



Clinical trial results:

A Randomized, Controlled, Open-label, Multicenter, Phase IIb Safety and Efficacy Study of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Early Stage

Summary

EudraCT number	2013-003450-24
Trial protocol	DE GB ES NL IT FR
Global end of trial date	01 June 2016

Results information

Result version number	v1 (current)
This version publication date	17 December 2016
First version publication date	17 December 2016

Trial information

Trial identification

Sponsor protocol code	HGT-SAN-093
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02060526
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Human Genetic Therapies, Inc
Sponsor organisation address	300 Shire Way, Lexington, MA, United States, 02421
Public contact	Study Physician, Shire, 1 866-842-5335,
Scientific contact	Study Physician, Shire, 1 866-842-5335,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001634-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the potential clinical efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) administered using a surgically implanted intrathecal drug delivery device (IDDD) in subjects with Sanfilippo Syndrome Type A.

Protection of trial subjects:

This study was designed to ensure that the sponsor and investigators abided by Good Clinical Practice (GCP) as described in the 21 Code of Federal Regulations Parts 50, 54, 56, and 312 and the International Council for Harmonisation (ICH) GCP Guidelines Compliance. These regulations and guidelines also constitute compliance with the ethical principles described in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 2014
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	Germany: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	21
EEA total number of subjects	14

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	4

months)	
Children (2-11 years)	17
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:

A total of 24 subjects were screened, of them 21 subjects were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	No HGT-1410
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Arm description:

Subjects received no treatment (HGT-1410).

Arm type	No intervention
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No investigational medicinal product assigned in this arm

Arm title	HGT-1410 45 mg Q2W
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Arm description:

Subjects received HGT-1410 45 milligram (mg) intrathecally once every two weeks (Q2W) using surgically implanted intrathecal drug delivery device (IDDD) or lumbar puncture (LP) for 48 weeks.

Arm type	Experimental
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Investigational medicinal product name	Recombinant Human Heparan N-Sulfatase
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Investigational medicinal product code	HGT-1410
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Other name	
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Pharmaceutical forms	Injection
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Routes of administration	Intrathecal use
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Dosage and administration details:

Subjects received 45 mg HGT-1410 intrathecally.

Arm title	HGT-1410 45 mg Q4W
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Arm description:

Subjects received HGT-1410 45 mg intrathecally once every four weeks (Q4W) using surgically implanted IDDD or LP for 48 weeks.

Arm type	Experimental
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Investigational medicinal product name	Recombinant Human Heparan N-Sulfatase
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Investigational medicinal product code	HGT-1410
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Other name	
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Pharmaceutical forms	Injection
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Routes of administration	Intrathecal use
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Dosage and administration details:

Subjects received 45 mg HGT-1410 intrathecally.

Number of subjects in period 1	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W
Started	7	7	7
Completed	7	7	7

Baseline characteristics

Reporting groups

Reporting group title	No HGT-1410
Reporting group description: Subjects received no treatment (HGT-1410).	
Reporting group title	HGT-1410 45 mg Q2W
Reporting group description: Subjects received HGT-1410 45 milligram (mg) intrathecally once every two weeks (Q2W) using surgically implanted intrathecal drug delivery device (IDDD) or lumbar puncture (LP) for 48 weeks.	
Reporting group title	HGT-1410 45 mg Q4W
Reporting group description: Subjects received HGT-1410 45 mg intrathecally once every four weeks (Q4W) using surgically implanted IDDD or LP for 48 weeks.	

Reporting group values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W
Number of subjects	7	7	7
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: months			
arithmetic mean	32.42	29.64	33.53
standard deviation	± 9.548	± 9.989	± 9.336
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	3	5	4
Male	4	2	3

Reporting group values	Total		
Number of subjects	21		
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	12		
Male	9		

End points

End points reporting groups

Reporting group title	No HGT-1410
Reporting group description: Subjects received no treatment (HGT-1410).	
Reporting group title	HGT-1410 45 mg Q2W
Reporting group description: Subjects received HGT-1410 45 milligram (mg) intrathecally once every two weeks (Q2W) using surgically implanted intrathecal drug delivery device (IDDD) or lumbar puncture (LP) for 48 weeks.	
Reporting group title	HGT-1410 45 mg Q4W
Reporting group description: Subjects received HGT-1410 45 mg intrathecally once every four weeks (Q4W) using surgically implanted IDDD or LP for 48 weeks.	

Primary: Overall Assessment of Response Using Bayley Scales of Infant Development Assessment Third Edition (BSID-III)

End point title	Overall Assessment of Response Using Bayley Scales of Infant Development Assessment Third Edition (BSID-III)
End point description: The BSID-III is a series of measurements to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers and consists of a series of developmental play tasks. The DQ is a means to express a neurodevelopmental/cognitive delay which was computed as a ratio and expressed as a percentage using the age-equivalent score divided by the age at testing ($[\text{age-equivalent score}/\text{chronological age}] \times 100$; range: 0, 100). The BSID-III DQ score is based on the cognitive domain. A positive value indicates improvement in health and cognition. Overall response was the maximum decline in the development quotient (DQ) of 10 points or less over 48 weeks. Number of subjects with the overall response were reported here. Intent-to-treat population included all randomized participants was analysed for this end point.	
End point type	Primary
End point timeframe: Baseline (Week 0) up to Week 48	

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: subjects	0	2	1	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: 95% exact unconditional confidence interval of the difference in proportion between each of the treatment groups and the untreated control group was considered for the parameter estimation.	
Comparison groups	HGT-1410 45 mg Q2W v No HGT-1410

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4615
Method	Fisher exact
Parameter estimate	Difference between proportions
Point estimate	0.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.297
upper limit	0.745

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

95% exact unconditional confidence interval of the difference in proportion between each of the treatment groups and the untreated control group was considered for the parameter estimation.

Comparison groups	No HGT-1410 v HGT-1410 45 mg Q4W
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Difference between proportions
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.423
upper limit	0.647

Secondary: Number of Subjects With Serious Adverse Events (SAE)

End point title	Number of Subjects With Serious Adverse Events (SAE)
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End point description:

An adverse event (AE) was any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product related. This included an exacerbation of a pre-existing condition. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; lifethreatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all subjects who received a dose of HGT-1410 either using IDDD implantation or LP; underwent the IDDD surgical implant procedure without receiving a dose of HGT-1410; were randomly assigned to the untreated group and had any safety follow-up data was analysed for this end point.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) up to Week 52

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: subjects	3	5	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs)
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End point description:

An adverse event (AE) was any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product related. This included an exacerbation of a pre-existing condition. TEAEs were defined as AE occurring on or after the time of first IDDD implantation or LP procedure to the end of study (EOS) visit (+30 days). Safety population was analysed for this end point.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) up to Week 52

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: subjects	6	7	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Anti-recombinant Human Heparan-N-Sulfatase (rhHNS) Antibody in Serum at Week 48

End point title	Number of Subjects With Positive Anti-recombinant Human Heparan-N-Sulfatase (rhHNS) Antibody in Serum at Week 48
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End point description:

A subject was considered positive if they had at least 1 positive result during the study. Once a subject reported antibody positive, they were considered positive for the remainder of the study. Safety population was analysed for this end point.

End point type	Secondary
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End point timeframe:

Baseline (Week 0) up to Week 48

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: subjects	1	7	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vineland Adaptive Behavior Scales Second Edition (VABS-II) Development Quotient (DQ) Score at Week 48

End point title	Change From Baseline in Vineland Adaptive Behavior Scales Second Edition (VABS-II) Development Quotient (DQ) Score at Week 48
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End point description:

The VABS-II test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. The DQ is a means to express a neurodevelopmental/cognitive delay. The DQ was computed as a ratio and expressed as a percentage using the age-equivalent score divided by the age at testing ($[\text{age-equivalent score}/\text{chronological age}] \times 100$; range, 0, 100). The overall DQ score is calculated from the mean age-equivalent score obtained by averaging out the age-equivalent scores for the all the sub-domains except for Gross and Fine motor skills. This test measures the following 5 key domains: communication, daily living skills, socialization, motor skills, and the adaptive behavior composite (a composite of the other 4 domains). A positive value indicates improvement in health and cognition. Intent-to-treat population included randomized subjects were analysed for this end point.

End point type	Secondary
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End point timeframe:

Baseline (Week 0), Week 48

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: percentage of chronological age arithmetic mean (standard deviation)				
Communication Domain (n=7,6,7)	-5.12 (\pm 10.981)	-20.83 (\pm 23.475)	-4.97 (\pm 17.253)	
Daily Living Skills Domain (n=6,6,6)	-4.2 (\pm 29.005)	-27.09 (\pm 21.444)	-11.74 (\pm 26.713)	
Socialization Domain (n=6,6,6)	-16.12 (\pm 23.32)	-24.24 (\pm 40.617)	-29.34 (\pm 29.425)	
Motor Skills Domain (n=6,6,6)	-5.37 (\pm 24.741)	-27.01 (\pm 20.82)	-17.88 (\pm 12.007)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Development Quotient (DQ) Using Bayley Scales of Infant Development Assessment Third Edition (BSID-III) at Week 48

End point title	Change From Baseline in Development Quotient (DQ) Using Bayley Scales of Infant Development Assessment Third Edition (BSID-III) at Week 48
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End point description:

The BSID-III is a series of measurements to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers and consists of a series of developmental play tasks. The DQ is a means to express a neurodevelopmental/cognitive delay which was computed as a ratio and expressed as a percentage using the age-equivalent score divided by the age at testing ($[\text{age-equivalent score}/\text{chronological age}] \times 100$; range: 0, 100). The BSID-III DQ score is based on the cognitive domain. A positive value indicates improvement in health and cognition. Intent-to-treat population included randomized subjects were analysed for this end point.

End point type	Secondary
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End point timeframe:

Baseline (Week 0), Week 48

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: percentage of chronological age				
arithmetic mean (standard deviation)				
Cognitive	-19.81 (\pm 3.974)	-23.82 (\pm 14.684)	-19.87 (\pm 12.724)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Cortical Grey Matter Volume at Week 48

End point title	Change from Baseline in Total Cortical Grey Matter Volume at Week 48
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End point description:

The change from baseline in grey matter volume at Week 48 was assessed by magnetic resonance imaging (MRI). Intent-to-treat population included randomized subjects were analysed for this end point.

End point type	Secondary
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End point timeframe:

Baseline (Week 0), Week 48

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	7	
Units: cubic centimeter (cc)				
arithmetic mean (standard deviation)	-45.1 (\pm 23.35)	-102 (\pm 68.12)	-58.8 (\pm 66.24)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Concentration of Glycosaminoglycan (GAG) in Cerebrospinal Fluid (CSF) at Week 48

End point title	Change from Baseline in Concentration of Glycosaminoglycan (GAG) in Cerebrospinal Fluid (CSF) at Week 48
End point description:	Change from baseline in concentration of GAG in CSF at Week 48 was reported.
End point type	Secondary
End point timeframe:	Baseline (Week 0), Week 48

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	7	
Units: micromolar				
arithmetic mean (standard deviation)	-0.193 (\pm 1.318)	-6.888 (\pm 5.388)	-5.924 (\pm 2.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Concentration of GAG in Urine at Week 48

End point title	Change from Baseline in Concentration of GAG in Urine at Week 48
End point description:	The concentration of GAG in urine was normalized to the urine creatinine value and reported as milligram (mg) GAG per millimole (mmol) creatinine. ITT population was analysed for this end point.
End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 48

End point values	No HGT-1410	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	5	
Units: mg GAG/mmol creatinine				
arithmetic mean (standard deviation)	-7.18 (\pm 39.175)	-31.81 (\pm 22.887)	-42.46 (\pm 29.861)	

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Recombinant Human Heparan-N-Sulfatase (rhHNS) in Cerebrospinal Fluid (CSF)

End point title	Concentration of Recombinant Human Heparan-N-Sulfatase (rhHNS) in Cerebrospinal Fluid (CSF) ^[1]
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End point description:

Concentration of rhHNS in CSF was assessed using validated enzyme-linked immunosorbent assay (ELISA) method. Pharmacokinetic (PK) population included all subjects who received HGT-1410, participated in the scheduled PK studies, and had sufficient samples available for analysis.

End point type	Secondary
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End point timeframe:

Pre-dose, 4, 48 hours on Week 0 and Week 48

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Pharmacokinetic analysis was performed for the arms which received the drug only.

End point values	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: nanogram per milliliter (ng/ml)				
arithmetic mean (standard deviation)				
Week 0: Predose (n=7,7)	0 (\pm 0)	0 (\pm 0)		
Week 0: 4h (n=5,5)	313392.49 (\pm 142748.885)	266021.6 (\pm 113340.887)		
Week 0: 48h (n=6,6)	366.05 (\pm 571.528)	2119.59 (\pm 2068.093)		
Week 48: Predose (n=6,7)	869.67 (\pm 1863.989)	365.04 (\pm 965.797)		
Week 48: 4h (n=5,5)	374544.38 (\pm 135047.7)	335203.84 (\pm 82918.537)		
Week 48: 48h (n=4,5)	104.49 (\pm 65.881)	8892.93 (\pm 19519.717)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Drug Concentration (Cmax) of Recombinant Human Heparan-N-Sulfatase (rhHNS) in serum

End point title	Maximum Observed Drug Concentration (Cmax) of Recombinant Human Heparan-N-Sulfatase (rhHNS) in serum ^[2]
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End point description:

Cmax of rhHNS in serum was evaluated using enzyme-linked immunosorbent assay (ELISA) method and liquid chromatography tandem mass spectrometry (LC-MS) method. Pharmacokinetic (PK) population was analysed for this end point.

End point type	Secondary
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End point timeframe:

Predose, 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, and 48 h post-dose on Week 0 and Week 48

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Pharmacokinetic analysis was performed for the arms which received the drug only.

End point values	HGT-1410 45 mg Q2W	HGT-1410 45 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: ng/ml				
arithmetic mean (standard deviation)				
ELISA Method: Week 0 (n=7,7)	120.9 (± 84.77)	237 (± 159.68)		
ELISA Method: Week 48 (n=7,4)	63.5 (± 149.76)	118.8 (± 161.98)		
LC-MS Method: Week 0 (n=7,7)	102.4 (± 63)	191 (± 125.84)		
LC-MS Method: Week 48 (n=7,5)	188.1 (± 127.4)	119.7 (± 133.18)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to Week 52

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	No HGT-1410
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Reporting group description:

Subjects received no treatment (HGT-1410).

Reporting group title	HGT-1410 45 mg Q4W
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Reporting group description:

Subjects received HGT-1410 45 mg intrathecally Q4W using surgically implanted IDDD or LP for 48 weeks.

Reporting group title	HGT-1410 45 mg Q2W
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Reporting group description:

Subjects received HGT-1410 45 mg intrathecally Q2W using surgically implanted IDDD or LP for 48 weeks.

Serious adverse events	No HGT-1410	HGT-1410 45 mg Q4W	HGT-1410 45 mg Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	6 / 7 (85.71%)	5 / 7 (71.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Incision site swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Tooth injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrospinal fluid leakage			

subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Adverse drug reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device breakage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Device failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site extravasation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
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			

Haematemesis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Infections and infestations			
Central nervous system infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Gastrointestinal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Postoperative wound infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Wound infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	No HGT-1410	HGT-1410 45 mg Q4W	HGT-1410 45 mg Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	7 / 7 (100.00%)	7 / 7 (100.00%)
Vascular disorders			
Diastolic hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Diastolic hypotension			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Systolic hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Catheter site haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Developmental delay			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Implant site erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Implant site extravasation			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 7 (28.57%) 4	1 / 7 (14.29%) 1
Implant site swelling subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0
Local swelling subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Pyrexia subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 10	4 / 7 (57.14%) 5	4 / 7 (57.14%) 22
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0
Reproductive system and breast disorders Vulvovaginal erythema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Respiratory, thoracic and mediastinal disorders Bronchospasm subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 7 (0.00%) 0	1 / 7 (14.29%) 2
Cough subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Nasal congestion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Nasal obstruction subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Rhinitis allergic			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1
Sinus disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0
Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Irritability subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1
Sleep terror subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Investigations			
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 2	0 / 7 (0.00%) 0
Blood pressure decreased			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood pressure diastolic decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	5	0
Blood pressure diastolic increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Blood pressure increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Blood pressure systolic decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	10	0
Crystal urine present			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Body temperature decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Csf test abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Csf protein increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Haematocrit decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Csf white blood cell count increased			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	1 / 7 (14.29%)
occurrences (all)	0	3	2
Heart rate decreased			

subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Haemoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Heart rate increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	8	0
Oxygen saturation decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	2	5
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Protein total increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory rate decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Urine uric acid			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Airway complication of anaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Arthropod bite			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Craniocerebral injury			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 7 (42.86%)
occurrences (all)	1	1	3
Incision site complication			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Postoperative fever			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Procedural dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Procedural headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	3 / 7 (42.86%)
occurrences (all)	1	0	4
Procedural hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Subdural haematoma			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1
Stab wound subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0
Tooth injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Tooth fracture subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Wound complication subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0
Nervous system disorders Aphasia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Cerebrospinal fluid leakage subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1
Cerebral atrophy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0
Cognitive disorder			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Demyelination			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Drooling			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Motor dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Motion sickness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Otorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Constipation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Enteritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	4
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Salivary gland enlargement			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	5 / 7 (71.43%)
occurrences (all)	2	4	12
Salivary hypersecretion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dry skin			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Ecchymosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Mucocutaneous rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Pityriasis rosea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rickets			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Bronchitis			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Ear infection			
subjects affected / exposed	2 / 7 (28.57%)	4 / 7 (57.14%)	0 / 7 (0.00%)
occurrences (all)	3	6	0
Gastroenteritis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	2	3
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Hand-Foot-And-Mouth disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Implant site infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Meningitis aseptic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	6	4	0
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	3 / 7 (42.86%)
occurrences (all)	0	1	3
Otitis media acute			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	4	1	3
Rhinitis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	3 / 7 (42.86%)
occurrences (all)	3	2	4
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Scarlet fever			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Stitch abscess			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tonsillitis streptococcal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tonsillitis bacterial			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	5 / 7 (71.43%)
occurrences (all)	6	2	18
Viral infection			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	2
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Vitamin d deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2014	<ul style="list-style-type: none">- Permitted subjects in the United States (US) to receive Intrathecal (IT) treatment with HGT-1410 by LP prior to FDA authorization of use of the SOPH-A-PORT Mini S device.- Removed the Sanfilippo-specific Behavioral Rating Scales as an evaluative tool.- Removed collection of plasma samples for exploratory investigation of biomarkers.- Required vital sign measurements to be recorded for at least 4 hours following each dose of HGT-1410.- Prothrombin time and activated partial thromboplastin time were to be performed at screening only.- Removed requirement for predose CSF cell counts to be available before study drug administration.- Updated the definition of the safety population to include subjects in the US who were treated with HGT-1410 via LP until the IDDD is available.- Limited the number of pharmacokinetic samples taken to reduce overall blood volume requirements.- Added appendices detailing blood and CSF volumes taken from each subject at each time point and overall.
15 July 2014	<ul style="list-style-type: none">- Removed language to allow administration of study drug by LP in the US until the IDDD is authorized for use by the FDA.- Clarified criterion for demonstrating deficiency of sulfamidase.- Clarified that use of catheter passers other than Phoenix Neuro disposable catheter passer were allowed.- Clarified that heparan sulfate was to be measured in CSF as opposed to total GAGs.- Added language to indicate that CSF may be assessed for leachables or extractables.- Clarified that MRI was to be performed prior to the administration of HGT-1410.
08 September 2014	<ul style="list-style-type: none">- Removed the Week 24 MRI assessment and collection of CSF by LP.- Clarified that the follow-up safety visit only applied to those subjects not continuing into extension study SHP -610-201 (2014-003960-20).- Clarified that CSF sample collection for GAG would occur 4 hours (not 6 hours) after IT injection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported