Clinical trial results:
A Phase I/II Multicenter Open-label Dose Escalation Study of HGT-1110 Administered Intrathecally in Children With Metachromatic Leukodystrophy

Summary

EudraCT number	2011-002044-28
Trial protocol	DE DK
Global end of trial date	20 January 2017

Results information

Result version number	v1 (current)
This version publication date	12 August 2017
First version publication date	12 August 2017

Trial information

Trial identification

Sponsor protocol code	HGT-MLD-070

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01510028
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to determine the safety of ascending doses of SHP611 administered by intrathecal (IT) injection for 38 weeks in children with metachromatic leukodystrophy (MLD) in cohorts 1 to 3 and to determine the safety of SHP611 produced with a revised drug substance manufacturing process administered by IT injection for 38 weeks in cohort 4.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH) of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	24
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	9
Children (2-11 years)	15

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 study was conducted at 5 main sites for cohorts 1 to 3 in Brazil, Denmark, Germany, France, and Australia and 3 main sites for cohort 4 in Denmark, France, and Germany between 02 February 2012 (first subject first visit) and 20 January 2017 (last subject last visit).

Pre-assignment

Screening details:

A total of 34 subjects were screened and 24 subjects were enrolled in the study. Out of which 23 subjects completed 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	SHP611 10 mg (Process A)

Arm description:

Subjects received 10 milligram (mg) dose of SHP611 (HGT-1110, recombinant human arylsulfatase A [rhASA]) every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.

Arm type	Experimental
Investigational medicinal product name	Recombinant human arylsulfatase A (rhASA)
Investigational medicinal product code	SHP611
Other name	HGT-1110
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received SHP611 injection every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks.

Arm title	SHP611 30 mg (Process A)

Arm description:

Subjects received 30 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.

Arm type	Experimental
Investigational medicinal product name	Recombinant human arylsulfatase A (rhASA)
Investigational medicinal product code	SHP611
Other name	HGT-1110
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received SHP611 injection every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks.

Arm title	SHP611 100 mg (Process A)

Arm description:

Subjects received 100 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.

Arm type	Experimental
Investigational medicinal product name	Recombinant human arylsulfatase A (rhASA)
Investigational medicinal product code	SHP611
Other name	HGT-1110
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received SHP611 injection every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks.

Arm title	SHP611 100 mg (Process B)

Arm description:

Subjects received 100 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the revised drug substance manufacturing process referred to as Process B.

Arm type	Experimental
Investigational medicinal product name	Recombinant human arylsulfatase A (rhASA)
Investigational medicinal product code	SHP611
Other name	HGT-1110
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subjects received SHP611 injection every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks.

Number of subjects in period 1	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)
Started	6	6	6
Completed	5	6	6
Not completed	1	0	0
Lack of efficacy	1	-	-

Number of subjects in period 1	SHP611 100 mg (Process B)
Started	6
Completed	6
Not completed	0
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	SHP611 10 mg (Process A)
Reporting group description:	
Subjects received 10 milligram (mg) dose of SHP611 (HGT-1110, recombinant human arylsulfatase A [rhASA]) every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 30 mg (Process A)
Reporting group description:	
Subjects received 30 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 100 mg (Process A)
Reporting group description:	
Subjects received 100 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 100 mg (Process B)
Reporting group description:	
Subjects received 100 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the revised drug substance manufacturing process referred to as Process B.	

Reporting group values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)
Number of subjects	6	6	6
Age categorical			
Units: Subjects			
Age continuous			
Units: months			
arithmetic mean	31.5	47.3	52.2
standard deviation	± 11.5	± 20.23	± 31.17
Gender categorical			
Units: Subjects			
Female	3	3	1
Male	3	3	5

Reporting group values	SHP611 100 mg (Process B)	Total	
Number of subjects	6	24	
Age categorical			
Units: Subjects			
Age continuous			
Units: months			
arithmetic mean	48.5		
standard deviation	± 24.22	-	

Gender categorical Units: Subjects			
Female	2	9	
Male	4	15	

End points

End points reporting groups

Reporting group title	SHP611 10 mg (Process A)
Reporting group description:	
Subjects received 10 milligram (mg) dose of SHP611 (HGT-1110, recombinant human arylsulfatase A [rhASA]) every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 30 mg (Process A)
Reporting group description:	
Subjects received 30 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 100 mg (Process A)
Reporting group description:	
Subjects received 100 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 100 mg (Process B)
Reporting group description:	
Subjects received 100 mg dose of SHP611 (HGT-1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the revised drug substance manufacturing process referred to as Process B.	

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) by Type and Severity

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) by Type and Severity[1]
End point description:	
An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAEs were defined as all AEs that occurred at or after the first dose of the investigational product or device implant surgery (whichever occurred earlier) and through the last follow-up date. Drug-related and device-related types of TEAEs were analyzed and reported. The severity of AEs was assessed by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 grading scale. Severity of all AEs or SAEs was recorded as grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or fatal. Here SDI refers to surgical device implantation. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.	
End point type	Primary
End point timeframe:	
From start of study treatment up to Week 42	

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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
TEAE	6	6	6	6
SHP611-related TEAE	3	4	4	2

SDI-related TEAE	5	3	4	4
IDDD-related TEAE	3	3	4	0
SOPH-A-PORT IDDD-related TEAE	0	0	4	0
IT administration process related TEAE	4	3	1	1
Severe TEAE	2	3	1	1
Serious TEAE	5	4	3	2

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinical Laboratory Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Clinical Laboratory Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)[2]

End point description:

Clinical laboratory test included serum chemistry, hematology and urinalysis. Clinical laboratory abnormalities were recorded and reported as TEAE. An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAEs were defined as all AEs that occurred at or after the first dose of the investigational product or device implant surgery (whichever occurred earlier) and through the last follow-up date. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Primary

End point timeframe:

From start of study treatment up to Week 40

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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Gamma-glutamyltransferase (GGT) increased	2	1	1	0
Alanine aminotransferase (ALT) increased	1	1	0	1
Aspartate aminotransferase (AST) increased	0	1	1	0
Blood iron decreased	0	1	1	0
Amylase increased	0	1	1	0
Blood alkaline phosphatase increased	1	0	0	0
Blood creatine phosphokinase increased	0	0	0	3
Hepatic enzymes increased	0	0	0	1
Eosinophil count increased	0	1	1	0
Eosinophilia	0	2	0	0
Mean cell volume decreased	0	1	0	0
Neutrophil count increased	0	1	0	0
White blood cell count increased	0	1	0	0
Lymphopenia	0	1	0	0
Leukocytosis	0	1	0	0

Proteinuria	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Vital Sign Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Vital Sign Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)[3]

End point description:

Vital sign assessments included blood pressure, heart rate, respiratory rate and body temperature. Vital sign abnormalities were recorded and reported as TEAE. An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAEs were defined as all AEs that occurred at or after the first dose of the investigational product or device implant surgery (whichever occurred earlier) and through the last follow-up date. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Primary

End point timeframe:

From start of study treatment up to Week 40

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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Pyrexia	5	3	5	5

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Electrocardiogram (ECG) Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Electrocardiogram (ECG) Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)[4]

End point description:

12-lead ECG was recorded and measured with the subject in rested supine position for at least 10 minutes. ECG abnormalities were recorded and reported as TEAE. An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAEs were defined as all AEs that occurred at or after the first dose of the investigational product or device implant surgery (whichever occurred earlier) and through the last follow-up date. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Primary

End point timeframe:

From start of study treatment up to Week 40

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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Abnormalities in Physical Examination Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Clinically Significant Abnormalities in Physical Examination Reported as Treatment Emergent Adverse Events (TEAEs)[5]

End point description:

Complete physical examination included evaluation of the port and catheter track. Height or length and weight were recorded and used to calculate growth. Body weight and height measurements were used to calculate the body mass index (BMI). Head circumference was measured in uniform manner for all subjects. Clinical significance was defined as any variation in physical findings that had medical relevance resulting in an alteration in medical care. Physical examination abnormalities were recorded and reported as TEAE. An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAEs were defined as all AEs that occurred at or after the first dose of the investigational product or device implant surgery (whichever occurred earlier) and through the last follow-up date. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Primary

End point timeframe:

From Start of Study Treatment up to Week 40

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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Cerebrospinal Fluid (CSF) Chemistry Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Cerebrospinal Fluid (CSF) Chemistry Abnormalities Reported as Treatment Emergent Adverse Events (TEAEs)[6]

End point description:

CSF chemistry assessments (including cell counts, glucose and protein) was measured. CSF chemistry abnormalities were recorded and reported as TEAE. An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAEs were defined as all AEs that occurred at or after the first dose of the investigational product or device implant surgery (whichever occurred earlier) and through the last follow-up date. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Primary

End point timeframe:

From start of study treatment up to Week 40

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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
CSF Protein Increased	0	0	1	1
CSF Albumin Increased	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Positive Anti-SHP611 Antibodies in Cerebrospinal Fluid (CSF) and or Serum

End point title	Number of Subjects With Positive Anti-SHP611 Antibodies in Cerebrospinal Fluid (CSF) and or Serum[7]

End point description:

Number of subjects with positive anti-SHP611 antibody results in serum and in CSF were reported. A subject was considered positive if they had at least 1 positive result during the study. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Primary

End point timeframe:

Baseline up to Week 40

Notes:

[7] - 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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Serum anti-SHP611 antibody (Ab) positive	4	3	1	2
Serum neutralizing anti-SHP611 antibody positive	3	2	1	1
CSF anti-SHP611 antibody positive	3	1	0	2
CSF neutralizing anti-SHP611 antibody positive	0	0	0	0
Serum or CSF anti-SHP611 antibody positive	4	3	1	2
Serum and CSF anti-SHP611 antibody positive	3	1	0	2
Serum or CSF neutralizing anti-SHP611 Ab positive	3	2	1	1
Serum and CSF neutralizing anti-SHP611 Ab positive	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Motor Function Using Gross Motor Function Measure 88 (GMFM-88) Total Score at Week 40

End point title	Change From Baseline in Motor Function Using Gross Motor Function Measure 88 (GMFM-88) Total Score at Week 40

End point description:

The GMFM-88 was used to measure motor function. The GMFM-88 item scores were used to calculate domain-specific percent score for each of the 5 GMFM-88 dimensions (lying and rolling; sitting; crawling and kneeling; standing; walking, running, and jumping), and a total GMFM-88 (percent) score was calculated based on each dimension score. Each of the 88 items was rated on a 4-point scale: 0=does not initiate; 1=initiates; 2=partially completes; and 3=completes. The GMFM-88 total scores ranged from 0% (no mobility) to a score of 100%, that is (i.e,) the score that can be obtained by an average 5-year-old or older child with normal motor abilities. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Secondary

End point timeframe:

Baseline, Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Score on a scale				
least squares mean (standard error)	-31.9 (± 8.76)	-29 (± 8.58)	-19.5 (± 8.54)	-18.1 (± 9.14)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing (FEES) for Texture Utilized at Week 40

End point title	Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing (FEES) for Texture Utilized at Week 40

End point description:

The FEES assessment was performed to evaluate the structure and function of the upper throat during swallowing and for an assessment of aspiration risk. Each subject had this assessment performed at the clinical site using transnasal flexible laryngoscopy. FEES for texture utilized was evaluated. Data was presented only for the shifts observed. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Secondary

End point timeframe:

Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Thin Liquids to Thin Liquids	2	2	2	4
Thin Liquids to Thickened Liquids	1	2	0	0
Thin Liquids to Puree Texture	1	2	1	4
Thin Liquids to Solids	0	2	0	0
Thickened Liquids to Thin Liquids	1	2	1	1
Thickened Liquids to Thickened Liquids	0	2	3	0
Thickened Liquids to Puree Texture	1	2	3	1
Thickened Liquids to Solids	0	2	0	0
Puree Texture to Thin Liquids	1	2	3	2
Puree Texture to Thickened Liquids	1	2	2	0
Puree Texture to Puree Texture	3	4	4	3
Puree Texture to Solids	0	2	0	0
Solids to Thin Liquids	0	2	0	1
Solids to Thickened Liquids	0	2	0	0
Solids to Puree Texture	0	2	0	1
Solids to Solids	0	2	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Feeding Assessment (Laryngeal Penetration) at Week 40

End point title	Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Feeding Assessment (Laryngeal

	Penetration) at Week 40

End point description:

The FEES assessment was performed to evaluate the structure and function of the upper throat during swallowing and for an assessment of aspiration risk. Each subject had this assessment performed at the clinical site using transnasal flexible laryngoscopy. Feeding assessment for laryngeal penetration was assessed. Data was presented only for the shifts observed. Here TL refers to thin liquids, THL refers to thickened liquids, PT refers to puree texture, WCC refers to with cough and clearance and WCNC refers to with cough and no clearance. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery. '99999' indicates data was not available for this texture as the assessment was considered normal.

End point type	Secondary

End point timeframe:

Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Normal to Normal (TL)	0	0	2	1
Normal to Without Cough (TL)	0	0	0	1
Without Cough to Without Cough (TL)	1	0	0	0
WCC to Without Cough (TL)	1	0	0	0
WCC to WCC (TL)	0	2	0	1
Normal to WCC (THL)	0	0	1	0
Without Cough to Normal (THL)	0	0	1	0
WCC to Normal (THL)	0	0	1	0
WCC to WCC (THL)	0	2	0	0
Normal to Normal (PT)	0	1	1	1
Normal to WCC (PT)	0	0	1	0
Normal to WCNC (PT)	1	0	0	0
Without Cough to Normal (PT)	0	0	2	0
Without Cough to WCC (PT)	1	0	0	0
WCC to Normal (PT)	0	0	0	1
WCC to WCC (PT)	0	2	0	0
WCNC to Normal (PT)	0	1	0	0
WCNC to Without Cough (PT)	1	0	0	0
WCC to WCC (Solids)	99999	2	99999	99999

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Feeding Assessment (Aspiration Through Vocal Cords) at Week 40

End point title	Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Feeding Assessment (Aspiration Through Vocal Cords) at Week 40

End point description:

The FEES assessment was performed to evaluate the structure and function of the upper throat during swallowing and for an assessment of aspiration risk. Each subject had this assessment performed at the clinical site using transnasal flexible laryngoscopy. Feeding assessment for aspiration through vocal cords were assessed. Data was presented only for the shifts observed. Here TL refers to thin liquids, THL refers to thickened liquids, PT refers to puree texture, WCC refers to with cough and clearance and WCNC refers to with cough and no clearance. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery. '99999' indicates data was not available for this texture as the assessment was considered normal.

End point type	Secondary

End point timeframe:

Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Normal to Normal (TL)	0	0	2	3
Without Cough to Without Cough (TL)	1	0	0	0
WCC to WCC (TL)	0	2	0	0
Normal to Normal (THL)	0	0	1	0
Without Cough to Normal (THL)	0	0	1	0
WCC to Normal (THL)	0	0	1	0
WCC to WCC (THL)	0	2	0	0
Normal to Normal (PT)	0	2	2	2
Without Cough to Normal (PT)	0	0	2	0
WCC to WCC (PT)	0	2	0	0
WCNC to Normal (PT)	1	0	0	0
WCC to WCC (Solids)	99999	2	99999	99999

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Dose Residue Clear After Subsequent Swallowing at Week 40

End point title	Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Dose Residue Clear After Subsequent Swallowing at Week 40

End point description:

The FEES assessment was performed to evaluate the structure and function of the upper throat during swallowing and for an assessment of aspiration risk. Each subject had this assessment performed at the clinical site using transnasal flexible laryngoscopy. FEES for dose residue clear after subsequent swallowing was assessed. Here TL refers to thin liquids, THL refers to thickened liquids, PT refers to puree texture. Data was presented only for the shifts observed. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery. '99999' indicates data was not available for this texture as the assessment was considered normal.

End point type	Secondary

End point timeframe:

Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Normal to Normal (TL)	0	0	1	0
Normal to Yes (TL)	0	0	1	0
Yes to Yes (TL)	1	2	0	1
Yes to No (TL)	0	0	0	1
No to Yes (TL)	0	0	0	1
No to No (TL)	1	0	0	0
Normal to Yes (THL)	0	0	2	0
Yes to Normal (THL)	0	0	1	0
Yes to Yes (THL)	0	2	0	0
Normal to Normal (PT)	0	1	0	1
Normal to Yes (PT)	0	0	2	0
Normal to No (PT)	1	0	0	0
Yes to Normal (PT)	0	0	1	0
Yes to Yes (PT)	1	2	0	1
Yes to No (PT)	1	0	0	0
No to Normal (PT)	0	1	1	0
Yes to Yes (Solids)	99999	2	99999	99999

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Aspiration Risk at Week 40

End point title	Number of Subjects With Shift in Functional Endoscopic Evaluation of Swallowing for Aspiration Risk at Week 40

End point description:

The FEES assessment was performed to evaluate the structure and function of the upper throat during swallowing and for an assessment of aspiration risk. Each subject had this assessment performed at the clinical site using transnasal flexible laryngoscopy. FEES for aspiration risk was assessed. Data was presented only for the shifts observed. Here TL refers to thin liquids, THL refers to thickened liquids, PT refers to puree texture, WCC refers to with cough and clearance and WCNC refers to with cough and no clearance. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery. '99999' indicates data was not available for this texture as the assessment was considered normal.

End point type	Secondary

End point timeframe:

Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Low to Low (TL)	2	2	2	3
Low to high (TL)	0	0	0	1
Low to Low (THL)	0	2	3	0
Low to Low (PT)	1	3	3	3
Low to high (PT)	1	0	0	0
Moderate to Low (PT)	0	1	1	0
Moderate to Moderate (PT)	1	0	0	0
Low to Low (Solids)	99999	2	99999	99999

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Nerve Conduction as Measured by Electroneurography (ENG) Assessments by Categorized Amplitude Values at Week 40

End point title	Number of Subjects With Change in Nerve Conduction as Measured by Electroneurography (ENG) Assessments by Categorized Amplitude Values at Week 40

End point description:

Evaluation of peripheral nerve function by ENG studies was performed to measure nerve conduction velocity (NCV), amplitude (AMP),distal latency (DL), and F-wave latency. Categorized amplitude values were assessed. Data was presented only for the number of subjects who reported change in amplitude greater than (>) 0. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Secondary

End point timeframe:

Baseline, Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
Median Motor Wrist Amplitude (Baseline)	6	5	5	6
Median Motor Wrist Amplitude (Week 40)	3	5	6	5
Median Motor Elbow Amplitude (Baseline)	0	2	4	6
Median Motor Elbow Amplitude (Week 40)	0	4	6	4
Median Sensory Wrist Amplitude (Baseline)	2	3	4	4
Median Sensory Wrist Amplitude (Week 40)	1	5	3	3

Peroneal Motor Fibular Head Amplitude (Baseline)	0	2	4	6
Peroneal Motor Fibular Head Amplitude (Week 40)	0	4	5	4
Peroneal Motor Ankle Amplitude (Baseline)	6	5	5	6
Peroneal Motor Ankle Amplitude (Week 40)	4	5	5	4
Sural Sensory B-point (Baseline)	2	2	3	4
Sural Sensory B-point (Week 40)	2	2	3	4
Tibial Motor Ankle Amplitude (Baseline)	4	3	3	3
Tibial Motor Ankle Amplitude (Week 40)	2	3	4	1
Tibial Motor Knee Amplitude (Baseline)	0	0	3	3
Tibial Motor Knee Amplitude (Week 40)	0	2	4	1
Ulnar Motor Wrist Amplitude (Baseline)	4	3	3	3
Ulnar Motor Wrist Amplitude (Week 40)	2	3	3	1
Ulnar Motor Elbow Amplitude (Baseline)	0	0	3	3
Ulnar Motor Elbow Amplitude (Week 40)	0	2	3	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Nerve Conduction as Measured by Electroneurography (ENG) Assessments by Categorized Nerve Conduction Velocity at Week 40

End point title	Number of Subjects With Change in Nerve Conduction as Measured by Electroneurography (ENG) Assessments by Categorized Nerve Conduction Velocity at Week 40

End point description:

Evaluation of peripheral nerve function by ENG studies was performed to measure nerve conduction velocity (NCV), amplitude (AMP),distal latency (DL), and F-wave latency. Categorized nerve conduction velocity values were assessed. Data was presented only for the number subjects who reported change in nerve conduction velocity > 0. Here MME refers to median motor elbow, WCV for wrist conduction velocity, PMA for peroneal motor ankle, FHCV to fibular head conduction velocity, TMA for tibial motor ankle, KCV for knee conduction velocity and UME for ulnar motor elbow. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Secondary

End point timeframe:

Baseline, Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
MME to WCV (Baseline)	6	6	6	6
MME to WCV (Week 40)	3	5	6	5
PMA to FHCV (Baseline)	6	6	6	6
PMA to FHCV (Week 40)	4	5	5	4
TMA to KCV (Baseline)	4	4	4	3

TMA to KCV (Week 40)	2	3	4	1
UME to WCV (Baseline)	4	4	4	3
UME to WCV (Week 40)	2	3	3	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Nerve Conduction as Measured by Electroneurography (ENG) Assessments by Categorized Distal Latency at Week 40

End point title	Number of Subjects With Change in Nerve Conduction as Measured by Electroneurography (ENG) Assessments by Categorized Distal Latency at Week 40

End point description:

Evaluation of peripheral nerve function by ENG studies was performed to measure nerve conduction velocity (NCV), amplitude (AMP), distal latency (DL), and F-wave latency. Categorized amplitude values were assessed. Data was presented only for the number of subjects who reported change in distal latency > 0. Here MMW refers to median motor wrist, APB for abductor pollicis brevis, MSW for median sensory wrist, DDL for digit distal latency, PMA for peroneal motor ankle, EDB for extensor digitorum brevis, SSB-point DL for sural sensory B-point distal latency, TMA for tibial motor ankle, abductor hallucis for AH distal latency and, UMW for ulnar motor wrist. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery.

End point type	Secondary

End point timeframe:

Baseline, Week 40

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subject				
MMW to APB distal latency (Baseline)	6	5	5	6
MMW to APB distal latency (Week 40)	3	5	6	5
MSW to DDL (Baseline)	0	1	2	3
MSW to DDL (Week 40)	0	3	2	3
PMA to EDB Distal Latency (Baseline)	6	5	5	6
PMA to EDB Distal Latency (Week 40)	4	5	5	3
SS B-Point Distal Latency (Baseline)	2	2	2	3
SS B-Point Distal Latency (Week 40)	1	2	1	4
TMA to AH Distal Latency (Baseline)	0	0	3	3
TMA to AH Distal Latency (Week 40)	0	2	4	0
UMW to ADM Distal Latency (Baseline)	4	3	3	3
UMW to ADM Distal Latency (Week 40)	2	3	3	1

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Adaptive Behavior Composite Standard Score as Measured by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Week 40

End point title	Change From Baseline in Adaptive Behavior Composite Standard Score as Measured by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at Week 40[8]

End point description:

VABS-II survey interview form was used to measure the personal and social skills of subjects serially over time; these scales were organized within a 4-domain structure: communication, daily living, socialization, and motor skills. Each domain score was standardized by age. A higher score indicates a higher level of function. CSS refers to composite standard score. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery. '99999' indicates standard deviation (SD) which was not calculated due to insufficient number of subjects. Here 'n' represents those subjects who were evaluated for this measure at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 40

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects from SHP611 10 mg and SHP611 30 mg were excluded from the analysis. Since, analysis was planned for subjects received SHP611 100 mg with different manufacturing processes (Process A and B).

End point values	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Communication(Baseline) (n=1,3)	52 (± 99999)	97.3 (± 2.52)		
Communication(Week 40) (n=1,3)	-10 (± 99999)	-25 (± 18.19)		
Daily Living Skills(Baseline) (n=2,3)	49 (± 1.41)	80.3 (± 9.02)		
Daily Living Skills(Week 40) (n=2,3)	-4 (± 5.66)	-27 (± 19.47)		
Socialization(Baseline) (n=2,3)	50 (± 1.41)	86 (± 3.61)		
Socialization(Week 40) (n=2,3)	-0.5 (± 0.71)	-18 (± 17.09)		
Motor Skills(Baseline) (n=2,3)	31 (± 0)	83.7 (± 24.83)		
Motor Skills(Week 40) (n=2,3)	6 (± 16.97)	-43.3 (± 23.18)		
Adaptive Behavior CSS(Baseline) (n=1,3)	43 (± 99999)	84 (± 10.54)		
Adaptive Behavior CSS(Week 40) (n=1,3)	-5 (± 99999)	-25.3 (± 16.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Domain-specific Caregiver Observed Metachromatic Leukodystrophy (MLD) Functioning and Outcomes Reporting Tool (COMFORT) Scores at Week 40

End point title	Change From Baseline in Domain-specific Caregiver Observed Metachromatic Leukodystrophy (MLD) Functioning and Outcomes Reporting Tool (COMFORT) Scores at Week 40[9]

End point description:

COMFORT questionnaire was used to assess health status and the impact of disease on the ability of subjects with MLD to carry out activities of daily life. The questionnaire was organized by 8 domains (ie, personal care; positioning, transfer, or mobility; eating; pain and discomfort during the day; sleep; emotions; communication; and play and leisure activities). The COMFORT scores range from 0 to 100, with higher scores indicating a decline in the functioning. Safety set consisted of subjects who received at least 1 dose of investigational product or underwent device implant surgery. Here 'n' represents those subjects who were evaluated for this measure at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 40

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects from SHP611 10 mg and SHP611 30 mg were excluded from the analysis. Since, analysis was planned for subjects received SHP611 100 mg with different manufacturing processes (Process A and B).

End point values	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Communication (Baseline) (n=5,6)	27.3 (± 13.27)	16.9 (± 8.65)		
Communication (Week 40) (n=5,6)	24.7 (± 26.81)	21.4 (± 20.92)		
Eating difficulty (Baseline) (n=5,6)	21.1 (± 22.94)	2.4 (± 5.77)		
Eating difficulty (Week 40) (n=5,6)	25.1 (± 22.44)	11.8 (± 10.29)		
Emotions (Baseline) (n=5,6)	60 (± 9.13)	55.6 (± 12.55)		
Emotions (Week 40) (n=5,6)	-15 (± 21.57)	-1.4 (± 6.27)		
Pain and discomfort during day (Baseline) (n=5,6)	16.6 (± 10.16)	6.9 (± 11.05)		
Pain and discomfort during day (Week 40) (n=5,6)	13.5 (± 15.23)	0 (± 11.74)		
Personal care (Baseline) (n=5,6)	48 (± 21.26)	36 (± 17.99)		
Personal care (Week 40) (n=5,6)	18.1 (± 37.94)	7.3 (± 18.95)		
Play and leisure activities (Baseline) (n=5,6)	46 (± 19.81)	16.7 (± 16.33)		
Play and leisure activities (Week 40) (n=5,6)	1 (± 28.15)	30 (± 25.88)		
Positioning, transfer/mobility(Baseline) (n=5,6)	42.2 (± 19.44)	18 (± 18.8)		
Positioning, transfer/mobility (Week 40) (n=5,6)	6.7 (± 21.82)	8.8 (± 13.14)		
Sleep (Baseline) (n=5,6)	11.9 (± 5.52)	18.9 (± 6.52)		
Sleep (Week 40) (n=5,6)	6.8 (± 17.08)	4.5 (± 15.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of SHP611

End point title	Maximum Observed Serum Concentration (Cmax) of SHP611

End point description:

Cmax is the maximum observed serum concentration of SHP611. Pharmacokinetic (PK) set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=6,6,6,5)	214.53 (± 162.104)	500.83 (± 260.978)	715.17 (± 339.856)	799.6 (± 494.452)
Week 38 (n=2,5,4,4)	157.5 (± 36.062)	275.4 (± 156.329)	888.75 (± 225.457)	1494.83 (± 1297.295)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Drug Concentration (Tmax) of SHP611 in Plasma

End point title	Time to Reach Maximum Observed Drug Concentration (Tmax) of SHP611 in Plasma

End point description:

Tmax is the time to reach maximum observed drug concentration of SHP611 during a dosing interval. Pharmacokinetic (PK) set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Hour (h)				
arithmetic mean (standard deviation)				
Baseline (n=6,6,6,5)	7.06 (± 1.086)	6.81 (± 3.462)	5.97 (± 4.802)	9.61 (± 8.344)

Week 38 (2,5,4,4)	5.08 (± 1.45)	11.22 (± 1.78)	18.16 (± 11.661)	7.02 (± 3.824)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to Infinity (AUC 0-inf) of SHP611

End point title	Area Under the Concentration-Time Curve From Time Zero to Infinity (AUC 0-inf) of SHP611

End point description:

The AUC 0-inf is the area under the concentration-time curve from time zero to infinity of SHP611. Pharmacokinetic (PK) set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points. '99999' indicates standard deviation (SD) which was not calculated due to insufficient number of subjects and '88888' indicates mean and SD were not calculated as the number of subjects analyzed were 0.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Hour*nanogram/milliliter (h*ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=1,4,2,3)	4355 (± 99999)	10105 (± 3307.4)	22123 (± 4217.4)	23117 (± 10380.1)
Week 38 (n=1,1,0,2)	2767 (± 99999)	9589 (± 99999)	88888 (± 88888)	48648 (± 6906.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUC0-last) of SHP611

End point title	Area Under the Concentration-Time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUC0-last) of SHP611

End point description:

AUC0-last is the area under the concentration-time curve from the time of dosing to the last measurable concentration of SHP611. PK set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of

SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Hour*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=6,6,6,5)	2532 (± 1178.4)	8738 (± 3106.4)	15022 (± 10755.2)	16288 (± 10691.4)
Week 38 (n=2,5,4,4)	1972 (± 211.5)	6156 (± 3904.5)	24820 (± 16954.3)	29219 (± 21261.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to 24 Hours (AUC0-24) of SHP611

End point title	Area Under the Concentration-Time Curve From Time Zero to 24 Hours (AUC0-24) of SHP611

End point description:

Area under the concentration-time curve over the interval from 0 to 24 hours after dosing of SHP611. PK set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Hour*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=6,6,5,5)	2530 (± 1178)	6258 (± 2995.3)	11918 (± 6376.1)	13114 (± 8012)
Week 38 (n=2,4,3,3)	1960 (± 224)	4596 (± 2316.1)	18264 (± 2162.7)	31115 (± 15805.6)

Statistical analyses

No statistical analyses for this end point

Secondary: First Order Rate Constant (Lambda z) Associated With the Terminal (Log-linear) Portion of the Curve for SHP611

End point title	First Order Rate Constant (Lambda z) Associated With the Terminal (Log-linear) Portion of the Curve for SHP611

End point description:

Lambda z is first order elimination rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve. PK set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points. '99999' indicates standard deviation (SD) which was not calculated due to insufficient number of subjects and '88888' indicates mean and SD were not calculated as the number of subjects analyzed were 0.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Per hour (/h)				
arithmetic mean (standard deviation)				
Baseline (n=1,4,2,3)	0.0934 (± 99999)	0.0561 (± 0.019)	0.0461 (± 0.02439)	0.0607 (± 0.01949)
Week 38 (n=1,1,0,2)	0.0506 (± 99999)	0.064 (± 99999)	88888 (± 88888)	0.0857 (± 0.04415)

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half Life (t1/2) of SHP611

End point title	Terminal Elimination Half Life (t1/2) of SHP611

End point description:

The t1/2 is the time in hours required for the concentration of the drug to reach half of its original value. PK set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points. '99999' indicates standard deviation (SD) which was not calculated due to insufficient number of subjects and '88888' indicates mean and SD were not calculated as the number of subjects analyzed were 0.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Hour (h)				
arithmetic mean (standard deviation)				
Baseline (n=1,4,2,3)	7.42 (± 99999)	13.6 (± 4.932)	17.47 (± 9.238)	12.34 (± 4.373)
Week 38 (n=1,1,0,2)	13.7 (± 99999)	10.83 (± 99999)	88888 (± 88888)	9.32 (± 4.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance (CL/F) After Intrathecal Administration of SHP611

End point title	Total Body Clearance (CL/F) After Intrathecal Administration of SHP611

End point description:

CL/F was defined as the total body clearance of the drug for extravascular administration divided by the fraction of dose absorbed. PK set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points. '99999' indicates standard deviation (SD) which was not calculated due to insufficient number of subjects and '88888' indicates mean and SD were not calculated as the number of subjects analyzed were 0.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Liter per hour (L/h)				
arithmetic mean (standard deviation)				
Baseline (n=1,4,2,3)	2.3 (± 99999)	3.25 (± 1.185)	4.6 (± 0.878)	5.28 (± 3.179)
Week 38 (n=1,1,0,2)	3.61 (± 99999)	3.13 (± 99999)	88888 (± 88888)	2.08 (± 0.295)

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vz/F) After Intrathecal Administration of SHP611

End point title	Volume of Distribution (Vz/F) After Intrathecal Administration of SHP611

End point description:

Volume of distribution was associated with the terminal slope following extravascular administration of SHP611 divided by the fraction of dose absorbed. PK set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points. '99999' indicates standard deviation (SD) which was not calculated due to insufficient number of subjects and '88888' indicates mean and SD were not calculated as the number of subjects analyzed were 0.

End point type	Secondary

End point timeframe:

Baseline: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose; Week 38: Predose, 0.5, 1, 2, 4, 8, 12, 24, 48 hours postdose

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Liter (L)				
arithmetic mean (standard deviation)				
Baseline (n=1,4,2,3)	24.58 (± 99999)	69.97 (± 49.912)	121.88 (± 83.481)	106.95 (± 100.026)
Week 38 (n=1,1,0,2)	71.41 (± 99999)	48.88 (± 99999)	88888 (± 88888)	28.95 (± 18.345)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of SHP611 in Cerebrospinal Fluid

End point title	Concentration of SHP611 in Cerebrospinal Fluid

End point description:

Concentration of SHP611 in CSF were determined using validated enzyme-linked immunosorbent assay (ELISA) method. PK set consisted of subjects who received at least 1 dose of investigational product and had at least 1 measurable serum concentration or 1 measurable CSF concentration of SHP611. Here 'n' represents those subjects who were evaluated for this measure at given time points.

End point type	Secondary

End point timeframe:
Baseline, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 40 weeks

End point values	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)	SHP611 100 mg (Process B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=6,6,6,5)	280 (± 685.857)	0 (± 0)	0 (± 0)	0 (± 0)
Week 4 (n=6,6,6,4)	182.93 (± 165.913)	78 (± 102.516)	2935.17 (± 2632.398)	6152.5 (± 6546.986)
Week 8 (n=6,6,5,4)	85.47 (± 79.316)	1854.07 (± 2633.858)	4171.2 (± 4874.122)	3825 (± 2182.056)
Week 12 (n=5,6,6,5)	57.5 (± 57.365)	1556.17 (± 1557.666)	2310 (± 2544.814)	2304 (± 2155.558)
Week 16 (n=6,6,6,5)	93.83 (± 147.188)	2805.68 (± 3499.878)	2395 (± 1550.648)	2606.2 (± 1212.857)
Week 20 (n=6,6,6,3)	112.78 (± 143.216)	1364.65 (± 2784.474)	5182.5 (± 5081.08)	4423.33 (± 4195.406)
Week 24 (n=6,6,6,5)	132.57 (± 235.783)	802.67 (± 903.025)	5402.5 (± 7352.246)	7914.6 (± 8243.114)
Week 28 (n=5,6,6,4)	525.06 (± 874.71)	3274.62 (± 4493.212)	6273.83 (± 6839.101)	3682.58 (± 4331.13)
Week 32 (n=5,6,5,5)	70.12 (± 126.513)	573.62 (± 376.224)	1831.4 (± 988.294)	6110 (± 4099.5)
Week 36 (n=5,6,6,3)	72.4 (± 125.574)	1046.05 (± 1087.321)	3917.5 (± 4650.791)	3116.67 (± 336.502)
Week 40 (n=6,2,6,4)	659.15 (± 1602.414)	243.6 (± 313.107)	2931.83 (± 4098.389)	6663.75 (± 7947.148)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment up to safety follow up (Week 42)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	SHP611 10 mg (Process A)
Reporting group description:	
Subjects received 10 milligram (mg) dose of SHP611 (HGT1110, recombinant human arylsulfatase A [rhASA]) every other week (EOW) by intrathecal drug delivery device (IDDD) for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 30 mg (Process A)
Reporting group description:	
Subjects received 30 mg dose of SHP611 (HGT1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 100 mg (Process A)
Reporting group description:	
Subjects received 100 mg dose of SHP611 (HGT1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the original drug substance manufacturing process referred to as Process A.	
Reporting group title	SHP611 100 mg (Process B)
Reporting group description:	
Subjects received 100 mg dose of SHP611 (HGT1110, rhASA) EOW by IDDD for 38 weeks. In this cohort, subjects received SHP611 produced with the revised drug substance manufacturing process referred to as Process B.	

Serious adverse events	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	4 / 6 (66.67%)	3 / 6 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Gamma-Glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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			
Convulsion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasticity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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			
Device dislocation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (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
Device failure			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device malfunction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (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 occlusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (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 effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
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 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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			
Aspiration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Nasopharyngitis			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (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
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (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
Respiratory tract infection viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pharyngitis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (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 upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SHP611 100 mg (Process B)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gamma-Glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile convulsion			

subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle spasticity				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Device dislocation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device failure				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device malfunction				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device occlusion				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Implant site effusion				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	0 / 6 (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 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (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 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 6 (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 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (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	SHP611 10 mg (Process A)	SHP611 30 mg (Process A)	SHP611 100 mg (Process A)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0

Complication of device removal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Crying			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Device dislocation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Device malfunction			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Implant site cyst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Implant site effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	3 / 6 (50.00%)
occurrences (all)	1	0	6
Implant site pain			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	5 / 6 (83.33%)	3 / 6 (50.00%)	5 / 6 (83.33%)
occurrences (all)	15	17	6

Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Bronchial obstruction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Choking			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Laryngeal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Nasal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1

Pharyngeal erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tonsillar hypertrophy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Decreased eye contact			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Initial insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Insomnia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Sleep disorder			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Albumin csf increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood iron decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Blood pressure increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Body temperature increased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Csf lymphocyte count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Csf mononuclear cell count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Csf protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Csf white blood cell count increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Eosinophil count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	2
Gamma-Glutamyltransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mean cell volume decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutrophil count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Red blood cells csf positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

White blood cell count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Endotracheal intubation complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Incision site oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Post procedural complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Post procedural oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Postoperative fever			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Postoperative wound complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	2	2	3
Vaccination complication			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Wrong technique in drug usage process			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Talipes			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Areflexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ataxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cerebellar syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Clonus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Convulsion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Drooling			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dystonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epilepsy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Febrile convulsion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Hypotonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle spasticity			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	4	3	1
Myoclonus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Speech disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Speech disorder developmental			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Visual acuity reduced			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Anal fissure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Constipation			

subjects affected / exposed	3 / 6 (50.00%)	4 / 6 (66.67%)	3 / 6 (50.00%)
occurrences (all)	4	7	3
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Dysphagia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Gingivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	0	1	4
Pancreatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Salivary duct obstruction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Salivary hypersecretion			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	4 / 6 (66.67%)	5 / 6 (83.33%)	4 / 6 (66.67%)
occurrences (all)	5	7	11
Hepatobiliary disorders			
Cytolytic hepatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Erythema nodosum			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hirsutism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Keloid scar			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Rash pruritic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Kyphosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Lordosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Tendinous contracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tendon disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Cystitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Enterovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Febrile infection			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Impetigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Implant site infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	4 / 6 (66.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	6	1	1
Oral candidiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Tonsillitis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	1	5	1
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	3
Viral pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	SHP611 100 mg (Process B)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Complication of device removal			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Crying			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Device dislocation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Device malfunction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Discomfort			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Disease progression			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Implant site cyst			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Implant site effusion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Implant site pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	5 / 6 (83.33%)		
occurrences (all)	11		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vulvovaginal erythema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Bronchial obstruction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Choking			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Laryngeal inflammation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nasal obstruction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pharyngeal erythema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tonsillar hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Agitation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Decreased eye contact			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Initial insomnia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Restlessness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Sleep disorder			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Albumin csf increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Blood iron decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood pressure increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Body temperature increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Csf lymphocyte count increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Csf mononuclear cell count increased			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Csf protein increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Csf white blood cell count increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eosinophil count increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gamma-Glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Mean cell volume decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Neutrophil count increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Red blood cells csf positive			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Contusion				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Endotracheal intubation complication				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Fall				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Incision site oedema				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Laceration				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Post procedural complication				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Post procedural oedema				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Postoperative fever				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Postoperative wound complication				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Procedural pain				
subjects affected / exposed	5 / 6 (83.33%)			
occurrences (all)	5			
Vaccination complication				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Wrong technique in drug usage process				

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Talipes			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Areflexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cerebellar syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Clonus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Convulsion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Drooling			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dysarthria			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dystonia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Epilepsy			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Febrile convulsion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Hypotonia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Motor dysfunction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Muscle spasticity			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Myoclonus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Speech disorder			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Speech disorder developmental			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Eosinophilia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eye swelling			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	4 / 6 (66.67%)		
occurrences (all)	5		
Diarrhoea			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pancreatitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Salivary duct obstruction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Salivary hypersecretion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	6		
Hepatobiliary disorders			
Cytolytic hepatitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Eczema			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Erythema nodosum			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hirsutism			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Keloid scar			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Urinary incontinence			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Kyphosis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Lordosis			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tendinous contracture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tendon disorder			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Enterovirus infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Febrile infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Gastroenteritis				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Gastroenteritis viral				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Impetigo				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Implant site infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Lung infection				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	2			
Oral candidiasis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Respiratory tract infection viral				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Tonsillitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 5		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Viral infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Viral pharyngitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Iron deficiency subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2011	Study design was updated to indicate that subjects randomized to receive investigational drug product would have the IDDD implanted between Days 7 and 1, eliminating the 7 day window; removal of patients from the trial or investigational product section was updated ; safetyrelated stopping rules section was updated.
17 August 2011	Exclusion criterion was replaced for subjects who were 8 years of age or older would not be eligible for the study.
20 October 2011	Exclusion criterion was modified to additionally restrict subject participation in any other study using an investigational device or agent during the conduct of this study.
05 April 2012	Protocol was updated to remove the no-treatment natural history cohort; study design was changed to open label, uncontrolled study; Change in title and removal of all references to randomization; change in sample size and all references to "treated subjects" or "untreated subjects" were removed and revised to read "subjects" only; for a subject with initial screen failure or withdrew prior to device implantation, 1 additional opportunity was allowed to get screened.
24 June 2013	Protocol was amended to incorporate new IDDD (the SOPH-A-PORT Mini S device); Two secondary clinical endpoints were added; age of the study population was increased from less than 8 years of age to less than 12 years of age.
31 July 2013	Protocol was amended to clarify the GMFM-88 scoring terminology by adding more detailed description; Descriptions of the VABS-II and COMFORT questionnaire domains were added for consistency; Reporting guidance for medical device reports was added.
10 February 2015	Protocol was amended to add descriptive exploratory analyses of GIMF-S and GIMF-C; Protocol was amended to add a fourth cohort of subjects to evaluate the SHP611 investigational drug product produced with the revised drug substance manufacturing process (referred to as Process B); Dose timing section was added to allow catch-up dosing in the cohorts receiving the 100 mg dose level.
26 August 2015	Protocol was amended to update the study design prior to enrollment start for Cohort 4; The revised study design for Cohort 4 changed the following: The age inclusion criterion (from <12 years of age to <8 years of age); Enrolled subjects with GMFM-88 total score (percent) ≥40 at screening with eligibility confirmed at baseline with a GMFM-88 score ≥35 and an additional inclusion criteria based on the walking dimension of the GMFM-88 permitted subjects to initiate treatment via lumbar puncture (LP), if IDDD implantation was delayed; Allowed use of local laboratories to confirm MLD diagnosis and eligibility with central laboratory confirmation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported