Clinical trial results:
A Phase 2, Open Label, Multi-Center, Single-Dose Pharmacokinetics, and Multiple Dose Study of the Safety, Efficacy and Tolerability of SSP-004184 (SPD602) in a Pediatric Population with Transfusional Iron Overload

Summary

EudraCT number	2011-001718-32
Trial protocol	IT
Global end of trial date	13 May 2014

Results information

Result version number	v1 (current)
This version publication date	12 October 2019
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	SPD602-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01363908
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	300 Shire Way, Lexington, Massachusetts, United States, 02421
Public contact	Study Physician, Shire Development LLC, +1 866 842 5335,
Scientific contact	Study Physician, Shire Development LLC, +1 866 842 5335,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001057-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the single-dose pharmacokinetics of SSP-004184AQ in the pediatric iron-overloaded population 6 years and older and to assess the long-term safety, tolerability, and efficacy of SSP-004184AQ in the pediatric iron-overloaded population 6 years and older.

Protection of trial subjects:

This study was conducted in accordance with the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1): 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	10 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	30
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	14
Adolescents (12-17 years)	16
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened for enrollment over a period of 45 days

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	6 to <12 year old- Screening/Enrollment

Arm description:

Subjects were screened for enrollment over a period of 45 days. Enrolled subjects then completed a washout period of 5 days.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	12 to <18 year old-Screening/Enrollment

Arm description:

Subjects were screened for enrollment over a period of 45 days. Enrolled subjects then completed a washout period of 5 days.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	6 to <12 years old- Pharmacokinetic Phase

Arm description:

During the pharmacokinetic phase, participants aged 6 to less than 12 years received a single oral dose of SPD602.

Arm type	Experimental
Investigational medicinal product name	SPD602-202
Investigational medicinal product code	
Other name	SSP-004184, FBS0701, deferitazole
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

On Day 1, subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 16mg/kg SPD602. Each subject's dose was based on the subject’s weight at Day 1 or as close to Day 1 as possible (e.g., Screening Visit, Baseline Visit, a blood transfusion visit prior to Day 1). Subjects received the study drug in the clinic.

Arm title	12 to <18 years old-Pharmacokinetic Phase

Arm description:

During the pharmacokinetic phase, participants aged 12 to less than 18 years received a single oral dose of SPD602.

Arm type	Experimental

Investigational medicinal product name	SPD602-202
Investigational medicinal product code	
Other name	SSP-004184, FBS0701, deferitazole
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

On Day 1, subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 16mg/kg SPD602. Each subject's dose was based on the subject's weight at Day 1 or as close to Day 1 as possible (e.g., Screening Visit, Baseline Visit, a blood transfusion visit prior to Day 1). Subjects received the study drug in the clinic.

Arm title	6 to <12 years old-Chronic Dosing Phase

Arm description:

During the chronic dosing phase, subjects 6 to less than 12 years commenced 48 weeks of treatment with SPD602.

Arm type	Experimental
Investigational medicinal product name	SPD602-202
Investigational medicinal product code	
Other name	SSP-004184, FBS0701, deferitazole
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For the chronic dosing phase, subjects were initially administered a combination of 50, 100, 200, 250, or 375 mg SPD602 capsules for a total dose of 26 or 36mg/kg/day; the amount of study drug administered was determined based on the intensity of the subject's iron overload, weight, and average daily transfusion iron intake. Dose adjustments were made if pharmacokinetic results supported a significantly different dosing algorithm for an age cohort or based upon clinical evidence of continued iron accumulation. Doses for continued treatment ranged from 8-60mg/kg/day.

Arm title	12 to <18 years old-Chronic Dosing Phase

Arm description:

During the chronic dosing phase, subjects aged 12 to less than 18 years commenced 48 weeks of treatment with SPD602.

Arm type	Experimental
Investigational medicinal product name	SPD602-202
Investigational medicinal product code	
Other name	SSP-004184, FBS0701, deferitazole
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For the chronic dosing phase, subjects were initially administered a combination of 50, 100, 200, 250, or 375 mg SPD602 capsules for a total dose of 26 or 36mg/kg/day; the amount of study drug administered was determined based on the intensity of the subject's iron overload, weight, and average daily transfusion iron intake. Dose adjustments were made if pharmacokinetic results supported a significantly different dosing algorithm for an age cohort or based upon clinical evidence of continued iron accumulation. Doses for continued treatment ranged from 8-60mg/kg/day.

Number of subjects in period 1	6 to <12 year old-Screening/Enrollment	12 to <18 year old-Screening/Enrollment	6 to <12 years old-Pharmacokinetic Phase
Started	14	16	8
Completed	13	16	8
Not completed	1	0	0
Physician decision	-	-	-

Patient decision	-	-	-
Early study termination	-	-	-
Adverse event	-	-	-
Did not receive study drug	1	-	-

Number of subjects in period 1	12 to <18 years old-Pharmacokinetic Phase	6 to <12 years old-Chronic Dosing Phase	12 to <18 years old-Chronic Dosing Phase
Started	8	13	16
Completed	8	3	10
Not completed	0	10	6
Physician decision	-	-	1
Patient decision	-	-	1
Early study termination	-	9	3
Adverse event	-	1	1
Did not receive study drug	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	11.8		
standard deviation	± 3.36	-	
Gender, Male/Female Units: participants			
Female	15	15	
Male	15	15	

End points

End points reporting groups

Reporting group title	6 to <12 year old- Screening/Enrollment
Reporting group description:	
Subjects were screened for enrollment over a period of 45 days. Enrolled subjects then completed a washout period of 5 days.	
Reporting group title	12 to <18 year old-Screening/Enrollment
Reporting group description:	
Subjects were screened for enrollment over a period of 45 days. Enrolled subjects then completed a washout period of 5 days.	
Reporting group title	6 to <12 years old- Pharmacokinetic Phase
Reporting group description:	
During the pharmacokinetic phase, participants aged 6 to less than 12 years received a single oral dose of SPD602.	
Reporting group title	12 to <18 years old-Pharmacokinetic Phase
Reporting group description:	
During the pharmacokinetic phase, participants aged 12 to less than 18 years received a single oral dose of SPD602.	
Reporting group title	6 to <12 years old-Chronic Dosing Phase
Reporting group description:	
During the chronic dosing phase, subjects 6 to less than 12 years commenced 48 weeks of treatment with SPD602.	
Reporting group title	12 to <18 years old-Chronic Dosing Phase
Reporting group description:	
During the chronic dosing phase, subjects aged 12 to less than 18 years commenced 48 weeks of treatment with SPD602.	

Primary: Maximum Observed Plasma Concentration (Cmax) of SPD602 After a Single Oral Dose

End point title	Maximum Observed Plasma Concentration (Cmax) of SPD602 After a Single Oral Dose[1][2]
End point description:	
The pharmacokinetic (PK) parameters of SPD602 were measured in plasma of all patients following a single capsule dose of SPD602 at 16 mg/kg at start of treatment on Day 1 and at the clinic visit on Day 2. Plasma concentrations of SPD602 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The PK parameters were determined from plasma concentration-time data for SPD602 (total) by non-compartmental analysis. This endpoint analyzed the PK set, defined as all subjects in the Safety Analysis Set for whom the primary PK data were considered sufficient and interpretable. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.	
End point type	Primary
End point timeframe:	
Day 1 and up to 24 hours post-dose; pre-dose on Day 1 (within 60 minutes prior to investigational product administration) and at 0.5, 1, 2, 3, 4, 8 hours (±3 minutes) and 24 hours (±30 minutes) post-dose.	
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: No statistical comparisons were made as part of this pharmacokinetic analysis.	
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Pharmacokinetic (PK) data were only collected while subjects took part in the PK phase of	

the study.

End point values	6 to <12 years old-Pharmacokinetic Phase	12 to <18 years old-Pharmacokinetic Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: ng/mL				
arithmetic mean (standard deviation)	31737.5 (± 10116.74)	28300 (± 7309.88)		

Statistical analyses

No statistical analyses for this end point

Primary: Time of Maximum Observed Plasma Concentration Sampled During a Dosing Interval (tmax) of SPD602 After a Single Oral Dose

End point title	Time of Maximum Observed Plasma Concentration Sampled During a Dosing Interval (tmax) of SPD602 After a Single Oral Dose[3][4]

End point description:

The pharmacokinetic (PK) parameters of SPD602 were measured in plasma of all patients following a single capsule dose of SPD602 at 16 mg/kg at start of treatment on Day 1 and at the clinic visit on Day 2. Plasma concentrations of SPD602 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The PK parameters were determined from plasma concentration-time data for SPD602 (total) by non-compartmental analysis.
This endpoint analyzed the PK set, defined as all subjects in the Safety Analysis Set for whom the primary PK data were considered sufficient and interpretable. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Day 1 and up to 24 hours post-dose; pre-dose on Day 1 (within 60 minutes prior to investigational product administration) and at 0.5, 1, 2, 3, 4, 8 hours (±3 minutes) and 24 hours (±30 minutes) post-dose.

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: No statistical comparisons were made as part of this pharmacokinetic analysis.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic (PK) data were only collected while subjects took part in the PK phase of the study.

End point values	6 to <12 years old-Pharmacokinetic Phase	12 to <18 years old-Pharmacokinetic Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: hours				
median (full range (min-max))	1 (0.5 to 1)	1 (0.6 to 2)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under The Plasma Concentration-Time Curve (AUC) From The Time of Dosing to The Last Measurable Concentration (AUClast) of SPD602 After a Single Oral Dose

End point title	Area Under The Plasma Concentration-Time Curve (AUC) From The Time of Dosing to The Last Measurable Concentration (AUClast) of SPD602 After a Single Oral Dose[5][6]

End point description:

The pharmacokinetic (PK) parameters of SPD602 were measured in plasma of all patients following a single capsule dose of SPD602 at 16 mg/kg at start of treatment on Day 1 and at the clinic visit on Day 2. Plasma concentrations of SPD602 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The PK parameters were determined from plasma concentration-time data for SPD602 (total) by non-compartmental analysis.
This endpoint analyzed the PK set, defined as all subjects in the Safety Analysis Set for whom the primary PK data were considered sufficient and interpretable. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Day 1 and up to 24 hours post-dose; pre-dose on Day 1 (within 60 minutes prior to investigational product administration) and at 0.5, 1, 2, 3, 4, 8 hours (±3 minutes) and 24 hours (±30 minutes) post-dose.

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: No statistical comparisons were made as part of this pharmacokinetic analysis.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic (PK) data were only collected while subjects took part in the PK phase of the study.

End point values	6 to <12 years old-Pharmacokinetic Phase	12 to <18 years old-Pharmacokinetic Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: h*mg/L				
arithmetic mean (standard deviation)	69.4 (± 27.39)	71.6 (± 22.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Half-life (t1/2) of SPD602 After a Single Oral Dose

End point title	Terminal Half-life (t1/2) of SPD602 After a Single Oral Dose[7][8]

End point description:

The pharmacokinetic (PK) parameters of SPD602 were measured in plasma of all patients following a single capsule dose of SPD602 at 16 mg/kg at start of treatment on Day 1 and at the clinic visit on Day 2. Plasma concentrations of SPD602 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The PK parameters were determined from plasma concentration-time data for SPD602 (total) by non-compartmental analysis.
This endpoint analyzed the PK set, defined as all subjects in the Safety Analysis Set for whom the primary PK data were considered sufficient and interpretable. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Day 1 and up to 24 hours post-dose; pre-dose on Day 1 (within 60 minutes prior to investigational product administration) and at 0.5, 1, 2, 3, 4, 8 hours (±3 minutes) and 24 hours (±30 minutes) post-dose.

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: No statistical comparisons were made as part of this pharmacokinetic analysis.

[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: Pharmacokinetic (PK) data were only collected while subjects took part in the PK phase of the study.

End point values	6 to <12 years old-Pharmacokinetic Phase	12 to <18 years old-Pharmacokinetic Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: hours				
arithmetic mean (standard deviation)	3.7 (± 0.93)	3.6 (± 0.97)		

Statistical analyses

No statistical analyses for this end point

Primary: Renal Clearance (CLr) of SPD602 After a Single Oral Dose

End point title	Renal Clearance (CLr) of SPD602 After a Single Oral Dose[9][10]

End point description:

The pharmacokinetic (PK) parameters of SPD602 were measured in urine of patients following a single capsule dose of SPD602 at 16 mg/kg at start of treatment on Day 1 and at the clinic visit on Day 2. Children who could cooperate provided urine samples for PK assessment on Day 1 over 3 time intervals: 04, 48, and 824 hours after the last dose (continued into Day 2). Urine concentrations of SPD602 were determined using a validated liquid chromatography tandem mass spectrometry (LCMS/ MS) method. The PK parameters were determined from urine concentration-time data for SPD602 (total) by non-compartmental analysis.
This endpoint analyzed the PK set, defined as all subjects in the Safety Analysis Set for whom the primary PK data were considered sufficient and interpretable. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Day 1 and up to 24 hours post-dose

Notes:

[9] - 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: No statistical comparisons were made as part of this pharmacokinetic analysis.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic (PK) data were only collected while subjects took part in the PK phase of the study.

End point values	6 to <12 years old-Pharmacokinetic Phase	12 to <18 years old-Pharmacokinetic Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: L/h				
arithmetic mean (standard deviation)	3.6 (± 2.06)	5.4 (± 2.38)		

Statistical analyses

No statistical analyses for this end point

Primary: Amount Excreted Into Urine (Ue) of SPD602 After a Single Oral Dose

End point title	Amount Excreted Into Urine (Ue) of SPD602 After a Single Oral Dose[11][12]

End point description:

The pharmacokinetic (PK) parameters of SPD602 were measured in urine of patients following a single capsule dose of SPD602 at 16 mg/kg at start of treatment on Day 1 and at the clinic visit on Day 2. Children who could cooperate provided urine samples for PK assessment on Day 1 over 3 time intervals: 0-4, 4-8, and 8-24 hours after the last dose (continued into Day 2). Urine concentrations of SPD602 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The PK parameters were determined from urine concentration-time data for SPD602 (total) by non-compartmental analysis.
This endpoint analyzed the PK set, defined as all subjects in the Safety Analysis Set for whom the primary PK data were considered sufficient and interpretable. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Day 1 and up to 24 hours post-dose

Notes:

[11] - 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: No statistical comparisons were made as part of this pharmacokinetic analysis.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic (PK) data were only collected while subjects took part in the PK phase of the study.

End point values	6 to <12 years old-Pharmacokinetic Phase	12 to <18 years old-Pharmacokinetic Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mg				
arithmetic mean (standard deviation)	227.9 (± 107.44)	369.7 (± 140.17)		

Statistical analyses

No statistical analyses for this end point

Primary: Fraction Of Orally Administered Drug Excreted Unchanged In Urine (fe) of SPD602 After a Single Oral Dose

End point title	Fraction Of Orally Administered Drug Excreted Unchanged In Urine (fe) of SPD602 After a Single Oral Dose[13][14]

End point description:

The pharmacokinetic (PK) parameters of SPD602 were measured in urine of patients following a single capsule dose of SPD602 at 16 mg/kg at start of treatment on Day 1 and at the clinic visit on Day 2. Children who could cooperate provided urine samples for PK assessment on Day 1 over 3 time intervals: 0-4, 4-8, and 8-24 hours after the last dose (continued into Day 2). Urine concentrations of SPD602 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The PK parameters were determined from urine concentration-time data for SPD602 (total) by non-compartmental analysis.
This endpoint analyzed the PK set, defined as all subjects in the Safety Analysis Set for whom the primary PK data were considered sufficient and interpretable. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Day 1 and up to 24 hours post-dose

Notes:

[13] - 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: No statistical comparisons were made as part of this pharmacokinetic analysis.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic (PK) data were only collected while subjects took part in the PK phase of the study.

End point values	6 to <12 years old-Pharmacokinetic Phase	12 to <18 years old-Pharmacokinetic Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: percentage of total dose				
arithmetic mean (standard deviation)	42.1 (± 14.34)	52.5 (± 20.52)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Liver Iron Concentration (LIC) Assessed by FerriScan R2 Magnetic Resonance Imaging (MRI)

End point title	Change From Baseline in Liver Iron Concentration (LIC) Assessed by FerriScan R2 Magnetic Resonance Imaging (MRI)[15][16]

End point description:

The efficacy of SPD602 was assessed by determining LIC. Abdominal MRI data were collected by using FerriScan R2 standard procedures and used to determine LIC. A negative change from baseline indicates that LIC decreased.
This endpoint analyzed the Full Analysis Set (FAS), defined as all participants in the Safety Analysis Set who had at least 1 post-baseline primary efficacy assessment, which was considered as the LICs assessed from FerriScan R2 MRI. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Baseline, 24 weeks, and 48 weeks

Notes:

[15] - 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: For each age cohort, differences for LIC, cardiac iron loads assessed by T2* MRI, and serum ferritin were compared between baseline and post-baseline visits. No between-cohort comparisons were made as part of this study.
[16] - 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: Efficacy data were only collected while subjects took part in the chronic dosing phase of the study.

End point values	6 to <12 years old-Chronic Dosing Phase	12 to <18 years old-Chronic Dosing Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 24, n=7,15	-1.8 (± 2.8)	0.8 (± 2.7)		
Week 48, n=2,10	0.8 (± 0.4)	-0.2 (± 1.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in LIC Adjusted by Transfusional Iron Intake And Assessed by FerriScan R2 MRI

End point title	Change From Baseline in LIC Adjusted by Transfusional Iron Intake And Assessed by FerriScan R2 MRI[17][18]

End point description:

The efficacy of SPD602 was assessed by determining LIC and adjusting for transfusional iron intake. Abdominal MRI data were collected by using FerriScan R2 standard procedures and used to determine LIC. A negative change from baseline indicates that LIC decreased.
This endpoint analyzed the FAS, defined as all participants in the Safety Analysis Set who had at least 1

post-baseline primary efficacy assessment, which was considered as the LICs assessed from FerriScan R2 MRI. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Primary

End point timeframe:

Baseline, 24 weeks, and 48 weeks

Notes:

[17] - 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: For each age cohort, differences for LIC, cardiac iron loads assessed by T2* MRI, and serum ferritin were compared between baseline and post-baseline visits. No between-cohort comparisons were made as part of this study.
[18] - 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: Efficacy data were only collected while subjects took part in the chronic dosing phase of the study.

End point values	6 to <12 years old-Chronic Dosing Phase	12 to <18 years old-Chronic Dosing Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 24, n=7,15	-8.3 (± 3.7)	-4 (± 3.1)		
Week 48, n=2,10	-13.7 (± 5.3)	-11.9 (± 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in LIC Assessed by R2* MRI

End point title	Change From Baseline in LIC Assessed by R2* MRI[19]

End point description:

The efficacy of SPD602 was assessed by determining LIC. Abdominal MRI data were collected by using R2* standard procedures and used to determine LIC. A negative change from baseline indicates that LIC decreased.
This endpoint analyzed the FAS, defined as all participants in the Safety Analysis Set who had at least 1 post-baseline primary efficacy assessment, which was considered as the LICs assessed from FerriScan R2 MRI. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline, 24 weeks, and 48 weeks

Notes:

[19] - 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: Efficacy data were only collected while subjects took part in the chronic dosing phase of the study.

End point values	6 to <12 years old-Chronic Dosing Phase	12 to <18 years old-Chronic Dosing Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 24, n=7,15	0.3 (± 1.7)	0.2 (± 1.4)		
Week 48, n=3,10	0.6 (± 4.1)	0.3 (± 1.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in LIC Adjusted by Transfusional Iron Intake And Assessed by R2* MRI

End point title	Change From Baseline in LIC Adjusted by Transfusional Iron Intake And Assessed by R2* MRI[20]

End point description:

The efficacy of SPD602 was assessed by determining LIC and adjusting for transfusional iron intake. Abdominal MRI data were collected by using R2* standard procedures and used to determine LIC. A negative change from baseline indicates that LIC decreased.
This endpoint analyzed the FAS, defined as all participants in the Safety Analysis Set who had at least 1 post-baseline primary efficacy assessment, which was considered as the LICs assessed from FerriScan R2 MRI. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline, 24 weeks, and 48 weeks

Notes:

[20] - 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: Efficacy data were only collected while subjects took part in the chronic dosing phase of the study.

End point values	6 to <12 years old-Chronic Dosing Phase	12 to <18 years old-Chronic Dosing Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 24, n=7,15	-6.2 (± 2.2)	-4.6 (± 3.4)		
Week 48, n=3,10	-9.1 (± 5.6)	-11.4 (± 5.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cardiac Iron Load Assessed by T2* MRI

End point title	Change From Baseline in Cardiac Iron Load Assessed by T2* MRI[21]

End point description:

The efficacy of SPD602 was assessed by determining cardiac iron load. Cardiac MRI data were collected by using T2* standard procedures and used to determine iron load. A negative change from baseline indicates that iron load increased.
This endpoint analyzed the FAS, defined as all participants in the Safety Analysis Set who had at least 1 post-baseline primary efficacy assessment, which was considered as the LICs assessed from FerriScan R2 MRI. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline, 24 weeks, and 48 weeks

Notes:

[21] - 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: Efficacy data were only collected while subjects took part in the chronic dosing phase of the study.

End point values	6 to <12 years old-Chronic Dosing Phase	12 to <18 years old-Chronic Dosing Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: milliseconds				
arithmetic mean (standard deviation)				
Week 24, n=7,15	-9.63 (± 10.766)	-6.27 (± 13.731)		
Week 48, n=3,10	-10.6 (± 20.893)	-9.4 (± 14.693)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Ferritin

End point title	Change From Baseline in Serum Ferritin[22]

End point description:

Serum ferritin levels were assessed to determine if a participant was a successful responder and were determined from serum biochemistry analyses conducted at the central laboratories. A negative change from baseline indicates that serum ferritin decreased.
This endpoint analyzed the FAS, defined as all participants in the Safety Analysis Set who had at least 1 post-baseline primary efficacy assessment, which was considered as the LICs assessed from FerriScan R2 MRI. The Safety Analysis Set was defined as all participants who had taken at least 1 dose of investigational product. Treatment assignment was based on the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline, 24 weeks, and 48 weeks

Notes:

[22] - 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: Efficacy data were only collected while subjects took part in the chronic dosing phase of the

study.

End point values	6 to <12 years old-Chronic Dosing Phase	12 to <18 years old-Chronic Dosing Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 24, n=7,15	73.19 (± 706.423)	-981.49 (± 1694.314)		
Week 48, n=3,10	-590.21 (± 843.249)	-1119.9 (± 1503.732)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 49 weeks after the start of treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	12 to <18 year old

Reporting group description:

During the pharmacokinetic phase, participants aged 12 to less than 18 years received a single oral dose of SPD602 16mg/kg. During the chronic dosing phase, participants commenced 48 weeks of treatment with an initial dose of SPD602 26mg/kg/day or 36mg/kg/day. Over the course of treatment, the dose could range from 8-60mg/kg/day depending on clinical response.

Reporting group title	6 to <12 year old

Reporting group description:

During the pharmacokinetic phase, participants aged 6 to less than 12 years received a single oral dose of SPD602 16mg/kg. During the chronic dosing phase, participants commenced 48 weeks of treatment with an initial dose of SPD602 26mg/kg/day or 36mg/kg/day. Over the course of treatment, the dose could range from 8-60mg/kg/day depending on clinical response.

Serious adverse events	12 to <18 year old	6 to <12 year old	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	12 to <18 year old	6 to <12 year old	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	13 / 13 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hyperaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
occurrences (all)	1	1	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Chest discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	2 / 16 (12.50%)	1 / 13 (7.69%)	
occurrences (all)	3	2	
Pyrexia			
subjects affected / exposed	5 / 16 (31.25%)	2 / 13 (15.38%)	
occurrences (all)	8	2	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 16 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	7	
Nasal congestion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 16 (12.50%)	5 / 13 (38.46%)	
occurrences (all)	3	5	
Pharyngeal erythema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pharyngeal haemorrhage			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Upper airway obstruction			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Glucose tolerance test abnormal			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Spleen palpable			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 16 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Foot fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Joint sprain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Head discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	8 / 16 (50.00%)	4 / 13 (30.77%)	
occurrences (all)	13	10	
Hypoaesthesia			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Hyporeflexia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Muscle contractions involuntary			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 13 (15.38%)	
occurrences (all)	2	3	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Sinus headache			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
occurrences (all)	4	2	
Lymphadenopathy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hearing impaired			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	3 / 16 (18.75%)	4 / 13 (30.77%)	
occurrences (all)	7	6	
Abdominal pain upper			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	5	0	
Diarrhoea			
subjects affected / exposed	3 / 16 (18.75%)	2 / 13 (15.38%)	
occurrences (all)	3	2	
Flatulence			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 16 (12.50%)	5 / 13 (38.46%)	
occurrences (all)	7	6	
Vomiting			
subjects affected / exposed	5 / 16 (31.25%)	4 / 13 (30.77%)	
occurrences (all)	5	6	
Skin and subcutaneous tissue disorders			
Blister			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Skin haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 16 (6.25%)	3 / 13 (23.08%)	
occurrences (all)	1	4	
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Osteochondrosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pain in extremity			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Sensation of heaviness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Hordeolum			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 16 (6.25%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
Molluscum contagiosum			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	2 / 16 (12.50%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Otitis externa			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	2 / 16 (12.50%)	1 / 13 (7.69%)	
occurrences (all)	5	1	
Rhinitis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 13 (15.38%)	
occurrences (all)	1	3	

Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2011	Summary of changes: - Inclusion 5 criterion amended to reflect that the decision to discontinue iron-chelation therapy should not be reliant on the willingness of the patient for pediatric patients aged 6-<18 years. The amendment reflected the need for the principal investigator and the patient's parents to determine if stopping iron-chelation therapy is appropriate for the patient. - In light of the recent approval of the Paediatric Implementation Plan by the European Medicines Agency, Section 11.1 was amended to add further information on the sample size considerations for the pharmacokinetic cohorts.
23 November 2011	Summary of changes: - Based on the FBS0701-CTP-12 data and the need for higher doses to ensure net negative iron balance, the maximum dose was increased to 60mg/kg/day. - New data from study FBS0701-CTP-12 were added to Section 3.3 of the protocol (summary of clinical studies). - Pituitary gland MRI assessments were added. - The frequency of height measurements and complete physical examinations was reduced. -The frequency of complete physical examinations was reduced. - The requirement for an ECG on Day 1 for chronic dosing patients was removed. - Fasting glucose assessments were added at Day 1, Week 24, and Week 48/EOT. - Trough plasma drug concentration measurements were added at Week 12 and Week 24. - The preliminary analysis of data from study FBS0701-CTP-4 in Sections 3.1 (rationale for development) and 3.3 (summary of clinical studies) of the protocol was revised. - Details of the FBS0701-CTP-15 extension protocol were added. - Animal toxicology data and potential risks text in Section 3.4 of the protocol (potential risks to human subjects) were corrected.
28 December 2011	Summary of changes: - Section 6.7.5 amended to allow physicians with safety concerns to closely monitor any patient who had his or her dose increased to greater than 40mg/kg/day. The suggested frequency of every 2 weeks was deemed sufficient to monitor for any potential untoward signs of toxicity, including renal changes, owing to the increased dose. - The rationale for and safety of the proposed doses in Section 3.5.1 were amended to provide additional information and data in support of the safety of the proposed maximum dose (up to 60 mg/kg/day once daily).

12 October 2012	Summary of changes: - It was clarified that AE collection was to commence at the signing of the consent/giving of assent as per Shire's requirement. - The sponsor details were updated: FerroKin Biosciences Inc was replaced with Shire Development LLC. The original FerroKin protocol numbers were updated to Shire protocol numbers as follows: SPD602-101 replaced FBS0701-CTP-03; SPD602-201 replaced FBS0701 CTP-04; SPD602-102 replaced FBS0701-CTP-12; SPD602-202 replaced FBS0701-CTP-07; and SPD602-301 replaced FBS0701-CTP-15. - The pregnancy and AE reporting requirements were revised to 24 hours. - The stopping rules and rescue therapy section were revised and replaced to reflect current opinion for removal of subjects from investigational product or therapy. - Information on gastrointestinal events deemed possibly or probably related to SSP-0040184 was added to Section 3.3 of the protocol (summary of clinical studies). - Text in Section 9.3 of the protocol (DNA and RNA analysis) was replaced with Shire standard wording. - Wording in Section 10 of the protocol (AE and SAE assessment) was replaced with Shire standard wording. - Section 12 of the protocol (investigational product accountability) was updated to include Shire standard language.
10 May 2013	Summary of changes: -The compound name was changed from SSP-004184 to SSP-004184AQ in all sections except the pharmacokinetic sections. - The description of investigational product was updated to include: provided as a magnesium salt (SSP-004184AQ). SSP-004184 is the free acid or active form. - Liver and pancreas were added to abdominal R2* MRI assessments to clarify the measurements required. - The AE and SAE collection time during chronic phase was reduced from 28 days after the last dose to 7 days after the last dose. - The pregnancy reporting time in the chronic dosing phase was reduced from 28 after the last dose to 7 days after the last dose. - The Week 52 EOS Visit was replaced by a Week 49 visit; the overall study duration therefore decreased from 417 days to 396 days. - A neurological examination was added to the study assessments to reflect current thinking on safety data capture; information on extended neurological examinations was added to Section 3.4 of the protocol (potential risks to human subjects) to reflect this change. - Cardiac LVEF was added to the exclusion criteria (criterion 12) and to the withdrawal criteria. - The baseline period (including the baseline MRI window), which was previously -14 to -7 days, was changed to -28 to -8 days. - Exclusion criterion 5 was amended to add that significant biliary disorder, e.g., chronic cholecystitis, would also exclude a subject from study entry, to reflect current clinical thinking. - A description of the data monitoring committee activities was added. - Details of possible drug interactions were added. - Information was added regarding events of potential interest to match neurological examination requirement. - Information was added regarding AEs of potential interest, including paraesthesia and hypoesthesia. Clarification was added that both the medical monitor and the Shire physician were to review and discuss SAE cases with the principal investigator.

26 September 2013	Summary of changes: - Exclusion criterion 5 was updated with removal of “chronic cholecystitis” to reflect IB version 7.0. - The contraception text within inclusion criterion 9 was revised to state that female subjects were required to have negative pregnancy tests, abstain from sexual activity, or use acceptable methods of contraception. The detailed discussion of contraceptives was removed and a cross-reference included to a newly created reproductive potential section (Section 6.3). - It was clarified that exclusion criterion 12 only applied to LVEF below (not outside) the locally determined normal range or in subjects with LVEF <50%. - It was clarified that echocardiograph is acceptable for LVEF measurement if MRI information is not available. - Primary endpoint 2 was amended to include LVEF as an example parameter. - A new section was included on reproductive potential, which included the following information: hormonal contraceptives were no longer considered approved forms of contraception when used alone and a second adequate method of contraception was required; hormonal contraceptives could be less efficient in the presence of SPD602 due to its potential induction of CYP3A4; and females of child-bearing potential had to agree to use acceptable contraception if they became sexually active during the study and for 30 days following the last dose of investigational product. - Text was added to Section 6.8.7 of the protocol (concomitant and prohibited treatments or therapies) to discuss that SPD602 is a potential inducer of CYP2B6 and CYP3A4 mRNA in vitro and that there may be potential drug interactions with these substrates in vivo.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 March 2014	This study was terminated due to treatment stop resulting in an inability to draw conclusions from the data. Evaluation of nonclinical rat findings is ongoing.	-

Notes:

Limitations and caveats

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

This study was terminated early because of non-clinical safety results. As such, not all subjects completed the study. The available efficacy data were summarized and analyzed as specified in the SAP; however, no efficacy conclusions could be drawn.

Notes: