Clinical trial results:
An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy Study of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Subjects with Mucopolysaccharidosis Type IIIA Disease

Summary

EudraCT number	2014-003960-20
Trial protocol	ES DE NL GB FR IT
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	SHP610-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02350816
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 8668425335, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, 1 8668425335, 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	28 June 2017
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 main objective of this study was to evaluate long-term safety in subjects with mucopolysaccharidosis type IIIA disease (MPS IIIA or Sanfilippo Type A) who received HGT-1410.

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:

Subjects who received HGT-1410 and completed through at least the Week 48 visit in Study HGT-SAN-093 (2013-003450-24) were eligible in this open label extension study.

Evidence for comparator: -

Actual start date of recruitment	08 April 2015
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?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Spain: 1
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: 6
Worldwide total number of subjects	17
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	3
Children (2-11 years)	14
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:

The first subject enrolled in the study on 08 April 2015 and study terminated on 28 June 2017.

Pre-assignment

Screening details:

A total of 17 subjects were enrolled and completed treatment period in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 milligrams (mg) administered intrathecally (IT) via IT drug delivery device (IDDD) every 2 weeks (Q2W) started at Week 50, with a cumulative treatment period of up to 42 months (168 weeks).

Arm type	Experimental
Investigational medicinal product name	HGT-1410
Investigational medicinal product code	HGT-1410
Other name	Recombinant Human Heparan N Sulfatase
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received HGT-1410 at a dose of 45 mg administered IT via IDDD.

Arm title	Group 2

Arm description:

Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 mg administered intrathecally IDDD every 4 weeks (Q4W) started at Week 52, with a cumulative treatment period of up to 42 months (168 weeks).

Arm type	Experimental
Investigational medicinal product name	HGT-1410
Investigational medicinal product code	HGT-1410
Other name	Recombinant Human Heparan N Sulfatase
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received HGT-1410 at a dose of 45 mg administered IT via IDDD.

Arm title	Group 3A

Arm description:

Subjects in Group 3A were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally IDDD Q2W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).

Arm type	Experimental

Investigational medicinal product name	HGT-1410
Investigational medicinal product code	HGT-1410
Other name	Recombinant Human Heparan N Sulfatase
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received HGT-1410 at a dose of 45 mg administered IT via IDDD.

Arm title	Group 3B

Arm description:

Subjects in Group 3B were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally via IDDD Q4W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).

Arm type	Experimental
Investigational medicinal product name	HGT-1410
Investigational medicinal product code	HGT-1410
Other name	Recombinant Human Heparan N Sulfatase
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received HGT-1410 at a dose of 45 mg administered IT via IDDD.

Number of subjects in period 1	Group 1	Group 2	Group 3A
Started	7	6	2
Completed	0	0	0
Not completed	7	6	2
Subjects Who Completed Treatment Period	7	6	2

Number of subjects in period 1	Group 3B
Started	2
Completed	0
Not completed	2
Subjects Who Completed Treatment Period	2

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 milligrams (mg) administered intrathecally (IT) via IT drug delivery device (IDDD) every 2 weeks (Q2W) started at Week 50, with a cumulative treatment period of up to 42 months (168 weeks).	
Reporting group title	Group 2
Reporting group description:	
Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 mg administered intrathecally IDDD every 4 weeks (Q4W) started at Week 52, with a cumulative treatment period of up to 42 months (168 weeks).	
Reporting group title	Group 3A
Reporting group description:	
Subjects in Group 3A were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally IDDD Q2W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).	
Reporting group title	Group 3B
Reporting group description:	
Subjects in Group 3B were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally via IDDD Q4W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).	

Reporting group values	Group 1	Group 2	Group 3A
Number of subjects	7	6	2
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	29.64	31.62	40.40
standard deviation	± 9.989	± 8.598	± 5.798
Gender categorical Units:			
Male	2	3	0
Female	5	3	2
Race (NIH/OMB) Units: Subjects			
White	7	6	2
Black or African American	0	0	0
Asian	0	0	0
American Indian or Native Alaskan	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	7	5	2

Not reported	0	0	0
Unknown	0	0	0

Reporting group values	Group 3B	Total	
Number of subjects	2	17	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.95		
standard deviation	± 7.142	-	
Gender categorical Units:			
Male	2	7	
Female	0	10	
Race (NIH/OMB) Units: Subjects			
White	2	17	
Black or African American	0	0	
Asian	0	0	
American Indian or Native Alaskan	0	0	
Native Hawaiian or other Pacific Islander	0	0	
Other	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	2	16	
Not reported	0	0	
Unknown	0	0	

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 milligrams (mg) administered intrathecally (IT) via IT drug delivery device (IDDD) every 2 weeks (Q2W) started at Week 50, with a cumulative treatment period of up to 42 months (168 weeks).

Reporting group title	Group 2

Reporting group description:

Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 mg administered intrathecally IDDD every 4 weeks (Q4W) started at Week 52, with a cumulative treatment period of up to 42 months (168 weeks).

Reporting group title	Group 3A

Reporting group description:

Subjects in Group 3A were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally IDDD Q2W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).

Reporting group title	Group 3B

Reporting group description:

Subjects in Group 3B were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally via IDDD Q4W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).

Primary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) Based on Type, Severity and Relationship to Treatment Drug

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) Based on Type, Severity and Relationship to Treatment Drug[1]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation subject administered as a pharmaceutical product that did not necessarily have a causal relationship with this treatment. TEAEs was defined as all AEs from the time of initial IDDD implantation (or first dose if earlier) in either Study NCT02060526 (HGT-SAN-093) or Study NCT02350816 (SHP-610-210) to the data cutoff date (28 Jun 2017), or 30 days after the date of the last dose or 2 weeks after the date of device explant (whichever was later) if early termination occurred. Treatment-emergent AEs were summarized by type (serious, life-threatening), severity (mild, moderate, severe) and degree of relationship to investigational product (Intrathecal Drug Delivery Device (IDDD), device surgical procedure, or intraThecal administration of HGT-1410). Safety population consisted of all subjects who had the IDDD implant or received at least 1 dose of investigational product in the extension study

End point type	Primary

End point timeframe:

From start of study drug administration up to follow-up (276 week)

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	Group 1	Group 2	Group 3A	Group 3B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	2	2
Units: Subjects				
Subjects with TEAEs	7	6	2	2
Subjects with Serious TEAEs	6	6	0	1
Subjects with Life-Threatening TEAEs	0	0	0	0
Subjects with Mild TEAEs	0	0	1	1
Subjects with Moderate TEAEs	4	4	1	1
Subjects with Severe TEAEs	3	2	0	0
Subjects with HGT-1410 Related TEAEs	5	5	1	1
Subjects with Surgery Related TEAEs	6	6	1	1
Subjects with IDDD Related TEAEs	5	6	0	1
Subjects with IT Administration Related TEAEs	3	6	0	1

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 (124 week).	
Adverse event reporting additional description:	
Event desc	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	nil
Dictionary version	17.1

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 milligrams (mg) administered intrathecally (IT) via IT drug delivery device (IDDD) every 2 weeks (Q2W) started at Week 50, with a cumulative treatment period of up to 42 months (168 weeks).	
Reporting group title	Group 2
Reporting group description:	
Subjects continued HGT-1410 treatment from HGT-SAN-093 (2013-003450-24) study at a dose of 45 mg administered intrathecally IDDD every 4 weeks (Q4W) started at Week 52, with a cumulative treatment period of up to 42 months (168 weeks).	
Reporting group title	Group 3A
Reporting group description:	
Subjects in Group 3A were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally IDDD Q2W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).	
Reporting group title	Group 3B
Reporting group description:	
Subjects in Group 3B were not treated in HGT-SAN-093 (2013-003450-24) study. Subjects received HGT-1410 treatment at a dose of 45mg administered intrathecally via IDDD Q4W started at Week 0 of the current extension study (SHP610-201=2014-003960-20), with a cumulative treatment period of up to 30 months (120 weeks).	

Serious adverse events	Group 1	Group 2	Group 3A
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	6 / 6 (100.00%)	0 / 2 (0.00%)
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 / 6 (16.67%)	0 / 2 (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	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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 dehiscence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (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
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	2 / 7 (28.57%)	4 / 6 (66.67%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (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			
Adverse drug reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	8 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device breakage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (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
Implant site extravasation			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Implant site pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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
Infections and infestations			
Central nervous system infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (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
Epstein-Barr virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (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 / 6 (16.67%)	0 / 2 (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	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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
Pharyngotonsillitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (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 / 6 (16.67%)	0 / 2 (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
Wound infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (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

Serious adverse events	Group 3B		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	1 / 2 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Incision site swelling			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth injury			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device breakage			

subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device failure				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Implant site extravasation				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Implant site pain				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Vomiting				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumonia aspiration				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillar hypertrophy				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Central nervous system infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epstein-Barr virus infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Implant site infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngotonsillitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group 1	Group 2	Group 3A
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 6 (100.00%)	2 / 2 (100.00%)
Vascular disorders			
Diastolic hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Diastolic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haematoma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Systolic hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Catheter site haemorrhage			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Device malfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Impaired healing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Implant site erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Implant site extravasation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	1 / 2 (50.00%)
occurrences (all)	1	5	1
Implant site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Implant site swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Local swelling			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Medical device pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	6 / 7 (85.71%)	3 / 6 (50.00%)	2 / 2 (100.00%)
occurrences (all)	30	6	12
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

Seasonal allergy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Vulvovaginal erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Bronchospasm			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Cough			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Nasal obstruction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Sinus disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			

Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Decreased interest			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Irritability			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Sleep terror			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Blood folate decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Blood pressure diastolic decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Blood pressure diastolic increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Blood pressure increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood pressure systolic decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	10	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Body temperature decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Body temperature increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
CSF protein increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
CSF test abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
CSF white blood cell count increased			
subjects affected / exposed	1 / 7 (14.29%)	3 / 6 (50.00%)	0 / 2 (0.00%)
occurrences (all)	3	4	0
Crystal urine present			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haematocrit decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Heart rate decreased			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Heart rate increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	7	0
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oxygen saturation decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	4	2	0
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Protein total increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory rate decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Urine uric acid			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vitamin D decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
White blood cell count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural			

complications			
Airway complication of anaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Contusion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 2 (50.00%)
occurrences (all)	1	1	1
Craniocerebral injury			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Face injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	4 / 7 (57.14%)	1 / 6 (16.67%)	1 / 2 (50.00%)
occurrences (all)	4	1	1
Head injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Incision site complication			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Incision site haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Postoperative fever			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Procedural dizziness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Procedural headache			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	5 / 7 (71.43%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	6	0	0
Skin abrasion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Subdural haematoma			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Tooth fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Tooth injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Wound complication			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Cerebral atrophy			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Demyelination			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Motor dysfunction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Psychomotor hyperactivity			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	3	0	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Motion sickness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Otorrhoea			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	1 / 2 (50.00%)
occurrences (all)	6	1	1
Dysphagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Enteritis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	4	0	0
Haematochezia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Salivary gland enlargement			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Salivary hypersecretion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Umbilical hernia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	5 / 7 (71.43%)	3 / 6 (50.00%)	0 / 2 (0.00%)
occurrences (all)	14	4	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Ecchymosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Mucocutaneous rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Photosensitivity reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Pityriasis rosea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Infections and infestations			

Acute tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Bronchopneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Ear infection			
subjects affected / exposed	0 / 7 (0.00%)	4 / 6 (66.67%)	1 / 2 (50.00%)
occurrences (all)	0	6	1
Folliculitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	6	2	0
Gastroenteritis viral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Gastrointestinal infection			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Implant site infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

Labyrinthitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Oral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	4 / 7 (57.14%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	4	1	0
Otitis media acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 2 (50.00%)
occurrences (all)	4	1	1
Respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	5 / 7 (71.43%)	1 / 6 (16.67%)	1 / 2 (50.00%)
occurrences (all)	11	2	1
Scarlet fever			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Stitch abscess			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Tinea pedis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Tonsillitis streptococcal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 7 (85.71%)	2 / 6 (33.33%)	1 / 2 (50.00%)
occurrences (all)	28	5	2
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Varicella			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Wound infection staphylococcal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Group 3B		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Vascular disorders			
Diastolic hypertension			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Diastolic hypotension			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Systolic hypertension			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Catheter site haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Device malfunction			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Impaired healing			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Implant site erythema			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Implant site extravasation			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Implant site pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Implant site swelling			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Local swelling			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Medical device pain			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	5		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			

Vulvovaginal erythema			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Bronchospasm			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Nasal obstruction			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Sinus disorder			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Decreased interest			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Sleep terror			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Blood folate decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Blood pressure diastolic decreased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood pressure diastolic increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	4		
Blood pressure increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood pressure systolic decreased			

subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	3			
Blood pressure systolic increased				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	4			
Body temperature decreased				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Body temperature increased				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
C-reactive protein increased				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
CSF protein increased				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
CSF test abnormal				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
CSF white blood cell count increased				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Crystal urine present				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Haematocrit decreased				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Haemoglobin decreased				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Heart rate decreased				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	1			
Heart rate increased				

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	6		
Neutrophil count increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Protein total increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Red blood cell count decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Respiratory rate decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Urine uric acid			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Vitamin D decreased			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
White blood cells urine positive			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Airway complication of anaesthesia			

subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Arthropod bite				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Contusion				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	2			
Craniocerebral injury				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Face injury				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Fall				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	2			
Head injury				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Incision site complication				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Incision site haemorrhage				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	1			
Postoperative fever				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Procedural dizziness				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Procedural headache				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Procedural pain				

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Subdural haematoma			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Tooth fracture			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Tooth injury			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Wound complication			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Left ventricular hypertrophy			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Cerebral atrophy			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Cerebrospinal fluid leakage			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Demyelination subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Lethargy subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Motor dysfunction subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Leukopenia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Ear and labyrinth disorders			
Motion sickness subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Otorrhoea subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Enteritis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Salivary gland enlargement			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Salivary hypersecretion			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Umbilical hernia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Dermatitis diaper			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Ecchymosis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Mucocutaneous rash			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Photosensitivity reaction			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Pityriasis rosea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		

Bronchopneumonia				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	1			
Cellulitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Conjunctivitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Ear infection				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	1			
Folliculitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	1			
Gastroenteritis viral				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Gastrointestinal infection				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Hand-foot-and-mouth disease				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Implant site infection				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Labyrinthitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			

Nasopharyngitis				
subjects affected / exposed	1 / 2 (50.00%)			
occurrences (all)	1			
Oral candidiasis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Oral infection				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Otitis media acute				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Scarlet fever				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Stitch abscess				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			
Tinea pedis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences (all)	0			

Tonsillitis streptococcal			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Varicella			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Wound infection staphylococcal			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Iron deficiency			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2015	Exclusion criteria on hypersensitivity were revised. Interim analysis were clarified device adjustment language was added to capture the full scope of device manipulations that could have occurred throughout the study.
25 January 2017	The subjects who did not have the IDDD removed at the end of the treatment period continued to be observed during a safety follow-up period with visits every 6 months to evaluate safety of the device for up to an additional 3 years or until the device was 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 prespecified efficacy criteria were not met and study did not yield clinical proof-of-concept, prompting a decision to discontinue further clinical development of HGT-1410. Hence efficacy parameters were not evaluated.

Notes: