Clinical trial results:
An Open-Label Extension of Study HGT-SAN-055 (NCT01155778) Evaluating Long Term Safety and Clinical Outcomes of Intrathecal Administration of rhHNS in Subjects with Sanfilippo Syndrome Type A (MPS IIIA)

Summary

EudraCT number	2010-021348-16
Trial protocol	GB NL
Global end of trial date	12 April 2019

Results information

Result version number	v2 (current)
This version publication date	14 June 2020
First version publication date	21 September 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	HGT-SAN-067

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01299727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, 1 866-8425335, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, 1 866-8425335, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	12 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2019
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 collect long-term safety and tolerability data in subjects with Sanfilippo Syndrome Type A (mucopolysaccharidosis [MPS] IIIA) who received HGT-1410 via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 (2009-015984-15) and elected to continue therapy in this study.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP) as described in the Code of United States Federal Regulations Title 21 Parts 50, 56, and 312; the International Council for Harmonisation (ICH) GCP guidelines; and the ethical principles described in the Declaration of Helsinki.

Background therapy:

All subjects who were enrolled in Study HGT-SAN-055 (2009-015984-15) through Week 26 and completed the end of study (EOS) evaluations were eligible for enrollment in this open-label extension study.

Evidence for comparator: -

Actual start date of recruitment	01 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	12
EEA total number of subjects	12

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	0

months)	
Children (2-11 years)	7
Adolescents (12-17 years)	3
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 study centers in the Netherlands and United Kingdom between 01 March 2011 (first subject first visit) and 12 April 2019 (last subject last visit).

Pre-assignment

Screening details:

A total of 12 subjects were enrolled in the extension study, with 4 subjects were included in each of the 3 dose groups. Out of them, 10 subjects completed the treatment period of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	HGT-1410/rhHNS 10 mg

Arm description:

Subjects received HGT-1410/Recombinant human heparan N-sulfatase (rhHNS) 10 milligram (mg) for every 4 weeks (Q4W) via an intrathecal drug delivery device (IDDD).

Arm type	Experimental
Investigational medicinal product name	Recombinant human heparan N-sulfatase (rhHNS)
Investigational medicinal product code	HGT-1410
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received HGT-1410/rhHNS via an intrathecal drug delivery device.

Arm title	HGT-1410/rhHNS 45 mg

Arm description:

Subjects received HGT-1410/rhHNS 45 mg for Q4W via IDDD.

Arm type	Experimental
Investigational medicinal product name	Recombinant human heparan N-sulfatase (rhHNS)
Investigational medicinal product code	HGT-1410
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received HGT-1410/rhHNS via an intrathecal drug delivery device.

Arm title	HGT-1410/rhHNS 90 mg

Arm description:

Subjects received HGT-1410/rhHNS 90 mg for Q4W via IDDD.

Arm type	Experimental
Investigational medicinal product name	Recombinant human heparan N-sulfatase (rhHNS)
Investigational medicinal product code	HGT-1410
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received HGT-1410/rhHNS via an intrathecal drug delivery device.

Number of subjects in period 1	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg
Started	4	4	4
Completed	0	0	0
Not completed	4	4	4
Consent withdrawn by subject	1	-	1
Subjects Who Completed the Treatment Period	3	4	3

Baseline characteristics

Reporting groups	
Reporting group title	HGT-1410/rhHNS 10 mg
Reporting group description:	
Subjects received HGT-1410/Recombinant human heparan N-sulfatase (rhHNS) 10 milligram (mg) for every 4 weeks (Q4W) via an intrathecal drug delivery device (IDDD).	
Reporting group title	HGT-1410/rhHNS 45 mg
Reporting group description:	
Subjects received HGT-1410/rhHNS 45 mg for Q4W via IDDD.	
Reporting group title	HGT-1410/rhHNS 90 mg
Reporting group description:	
Subjects received HGT-1410/rhHNS 90 mg for Q4W via IDDD.	

Reporting group values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg
Number of subjects	4	4	4
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.145	9.070	10.638
standard deviation	± 4.6956	± 9.7916	± 8.6645
Gender categorical Units:			
Male	3	2	3
Female	1	2	1
Race Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	4	3	3
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4	4	4

Reporting group values	Total		
Number of subjects	12		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units:			
Male	8		
Female	4		
Race Units: Subjects			
American Indian or Alaskan Native	0		
Asian	2		
Black or African American	0		
Native Hawaiian or other Pacific Islander	0		
White	10		
Other	0		
Ethnicity Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	12		

End points

End points reporting groups

Reporting group title	HGT-1410/rhHNS 10 mg
Reporting group description:	
Subjects received HGT-1410/Recombinant human heparan N-sulfatase (rhHNS) 10 milligram (mg) for every 4 weeks (Q4W) via an intrathecal drug delivery device (IDDD).	
Reporting group title	HGT-1410/rhHNS 45 mg
Reporting group description:	
Subjects received HGT-1410/rhHNS 45 mg for Q4W via IDDD.	
Reporting group title	HGT-1410/rhHNS 90 mg
Reporting group description:	
Subjects received HGT-1410/rhHNS 90 mg for Q4W via IDDD.	

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) And Treatment Emergent Serious Adverse Events (SAE)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) And Treatment Emergent Serious Adverse Events (SAE)[1]

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 study drug related. Treatment-emergent Adverse events (TEAEs) were defined as all adverse events (AEs) from the time of the surgery for first IDDD implantation or first dose of HGT-1410 in study HGT-SAN-055 (2009-015984-15) to the data cutoff date, or 30 days after the date of the last dose or 2 weeks after the date of device explant if early termination occurred. TEAEs included subjects with any AE, any drug-related AE, any surgery-related AE, any IDDD-related AE, and any IT administration process-related AE, any SAE, any serious drug-related AE. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067.

End point type	Primary

End point timeframe:

From start of study drug administration up to follow-up (Month 103)

Notes:

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

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: subjects				
Subjects with at least one TEAEs	4	4	4	
Subjects with at least one HGT-1410 related TEAEs	4	4	2	
Subjects with at least one surgery related TEAEs	4	4	3	
Subjects with at least one IDDD related TEAEs	4	4	4	
Subjects with at least IT related TEAEs	3	3	2	
Subjects with at least one serious TEAEs	4	4	3	

Subjects with at least drug related serious TEAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) Based on Severity

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) Based on Severity[2]

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 study drug related. Treatment-emergent Adverse events (TEAEs) were defined as all adverse events (AEs) from the time of the surgery for first IDDD implantation or first dose of HGT-1410 in study HGT-SAN-055 (2009-015984-15) to the data cutoff date, or 30 days after the date of the last dose or 2 weeks after the date of device explant if early termination occurred. Severity of an AE is determined by following definitions: Mild: No limitation of usual activities; Moderate: Some limitation of usual activities; Severe: Inability to carry out usual activities. Analysis was performed based on safety population.

End point type	Primary

End point timeframe:

From start of study drug administration up to follow-up (Month 103)

Notes:

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

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: subjects				
Subjects with Mild TEAEs	4	4	4	
Subjects with Moderate TEAEs	4	4	3	
Subjects with Severe TEAEs	1	2	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Laboratory Abnormalities Reported as TEAEs

End point title	Number of Subjects With Clinically Significant Laboratory Abnormalities Reported as TEAEs[3]

End point description:

Clinical laboratory assessments include hematology, serum chemistry including liver function tests, coagulation urinalysis and cerebrospinal fluid (CSF). The safety population consisted of all eligible

subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067.

End point type	Primary

End point timeframe:

From start of study drug administration up to follow-up (Month 103)

Notes:

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

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: subjects				
Hematology	3	0	1	
Serum Chemistry	1	4	1	
Urinalysis	0	1	1	
Cerebrospinal fluid (CSF)	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Change in Electrocardiogram (ECG) Reported as TEAEs

End point title	Number of Subjects With Clinically Significant Change in Electrocardiogram (ECG) Reported as TEAEs[4]

End point description:

Electrocardiogram (ECG) included an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and corrected QT intervals. Any change in ECG assessments which were deemed clinically significant findings and abnormalities were recorded as TEAEs. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067.

End point type	Primary

End point timeframe:

From start of study drug administration up to follow-up (Month 103)

Notes:

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

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Postive Anti-rhHNS Antibody Status in Serum by Recombinant Human Heparan N-Sulfatase (rhHNS)

End point title	Number of Subjects with Postive Anti-rhHNS Antibody Status in Serum by Recombinant Human Heparan N-Sulfatase (rhHNS)[5]

End point description:

Antibody status (i.e, positive or negative) was determined at each assessment time point. Antibody titers were determined for the samples that tested positive for anti-rhHNS antibodies. Subjects with positive Anti-rhHNS antibody status in serum were reported. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067.

End point type	Primary

End point timeframe:

Month 103

Notes:

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

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Positive Anti-rhHNS Antibody Status in Cerebrospinal Fluid (CSF) by Recombinant Human Heparan N-Sulfatase (rhHNS)

End point title	Number of Subjects with Positive Anti-rhHNS Antibody Status in Cerebrospinal Fluid (CSF) by Recombinant Human Heparan N-Sulfatase (rhHNS)[6]

End point description:

Antibody status (i.e, positive or negative) was determined at each assessment time point. Antibody titers were determined for the samples that tested positive for anti-rhHNS antibodies. Subjects with positive anti-rhHNS antibody in CSF were reported. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067.

End point type	Primary

End point timeframe:

Month 103

Notes:

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

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bayley Scales of Infant Development Third Edition (BSID III) at Month 103

End point title	Change From Baseline in Bayley Scales of Infant Development Third Edition (BSID III) at Month 103

End point description:

The BSID III was a standard series of measurements used primarily to assess the motor fine and gross, language (receptive and expressive), and cognitive development of infants and toddlers, aged 0-42 months.
This measure consisted of a series of developmental play tasks and took between 45 to 60 minutes to administer. Composite scores were derived for cognitive, language, and motor development and scaled to a metric, with a mean of 100, standard deviation of 15. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067. Here, n = subjects evaluable for specified category for each arm, respectively. Here, '99999' indicates that no data was analyzed for that category as there were no subjects at specified time points. Here, '88888' indicates that the standard deviation was not calculated as only one subject was evaluated.

End point type	Secondary

End point timeframe:

Baseline, Month 103

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cognitive: Baseline (n=1,3,2)	19.00 (± 88888)	23.33 (± 12.097)	21.50 (± 0.707)	
Cognitive: Change at Month 103 (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	3.0 (± 88888)	
Receptive: Baseline (n=1,3,2)	17.00 (± 88888)	24.00 (± 16.093)	17.50 (± 2.121)	
Receptive: Change at Month 103 (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	0.00 (± 88888)	
Expressive: Baseline (n=1,3,2)	22.00 (± 88888)	26.00 (± 13.528)	22.50 (± 0.707)	
Expressive: Change at Month 103 (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	0.00 (± 88888)	
Fine Motor: Baseline (n=1,3,2)	25.00 (± 88888)	27.67 (± 12.423)	23.50 (± 2.121)	

Fine Motor: Change at Month 103 (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	0.00 (± 88888)	
Gross Motor: Baseline (n=1,3,2)	21.00 (± 88888)	26.67 (± 13.868)	35.50 (± 9.192)	
Gross Motor: Change at Month 103 (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	-21.00 (± 88888)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bayley Scales of Infant Development Third Edition (BSID III)/Kaufman Assessment Battery for Children Second Edition (KABC II) Age-Equivalent Scores at Month 103

End point title	Change From Baseline in Bayley Scales of Infant Development Third Edition (BSID III)/Kaufman Assessment Battery for Children Second Edition (KABC II) Age-Equivalent Scores at Month 103

End point description:

BSID-III was used to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers. KABC-II was an individually administered measure of the processing and reasoning abilities of children and adolescents between the ages of 3 and 18 years and is an alternative to BSID-III. Raw scores of successfully completed items were converted to developmental age-equivalent scores as well as composite scores .The global scales on the KABC-II each have a mean or average score of 100 and a standard deviation of 15. Analysis was performed based on safety population. Here, n = subjects evaluable for specified category for each arm, respectively. Here, '99999' indicates that no data was analyzed for that category as there were no subjects at specified time points. Here, '88888' indicates that the standard deviation was not calculated as only one subject was evaluated.

End point type	Secondary

End point timeframe:

Baseline, Month 103

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2,4,4)	66.00 (± 66.468)	35.17 (± 21.678)	60.90 (± 60.210)	
Change at Month 103 (n=0,0,1)	99999 (± 99999)	99999 (± 99999)	3.00 (± 88888)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Developmental Quotient (DQ) Using Bayley

Scales of Infant Development Third Edition (BSID III) and Kaufman Assessment Battery for Children Second Edition (KABC II) at Month 103

End point title	Change From Baseline in Developmental Quotient (DQ) Using Bayley Scales of Infant Development Third Edition (BSID III) and Kaufman Assessment Battery for Children Second Edition (KABC II) at Month 103

End point description:

BSID-III was used to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers. This measure consists of a series of developmental play tasks. Raw scores of successfully completed items are converted to scale scores and to composite scores. Composite scores were derived for cognitive, language, and motor development and scaled to a metric, with a mean of 100, standard deviation of 15. Higher scores are indicative of decreased development. KABC-II was an individually administered measure of the processing and reasoning abilities of children and adolescents between the ages of 3 and 18 years and is an alternative to BSID-III. BSID-III DQ score was based on the Cognitive domain. Analysis was performed based on safety population. Here, n = subjects evaluable for specified category for each arm, respectively. Here, '99999' indicates that no data was analyzed for that category as there were no subjects at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Month 103

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 2,4,4)	51.91 (± 27.292)	43.24 (± 23.112)	51.87 (± 36.095)	
Change at Month 103 (n= 0,0,1)	99999 (± 99999)	99999 (± 99999)	-10.96 (± 88888)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vineland Adaptive Behavioral Scales Second Edition (VABS-II) at Month 103

End point title	Change From Baseline in Vineland Adaptive Behavioral Scales Second Edition (VABS-II) at Month 103

End point description:

VABS-II measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. It is an instrument that supports the diagnosis of intellectual and developmental disabilities in subjects. This test measures 5 key domains: communication, daily living skills, socialization, motor skills, and the adaptive behavior composite. The raw scores was converted to domain standard scores (mean 100, SD 15). Higher scores indicate undesirable behavior. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067. Here, n = subjects evaluable for specified category for each arm, respectively. Here, '99999' indicates that no data was analyzed for that category as there were no subjects at specified time points. Here, '88888' indicates that the standard deviation was not calculated as only one subject was evaluated.

End point type	Secondary

End point timeframe:

Baseline, Month 103

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: units on a scale				
arithmetic mean (standard deviation)				
Adaptive Behavior: Baseline (n= 4,4,4)	63.3 (± 14.61)	59.0 (± 26.96)	59.5 (± 29.77)	
Adaptive Behavior:Change at Month 103 (n= 1,0,1)	-18.0 (± 88888)	99999 (± 99999)	-20.0 (± 88888)	
Communication: Baseline (n= 4, 4, 4)	68.3 (± 19.03)	57.5 (± 25.94)	60.3 (± 30.86)	
Communication: Change at Month 103 (n= 1,0,1)	-27.0 (± 88888)	99999 (± 99999)	-20.0 (± 88888)	
Daily Living: Baseline (n= 4,4,4)	62.5 (± 15.52)	62.3 (± 27.58)	60.0 (± 30.00)	
Daily Living: Change at Month 103 (n= 1,0,1)	-19.0 (± 88888)	99999 (± 99999)	-34.0 (± 88888)	
Socialization: Baseline (n= 4,4,3)	64.3 (± 12.50)	65.5 (± 32.42)	58.7 (± 35.92)	
Socialization: Change at Month 103 (n= 1,0,0)	-15.0 (± 88888)	99999 (± 99999)	0 (± 88888)	
Motor Skills: Baseline (n= 3,3,2)	82.7 (± 29.77)	76.3 (± 5.69)	72.5 (± 12.02)	
Motor Skills: Change at Month 103 (n= 1,0,1)	-18.0 (± 88888)	99999 (± 99999)	-14.0 (± 88888)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cerebrospinal Fluid (CSF) Total Heparan Sulfate Levels at Month 103

End point title	Change From Baseline in Cerebrospinal Fluid (CSF) Total Heparan Sulfate Levels at Month 103

End point description:

Change from baseline in CSF total heparan sulfate at month 103 were recorded. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067. Here, n = subjects evaluable for specified category for each arm, respectively. Here, '99999' indicates that no data was analyzed for that category as there were no subjects at specified time points. Here, '88888' indicates that the standard deviation was not calculated as only one subject was evaluated.

End point type	Secondary

End point timeframe:

Baseline, Month 103

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: micrometer (µm)				
arithmetic mean (standard deviation)				
Baseline (n= 4,4,4)	5.775 (± 3.465)	4.710 (± 2.968)	3.795 (± 1.611)	
Change at Month 103 (n= 1,0,0)	-4.010 (± 88888)	99999 (± 99999)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urine Glycosaminoglycan (GAG) Levels at Month 103

End point title	Change From Baseline in Urine Glycosaminoglycan (GAG) Levels at Month 103

End point description:

Change from baseline in Urine GAG at month 103 were recorded. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067. Here, '99999' indicates that no data was analyzed for that outcome as the trial was prematurely terminated.

End point type	Secondary

End point timeframe:

Baseline, Month 103

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: microgram per milliliter (µg/mL)				
arithmetic mean (standard deviation)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brain Magnetic Resonance Imaging (MRI) at Month 103

End point title	Change From Baseline in Brain Magnetic Resonance Imaging (MRI) at Month 103

End point description:

Brain MRI was measured for grey matter volume (GMV), white matter volume (WMV) and Intracranial

cerebrospinal fluid Volume (ICSFV). Change from baseline in brain MRI at Month 103 were reported. The safety population consisted of all eligible subjects from Study HGT-SAN-055 (2009-015984-15) who agreed to subjects in the extension study, HGT-SAN-067. Here, n = subjects evaluable for specified category for each arm, respectively. Here, '99999' indicates that no data was analyzed for that category as there were no subjects at specified time points. Here, '88888' indicates that the standard deviation was not calculated as only one subject was evaluated.

End point type	Secondary

End point timeframe:

Baseline, Month 103

End point values	HGT-1410/rhHNS 10 mg	HGT-1410/rhHNS 45 mg	HGT-1410/rhHNS 90 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: milliliter (mL)				
arithmetic mean (standard deviation)				
GMV: Baseline (n= 4,4,4)	550.50 (± 111.043)	534.25 (± 117.291)	600.28 (± 67.884)	
GMV: Change at Month 103 (n= 1,0,0)	-99.49 (± 88888)	99999 (± 99999)	99999 (± 99999)	
WMV: Baseline (n= 4,4,4)	403.72 (± 105.575)	348.28 (± 76.854)	442.45 (± 79.814)	
WMV: Change at Month 103 (n= 1,0,0)	-33.19 (± 88888)	99999 (± 99999)	99999 (± 99999)	
ICSFV: Baseline (n= 4,4,4)	26.152 (± 9.2975)	22.904 (± 20.8459)	20.925 (± 15.9681)	
ICSFV: Change at Month 103 (n= 1,0,0)	18.753 (± 88888)	99999 (± 99999)	99999 (± 99999)	

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 follow-up (Month 103)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	HGT-1410/rhHNS-10 mg
Reporting group description:	
Subjects received HGT-1410/Recombinant human heparan N-sulfatase (rhHNS) 10 mg for every 4 weeks (Q4W) via an intrathecal drug delivery device (IDDD).	
Reporting group title	HGT-1410/rhHNS-45 mg
Reporting group description:	
Subjects received HGT-1410/rhHNS 45 mg for Q4W via IDDD.	
Reporting group title	HGT-1410/rhHNS-90 mg
Reporting group description:	
Subjects received HGT-1410/rhHNS 90 mg for Q4W via IDDD.	

Serious adverse events	HGT-1410/rhHNS-10 mg	HGT-1410/rhHNS-45 mg	HGT-1410/rhHNS-90 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	3 / 4 (75.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
CSF white blood cell count increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	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
Subdural haematoma			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (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
Wound dehiscence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	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
Surgical and medical procedures			
Medical device change			
subjects affected / exposed	3 / 4 (75.00%)	3 / 4 (75.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device removal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
Nervous system disorders			
Intracranial hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	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
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
General disorders and administration site conditions			
Device breakage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
Device component issue			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
Device failure			
subjects affected / exposed	2 / 4 (50.00%)	4 / 4 (100.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device leakage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
Device material issue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	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
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Auricular pseudocyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (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			
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (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
Infections and infestations			
Central nervous system infection			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device related infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
Implant site infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	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
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	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
Meningitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
Postoperative wound infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (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
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	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

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

Non-serious adverse events	HGT-1410/rhHNS-10 mg	HGT-1410/rhHNS-45 mg	HGT-1410/rhHNS-90 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pallor			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Infection prophylaxis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Medical device removal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	2
General disorders and administration site conditions			
Administration site pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Catheter site erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Catheter site haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Catheter site inflammation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	7	0	0
Catheter site pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Chills			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Complication of device insertion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Complication of device removal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Device breakage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Device failure			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Device leakage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	4	3	1
Feeling hot			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Implant site effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Implant site swelling			
subjects affected / exposed	2 / 4 (50.00%)	3 / 4 (75.00%)	2 / 4 (50.00%)
occurrences (all)	4	7	3
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Irritability			
subjects affected / exposed	3 / 4 (75.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	0	2
Local swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	17	2	7
Medical device complication			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	4 / 4 (100.00%)	3 / 4 (75.00%)	3 / 4 (75.00%)
occurrences (all)	18	31	5
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	5
Hypersensitivity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	2
Seasonal allergy			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Labia enlarged			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Penile adhesion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Penile erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Uterine haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	4 / 4 (100.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	6	2	2
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	10	1	7
Hyperventilation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Pharyngeal erythema			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	3 / 4 (75.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	6	5	3
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	0	0	3
Conversion disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Depressed mood			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Intentional self-injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Obsessive-compulsive disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	3	2	1
Sleep disorder			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	6	1	0
Stereotypy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Blood uric acid increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Body temperature increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	2	5	2
CSF protein increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
CSF white blood cell count increased			
subjects affected / exposed	2 / 4 (50.00%)	3 / 4 (75.00%)	0 / 4 (0.00%)
occurrences (all)	4	3	0
Haematocrit decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Lymphocyte count increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Mean cell haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Mean cell volume decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Monocyte count decreased			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Norovirus test positive			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Red blood cells CSF positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Serum ferritin decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Drug toxicity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Excoriation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fall			

subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	7	1	4
Feeding tube complication			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Head injury			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Nail injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Open wound			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Post procedural discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Procedural headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Procedural nausea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	3 / 4 (75.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	1
Procedural site reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Procedural vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Scratch			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin laceration			

subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
Thermal burn			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Thalassaemia trait			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Balance disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Bulbar palsy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cauda equina syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	7
Cognitive disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Crying			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Drooling			

subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Dyskinesia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Head titubation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	13	6	91
Hyperreflexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypertonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Intracranial hypotension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Memory impairment			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Motor dysfunction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nervous system disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	12	12	10
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Psychomotor hyperactivity			

subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Eosinophilia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear canal erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	3
Middle ear effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Otorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Tympanic membrane disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Tympanic membrane perforation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Eye disorders			
Lacrimation increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Myopia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Abnormal faeces			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	8	2	6
Defaecation urgency			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)	3 / 4 (75.00%)	1 / 4 (25.00%)
occurrences (all)	10	10	1
Dysphagia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Eructation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Faeces discoloured			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Mouth ulceration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	2	1	2
Regurgitation			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Retching			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	3 / 4 (75.00%)	3 / 4 (75.00%)	3 / 4 (75.00%)
occurrences (all)	16	23	3
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dermatitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dermatitis diaper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Eczema			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	3	1	2

Erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Hyperkeratosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Onycholysis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Pruritus generalised			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Rash macular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rosacea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Scar			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin chapped			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Incontinence			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Micturition urgency			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	5	4	14
Urinary incontinence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Acquired claw toe			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	2
Growing pains			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Joint swelling			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Mobility decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pain in extremity			

subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Scoliosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Synovial cyst			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Toe walking			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Trigger finger			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Weight bearing difficulty			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abscess oral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Candida nappy rash			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Catheter site infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	0	0
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Central nervous system infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Ear infection			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	1	3	12
Enterobiasis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Gastroenteritis			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Helminthic infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Influenza			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	2
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	2 / 4 (50.00%)	3 / 4 (75.00%)	2 / 4 (50.00%)
occurrences (all)	7	7	4
Onychomycosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Oral candidiasis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2

Otitis externa			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	4
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	0	2	3
Otitis media acute			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Pharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Post procedural infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	2	1	3
Proteus infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	4 / 4 (100.00%)	2 / 4 (50.00%)	3 / 4 (75.00%)
occurrences (all)	6	16	5
Staphylococcal infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Tinea pedis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Upper respiratory tract infection			
subjects affected / exposed	3 / 4 (75.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	3	2	1
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Varicella			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Viral rash			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Wound infection staphylococcal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Polydipsia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2011	The study duration was clarified to be 4 years.
13 January 2012	The protocol was revised to change the dose and regimen administered to subjects in Group 3, the dose was changed from 45 mg every 2 weeks to 90 mg Q4W. This change was made to ensure consistency with the revised HGT-SAN-055 study protocol and allowed subjects to continue to receive the same dose in this extension study as they did in the original study.
28 August 2012	The protocol HGT-SAN-067 was revised to update the study drug description to reflect a change in formulation. Other changes included: clarification of the timing of the neurological examination on days of study drug administration; clarification that full neurodevelopmental testing included VABS-II.
03 May 2013	The protocol was amended to include language to indicate that subjects in the lowest dose group (10 mg Q4W) were to have the dose increased to that of the mid-dose, i.e, 45 mg at the first visit following the full approval of this protocol. A decline in the primary pharmacodynamic parameter, CSF HS, was observed in data collected during the 6-month study, HGT-SAN-055. This response to therapy was exhibited at all dose levels; however, the greatest impact was at the 2 higher dose levels. An effect on CSF HS demonstrated in vivo activity of HGT-1410 in the target anatomical compartment and is thought to have central importance in mediating the potential therapeutic benefit of HGT-1410; The protocol was also amended to reduce the number of hours a subject was monitored at the site after administration of HGT-1410 from 8 hours to 4 hours. The monitoring time after each administration of HGT-1410 was reconsidered based on experience with IT administration of HGT-1410, a lack of injection associated safety issues occurring between 4 and 8 hours after administration.
17 January 2014	The protocol was amended to remove the requirement for subjects to have a WBC count greater than 100 cubic millimeters in CSF just prior to dosing. It was believed that sufficient experience with HGT-1410 existed so that it was safe to proceed with dosing without waiting for CSF clinical laboratory results. This also reduced the time that a needle was in the device port, thus reducing the risk of introducing infection.
10 July 2014	The protocol was amended to extend the study and provide treatment with HGT-1410 for an additional 24 months (to Month 79 from start of Study HGT-SAN-055); the frequency of hematology, serum chemistry, and urinalysis assessments and the frequency of ECGs were reduced to every 3 months and the frequency of urine and plasma HS and anti-rhHNS assessments was changed to every 6 months within this extended period.
08 February 2016	The main purpose of this amendment was to extend the study and provide treatment with HGT-1410 for an additional 24 months (to Month 103 from start of Study HGT-SAN-055), and the addition of local (satellite) sites to reduce the burden imposed by monthly travel.
01 February 2017	Subjects who did not have the IDDD removed at the end of the treatment period were to continue to be observed during a safety follow-up period with visits every 6 months to evaluate subject safety of the device up to an additional 3 years or until the device is removed in the last subject.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated as pre-specified efficacy criteria were not met. Data was not presented for efficacy parameters: ABR, Children’s Sleep Habits Rating Scale, Infant Toddler QoL Questionnaire, SBRS.

Notes: