverse event reporting additional description:

All other adverse events (AEs) (>5% reporting frequency) reported here are related to drug administration, all were infusion-related reactions.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	8.1
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Reporting groups

Reporting group title	200 U/kg HGT-1111
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Reporting group description:

Subjects received 200 U/kg of HGT-1111 IV infusion every other week.

Reporting group title	100 U/kg HGT-1111
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Reporting group description:

Subjects received 100 U/kg of HGT-1111 IV infusion every other week.

Serious adverse events	200 U/kg HGT-1111	100 U/kg HGT-1111	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	2 / 6 (33.33%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis acute			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	200 U/kg HGT-1111	100 U/kg HGT-1111	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	6 / 6 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 5 (60.00%)	1 / 6 (16.67%)	
occurrences (all)	8	1	
Pallor			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Adverse drug reaction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Generalised oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	4 / 5 (80.00%)	4 / 6 (66.67%)	
occurrences (all)	4	16	
Reproductive system and breast disorders			

Phimosis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 6 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Increased bronchial secretion subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Bronchospasm subjects affected / exposed occurrences (all) Asthma subjects affected / exposed occurrences (all) Respiratory distress subjects affected / exposed occurrences (all) Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 2 / 5 (40.00%) 2	 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 3 / 6 (50.00%) 5 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1	
Psychiatric disorders Mental status changes subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 2 / 5 (40.00%) 2	 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0	
Investigations Weight decreased subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0	 1 / 6 (16.67%) 1	

Platelet count increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Heart rate increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Blood iron increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 6 (16.67%) 1	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Injury, poisoning and procedural complications			
Feeding tube complication subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	1 / 6 (16.67%) 1	
Joint dislocation subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 6 (0.00%) 0	
Nervous system disorders			
Muscle spasticity subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 3	2 / 6 (33.33%) 5	
Hypotonia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Febrile convulsion subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Epilepsy subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 3	1 / 6 (16.67%) 1	
Dystonia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	1 / 6 (16.67%) 1	
Depressed level of consciousness			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Syncope subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 6 (0.00%) 0	
Convulsion subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3	0 / 6 (0.00%) 0	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Eye disorders Conjunctival oedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Eyelid oedema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 6 (33.33%) 2	
Gastrointestinal disorders Gastritis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 6 (33.33%) 2	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 2	
Constipation subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	1 / 6 (16.67%) 1	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Vomiting			

subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 10	3 / 6 (50.00%) 15	
Toothache subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Regurgitation of food subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Reflux gastritis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 6 (16.67%) 1	
Nausea subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 3	3 / 6 (50.00%) 9	
Skin and subcutaneous tissue disorders Urticaria generalised subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 4	0 / 6 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 11	1 / 6 (16.67%) 13	
Swelling face subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 6 (16.67%) 4	
Rash subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 6	2 / 6 (33.33%) 9	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 6 (0.00%) 0	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 4	3 / 6 (50.00%) 4	
Infection			

subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	1	0
Herpes simplex		
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences (all)	2	1
Eye infection		
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)
occurrences (all)	3	1
Ear infection		
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Bronchitis acute		
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)
occurrences (all)	2	1
Influenza		
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences (all)	2	2
Pneumonia		
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)
occurrences (all)	1	1
Pharyngitis		
subjects affected / exposed	2 / 5 (40.00%)	2 / 6 (33.33%)
occurrences (all)	4	5
Oral candidiasis		
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
subjects affected / exposed	1 / 5 (20.00%)	4 / 6 (66.67%)
occurrences (all)	2	12
Lung infection		
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Laryngitis		

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Scarlet fever			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Viral pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2008	<ul style="list-style-type: none">• Clarifications of financial conditions requested by the Ethics Committee• Language added regarding publication of negative results• Addition of a section on biobank• Clarification of minor study procedures
09 February 2009	<ul style="list-style-type: none">• Change in Sponsor from Metazym to Shire HGT• Change in protocol number from rhASA-05 to HGT-MLD-049• Change in medical monitor and legal representative• All sponsor contact information was updated to reflect the acquisition of Metazym by Shire Human Genetic Therapies, Inc., on 04 June 2008.• The product name changed from Metazym to Shire product code: HGT-1111.• The title of the study was changed to clarify that the study was an extension study and not a compassionate use study and to reflect the new product name.• Subjects who had safely tolerated their HGT-1111 infusions were given the option of receiving subsequent infusions at an infusion site in their home country, once the necessary approvals were obtained. This amendment adapted the relevant language for the inclusion of those countries.• As the focus of the study was to provide continued access of HGT-1111 treatment to subjects who completed study HGT-MLD-048 (formerly study rhASA-03), a number of assessments were eliminated, including gross motor function classification, concentration of neurofilament protein, glial fibrillary acidic protein, tau protein in cerebrospinal fluid, concentration of serum chitotriosidase, diffuser tensor imaging, Loes score, Somatosensory Evoked Potential (SSEP), and nerve conduction and electromyography.• The frequency of anti-rhASA antibody testing was changed from every other week to every 6 weeks plus week 26.• The frequency of hematology, routine serum chemistry and urinalysis assessments was increased to include assessments every 6 weeks as well as the original 26 week assessment.• The format of the protocol, all introductory text, protocol section numbers, most administrative text and adverse event reporting language were updated to reflect the current standard of care and Shire's document template and standards.• The concentration of the investigational product was changed from milligram per milliliter (mg/mL) to U/mL.
19 February 2009	The protocol was amended to clarify that the concentration of investigational medicinal product ((IMP), HGT-1111 for IV infusion) would be as indicated on the label, with dosing instructions included as a package insert with each shipment of IMP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 October 2010	Study got terminated prior to planned completion date due to lack of efficacy.	-

Notes:

Limitations and caveats

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

Early termination due to lack of efficacy.

Notes: