



Clinical trial results:

A Phase 2, 24 Week, Open Label, Multi-Center Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of SSP-004184 (SPD602) in the Treatment of Chronic Iron Overload Requiring Chelation Therapy

Summary

EudraCT number	2011-005675-16
Trial protocol	IT
Global end of trial date	18 April 2014

Results information

Result version number	v1 (current)
This version publication date	12 October 2019
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	SPD602-203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01604941
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)	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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 April 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the steady-state pharmacokinetic parameters in subjects taking an SSP-004184AQ twice daily (BID) dose in the iron-overloaded population; to evaluate the changes in LIC after 12 and 24 weeks in subjects taking an SSP-004184AQ BID dose; and to assess the safety and tolerability of SSP-004184AQ when administered daily for 24 weeks in iron-overloaded subjects.

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	14 September 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	Italy: 13
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Lebanon: 11
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	32
EEA total number of subjects	13

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started as a double-arm study with once daily (QD) dosing but was amended first to a double-arm study with twice daily (BID) dosing and then to a single-arm study after removing the higher dose. Some participants were enrolled directly to BID dosing, some to QD dosing and then re-enrolled to BID dosing, some completed with QD dosing.

Pre-assignment

Screening details:

Subjects 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?	Yes
Arm title	SPD602 50mg/kg/day Twice Daily Dosing (BID)

Arm description:

Subjects were randomly assigned to 50 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.

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

Dosage and administration details:

Subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 50 mg/kg/day twice daily. Initial dosing was based on the subject's weight at Day 1 or as close to Day 1 as possible (e.g., screening, baseline, a blood transfusion clinic visit prior to Day 1). If during the course of the study the subject's weight differed from the weight used for Day 1 by more than 10%, the amount of SSP-004184AQ dispensed was to be corrected.

Arm title	SPD602 75mg/kg/day Twice Daily Dosing (BID)
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Arm description:

Subjects were randomly assigned to 75 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.

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

Dosage and administration details:

Subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 75 mg/kg/day twice daily. Initial dosing was based on the subject's weight at Day 1 or as close to Day 1 as possible (e.g., screening, baseline, a blood transfusion clinic visit prior to Day 1). If during the course of the study the subject's weight differed from the weight used for Day 1 by more than 10%, the amount of SSP-004184AQ dispensed was to be corrected.

Arm title	SPD602 50mg/kg/day Once (QD) Then Twice Daily Dosing (BID)
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Arm description:

Subjects were randomly assigned to QD dosing then re-enrolled to 50 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.

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

Dosage and administration details:

Subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 50 mg/kg/day once then twice daily. Initial dosing was based on the subject's weight at Day 1 or as close to Day 1 as possible (e.g., screening, baseline, a blood transfusion clinic visit prior to Day 1). If during the course of the study the subject's weight differed from the weight used for Day 1 by more than 10%, the amount of SSP-004184AQ dispensed was to be corrected.

Arm title	SPD602 75mg/kg/day Once (QD) Then Twice Daily Dosing (BID)
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Arm description:

Subjects were randomly assigned to QD dosing then re-enrolled to 75 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.

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

Dosage and administration details:

Subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 75 mg/kg/day once then twice daily. Initial dosing was based on the subject's weight at Day 1 or as close to Day 1 as possible (e.g., screening, baseline, a blood transfusion clinic visit prior to Day 1). If during the course of the study the subject's weight differed from the weight used for Day 1 by more than 10%, the amount of SSP-004184AQ dispensed was to be corrected.

Arm title	SPD602 50mg/kg/day Once Daily Dosing (QD)
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Arm description:

Subjects were randomly assigned to 50 mg/kg/day oral QD dosing and continued QD dosing until the end of study (24 weeks) or early discontinuation.

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

Dosage and administration details:

Subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 50 mg/kg/day once daily. Initial dosing was based on the subject's weight at Day 1 or as close to Day 1 as possible (e.g., screening, baseline, a blood transfusion clinic visit prior to Day 1). If during the course of the study the subject's weight differed from the weight used for Day 1 by more than 10%, the amount of SSP-004184AQ dispensed was to be corrected.

Arm title	SPD602 75mg/kg/day Once Daily Dosing (QD)
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Arm description:

Subjects were randomly assigned to 75 mg/kg/day oral QD dosing and continued QD dosing until the end of study (24 weeks) or early discontinuation.

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

Dosage and administration details:

Subjects were administered a combination of 50, 100, 200, 250, or 375 mg capsules for a total dose of 75 mg/kg/day once daily. Initial dosing was based on the subject's weight at Day 1 or as close to Day 1 as possible (e.g., screening, baseline, a blood transfusion clinic visit prior to Day 1). If during the course of the study the subject's weight differed from the weight used for Day 1 by more than 10%, the amount of SSP-004184AQ dispensed was to be corrected.

Number of subjects in period 1	SPD602 50mg/kg/day Twice Daily Dosing (BID)	SPD602 75mg/kg/day Twice Daily Dosing (BID)	SPD602 50mg/kg/day Once (QD) Then Twice Daily Dosing (BID)
	Started	11	4
Completed	0	0	0
Not completed	11	4	3
Participant decision	-	-	-
Early study termination	9	2	3
Adverse event	1	2	-
Non-compliance	1	-	-

Number of subjects in period 1	SPD602 75mg/kg/day Once (QD) Then Twice Daily Dosing (BID)	SPD602 50mg/kg/day Once Daily Dosing (QD)	SPD602 75mg/kg/day Once Daily Dosing (QD)
	Started	3	4
Completed	0	3	0
Not completed	3	1	7
Participant decision	-	-	2
Early study termination	3	-	-
Adverse event	-	1	5
Non-compliance	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description:

All randomized subjects

Reporting group values	Overall Study	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	29.2 ± 7.99	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	12	12	

End points

End points reporting groups

Reporting group title	SPD602 50mg/kg/day Twice Daily Dosing (BID)
Reporting group description: Subjects were randomly assigned to 50 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.	
Reporting group title	SPD602 75mg/kg/day Twice Daily Dosing (BID)
Reporting group description: Subjects were randomly assigned to 75 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.	
Reporting group title	SPD602 50mg/kg/day Once (QD) Then Twice Daily Dosing (BID)
Reporting group description: Subjects were randomly assigned to QD dosing then re-enrolled to 50 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.	
Reporting group title	SPD602 75mg/kg/day Once (QD) Then Twice Daily Dosing (BID)
Reporting group description: Subjects were randomly assigned to QD dosing then re-enrolled to 75 mg/kg/day oral BID dosing and continued BID dosing until the end of study (24 weeks) or early discontinuation.	
Reporting group title	SPD602 50mg/kg/day Once Daily Dosing (QD)
Reporting group description: Subjects were randomly assigned to 50 mg/kg/day oral QD dosing and continued QD dosing until the end of study (24 weeks) or early discontinuation.	
Reporting group title	SPD602 75mg/kg/day Once Daily Dosing (QD)
Reporting group description: Subjects were randomly assigned to 75 mg/kg/day oral QD dosing and continued QD dosing until the end of study (24 weeks) or early discontinuation.	
Subject analysis set title	SPD602 50mg/kg/Day
Subject analysis set type	Full analysis
Subject analysis set description: Participants received SPD602 50mg/kg/day oral dosing either twice daily (BID) or once daily (QD), then BID.	
Subject analysis set title	All participants with BID dosing
Subject analysis set type	Full analysis
Subject analysis set description: Of the 21 subjects randomly assigned to BID dosing (including re-enrolled participants), 10 were excluded from the Full Analysis Set. Data for this arm were analyzed to verify that the protocol, as finally amended, was not impacted by using only the lower dose.	

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

End point title	Change From Baseline in Liver Iron Concentration (LIC) as Assessed by FerriScan R2 Magnetic Resonance Imaging (MRI) ^[1]
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. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 subjects. This endpoint analyzed the Full Analysis Set (FAS), defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.	
End point type	Primary

End point timeframe:

Baseline, 12 and 24 weeks

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: Differences for LIC were compared between baseline and post-baseline visits. No between-group comparisons were made as part of this study.

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 12, n=5,10	-3.4 (± 6.4)	-3.8 (± 5)		
Week 24, n=1,2	-5.3 (± 0)	-2.1 (± 4.5)		

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 ^[2]
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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. For participants who had a blood transfusion on the MRI exam date, the blood transfusion done immediately prior to the MRI exam date was included in the calculation of daily transfusion intake. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 subjects. This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type	Primary
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End point timeframe:

Baseline, 12 and 24 weeks

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: Differences for LIC were compared between baseline and post-baseline visits. No between-group comparisons were made as part of this study.

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 12, n=5,10	-6.3 (± 8.4)	-6.6 (± 6.7)		
Week 24, n=1,2	-12.8 (± 0)	-9.3 (± 5)		

Statistical analyses

No statistical analyses for this end point

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

End point title | Change From Baseline in LIC as Assessed by R2* MRI

End point description:

The efficacy of SPD602 was assessed by determining LIC. Abdominal MRI data were collected by using R2* standard procedures (liver and pancreas) and used to determine LIC. A negative change from baseline indicates that LIC decreased. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 subjects.

This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type | Secondary

End point timeframe:

Baseline, 12 and 24 weeks

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 12, n=5,9	-3.2 (± 2.3)	-3.2 (± 2.1)		
Week 24, n=1,2	-2.4 (± 0)	-3.3 (± 1.3)		

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

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 (liver and pancreas) and used to determine LIC. A negative change from baseline indicates that LIC decreased. For participants who had a blood transfusion on the MRI exam date, the blood transfusion done immediately prior to the MRI exam date was included in the calculation of daily transfusion intake. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 subjects.

This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type	Secondary
End point timeframe:	
Baseline, 12 and 24 weeks	

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: mg Fe/g*dw				
arithmetic mean (standard deviation)				
Week 12, n=5,9	-6 (± 4.5)	-6.2 (± 3.2)		
Week 24, n=1,2	-9.9 (± 0)	-10.5 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cardiac T2* Relaxation Rate, an MRI Parameter Used to Estimate Cardiac Iron Load

End point title	Change From Baseline in Cardiac T2* Relaxation Rate, an MRI Parameter Used to Estimate Cardiac Iron Load
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End point description:

The efficacy of SPD602 was assessed by estimating cardiac iron load. T2* data from cardiac MRI were collected by using standard procedures and used as an estimate of cardiac iron load. T2* is an MR relaxation parameter that is reported in milliseconds. Iron within a tissue decreases homogeneity of the magnetic field and shortens the T2* relaxation rate (Anderson, 2001). Low cardiac T2* values are associated with increased risk of heart failure (Kirk, 2009). A negative change from baseline in the T2* relaxation rate indicates that iron load increased. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 subjects.

This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type	Secondary
End point timeframe:	
Baseline, 12 and 24 weeks	

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: milliseconds				
arithmetic mean (standard deviation)				
Week 12, n=5,7	-0.64 (± 3.08)	-0.24 (± 3.91)		

Week 24, n=1,2	-4.1 (\pm 0)	-2.6 (\pm 2.121)		
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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
End point description:	
Serum ferritin levels were determined from serum biochemistry analyses. A negative change from baseline indicates that serum ferritin decreased.	
This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.	
End point type	Secondary
End point timeframe:	
Baseline, 8 and 16 weeks	

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 8, n=5,11	-762.63 (\pm 2100.683)	-568.08 (\pm 1426.687)		
Week 16, n=1,4	586.47 (\pm 0)	137.63 (\pm 972.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Classified as a Responder by FerriScan R2 MRI Analysis of LIC

End point title	Number of Participants Classified as a Responder by FerriScan R2 MRI Analysis of LIC
End point description:	
A responder was defined as a participant whose observed liver iron concentration (LIC) at the measured time point was less than the baseline value. LIC was assessed by abdominal MRI with the FerriScan R2 according to standard procedures. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 participants.	
This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.	

End point type	Secondary
End point timeframe:	
12 and 24 weeks	

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: subjects				
Week 12, n=5,10	4	8		
Week 24, n=1,2	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Classified as a Responder by FerriScan R2 MRI Analysis of LIC Adjusted For Transfusional Iron Intake

End point title	Number of Participants Classified as a Responder by FerriScan R2 MRI Analysis of LIC Adjusted For Transfusional Iron Intake
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End point description:

A responder was defined as a participant whose observed liver iron concentration (LIC) at the measured time point was less than the baseline value. LIC was assessed by abdominal MRI with the FerriScan R2 according to standard procedures, and the results were adjusted for transfusional iron intake. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 participants. For participants who had a blood transfusion on the MRI exam date, the blood transfusion done immediately prior to the MRI exam date was included in the calculation of daily transfusion intake.

This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type	Secondary
End point timeframe:	
12 and 24 weeks	

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: subjects				
Week 12, n=5,10	4	8		
Week 24, n=1,2	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Classified as a Responder by R2* MRI Analysis of LIC

End point title	Number of Participants Classified as a Responder by R2* MRI Analysis of LIC
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End point description:

A responder was defined as a participant whose observed liver iron concentration (LIC) at the measured time point was less than the baseline value. LIC was assessed by abdominal MRI with the R2* according to standard procedures (liver and pancreas). Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 participants.

This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type	Secondary
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End point timeframe:

12 and 24 weeks

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: subjects				
Week 12, n=5,9	5	9		
Week 24, n=1,2	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Classified as a Responder by R2* MRI Analysis of LIC Adjusted For Transfusional Iron Intake

End point title	Number of Participants Classified as a Responder by R2* MRI Analysis of LIC Adjusted For Transfusional Iron Intake
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End point description:

A responder was defined as a participant whose observed liver iron concentration (LIC) at the measured time point was less than the baseline value. LIC was assessed by abdominal MRI with the R2* according to standard procedures (liver and pancreas), and the results were adjusted for transfusional iron intake. Early Termination was within the protocol defined visit date +/- 14 days window and was mapped to next scheduled MRI visit for 3 participants. For participants who had a blood transfusion on the MRI exam date, the blood transfusion done immediately prior to the MRI exam date was included in the calculation of daily transfusion intake.

This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type	Secondary
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End point timeframe:

12 and 24 weeks

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: subjects				
Week 12, n=5,9	5	9		
Week 24, n=1,2	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Classified as a Responder by Serum Ferritin

End point title	Number of Participants Classified as a Responder by Serum Ferritin
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End point description:

A responder was defined as a participant whose observed serum ferritin level at the measured time point was less than the baseline value. Serum ferritin levels were determined from serum biochemistry analyses.

This endpoint analyzed the FAS, defined as all subjects in the Safety Set who had at least 1 post-baseline primary efficacy assessment. The Safety Set was defined as all subjects who had taken at least 1 BID dose of investigational product.

End point type	Secondary
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End point timeframe:

8 and 16 weeks

End point values	SPD602 50mg/kg/Day	All participants with BID dosing		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	11		
Units: subjects				
Week 8, n=5,11	3	8		
Week 16, n=1,4	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

25 weeks

Adverse event reporting additional description:

All safety analyses, including analyses of AEs, were based on the Safety Set, which included subjects in the 50mg/kg/day BID and 75mg/kg/day BID dosing groups who had taken at least 1 BID dose of investigational product. Subjects in the QD only dosing groups were not included in the Safety Set.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	SPD602 50mg/kg/day
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Reporting group description:

Participants received SPD602 50mg/kg/day oral dosing BID either as originally randomized or as a re-enrolled subject.

Reporting group title	SPD602 75mg/kg/Day
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Reporting group description:

Participants received SPD602 75mg/kg/day oral dosing BID either as originally randomized or as a re-enrolled subject.

Serious adverse events	SPD602 50mg/kg/day	SPD602 75mg/kg/Day	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	2 / 7 (28.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SPD602 50mg/kg/day	SPD602 75mg/kg/Day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)	7 / 7 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pallor			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Axillary pain			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Fatigue subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Influenza like illness subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Pyrexia subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 7	1 / 7 (14.29%) 1	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	0 / 7 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3	1 / 7 (14.29%) 1	
Throat irritation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Wheezing			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Anion gap increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Blood urea increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Electrocardiogram T wave abnormal subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
International normalised ratio increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Nitrite urine present subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Red blood cells urine positive subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Urine protein/creatinine ratio increased			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
pH urine increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Injury, poisoning and procedural complications Allergic transfusion reaction subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Congenital, familial and genetic disorders Sickle cell anaemia with crisis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 5	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Headache subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4	2 / 7 (28.57%) 2	
Hypoaesthesia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4	2 / 7 (28.57%) 3	
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Paraesthesia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3	4 / 7 (57.14%) 5	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Constipation subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	3 / 7 (42.86%) 4	

Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Faeces discoloured			
subjects affected / exposed	1 / 12 (8.33%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Frequent bowel movements			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hiatus hernia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Regurgitation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 12 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pruritus allergic			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	2 / 7 (28.57%) 2	
Glycosuria			
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Leukocyturia			
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Polyuria			
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Proteinuria			
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	0 / 7 (0.00%) 0	
Back pain			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 8	1 / 7 (14.29%) 1	
Flank pain			
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Limb discomfort			
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Muscle spasms			
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 2	
Myalgia			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Neck pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	2 / 7 (28.57%) 4	
Sensation of heaviness subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	0 / 7 (0.00%) 0	
Infections and infestations			
Bacteriuria subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Influenza subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	0 / 7 (0.00%) 0	
Rhinitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Tonsillitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 7 (14.29%) 1	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Metabolism and nutrition disorders			
Folate deficiency			

subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2013	<p>Summary of key changes:</p> <ul style="list-style-type: none">- Increased the number of potential sites- Revised the timeframe for non-directive questions to query subjects regarding AEs and the withdrawal criteria for subjects with protocol deviations/violations or related serious AEs- Removed PK serum iron assessment- Clarified the following: number of subjects for BID dosing; Endpoint 3; study population; use of liver and pancreas in R2* MRI; time and nature of end-of-treatment visit; start of screening procedures; subjects who have already consented and provided a DNA sample while under QD dosing were not asked for another; eligibility for another SPD602 study- Changed the following: dosing regimen-QD to BID; Inclusion criteria 3, 7, and 9 and exclusion criterion 3; pre-visit timing of MRIs; baseline period- Updated the following: MRI windows; study design; PK parameters; AE collection window; potential study duration; blood samples for plasma PK assessment; follow-up period for reporting pregnancies- Added the following: cardiac (T2*) iron and left ventricular ejection fraction (LVEF) assessment, neurological examination; Exclusion Criterion 13; LVEF <50% to withdrawal criteria and subjects who are re-randomly assigned from QD to BID dosing will not be re-screened; subsections to explain modified baseline procedures for subjects' re-randomly assigned to BID dosing; subjects who received QD dosing then BID dosing only needed to be re-assessed for Exclusion Criterion 13 and downward dose titration under QD dosing; to footnote b that MRI R2* was to be collected wherever possible; times of serum ferritin measurements; subsections on how to transition subjects on QD to BID dosing- Specified the following: calculation and summary of LVEF and change from baseline to Weeks 12 and 24 by dose group; pancreatic iron concentrations from R2* MRI were to be listed and used as a safety signal; Safety Analysis Set; when subjects should be randomly assigned; time of LVEF
02 October 2013	<p>Summary of key changes:</p> <ul style="list-style-type: none">- Updated Exclusion Criterion 3 with removal of "chronic cholecystitis" to reflect Investigator's Brochure Version 7.0.- Updated Exclusion Criterion 5 with preliminary data from the completed SPD602-104 study that suggested a reduction in elimination of SPD602 in subjects with impaired renal function (estimated glomerular filtration rate <60mL/min, previously <40mL/min).- Clarified that Exclusion Criterion 13 only applied to LVEF below (not outside) the locally determined normal range or in subjects with LVEF <50%.- Clarified that echocardiograph was acceptable to assess LVEF if MRI information was not available.- Added information regarding preliminary data indicating that SPD602 was an inducer of cytochrome P450 2B6 isozyme (CYP2B6) and CYP3A4 in vitro and may have had potential drug interactions with these substrates in vivo.- Amended Primary Endpoint 3 to include LVEF as an example parameter.- Clarified that if a subject did not roll over to BID from QD he or she should have proceeded to the End-of-Treatment/Early Discontinuation Visit.

31 January 2014	<p>Summary of key changes:</p> <ul style="list-style-type: none"> - Changed title to reflect single treatment-arm analysis. - Specified sample size to enroll approximately 50 subjects to reach approximately 25 evaluable subjects enrolled at 50mg/kg/day administered BID dosing. - Adjusted objectives to reflect single treatment-arm analysis. - Removed the 75mg/kg/day treatment-arm to reflect single treatment-arm study and adjusted objectives, statistical endpoints, and analysis accordingly. - Changed the maximum dosage allowed from 75 to 50mg/kg/day. - Confirmed that subjects who were randomly assigned to 75mg/kg/day under the prior protocol version should immediately have their doses titrated downward to a total daily dose of 50mg/kg. - Added safety laboratory tests to screen for any underlying metabolic abnormalities that could have contributed to the development of suspected PN-related events. - Added guidance for evaluation of suspected PN-related events (including paresthesia and/or hypoesthesia) by investigators. Updated statistical endpoints and analysis to reflect single treatment-arm study design. - Added PN to AEs for management of study toxicities. - Clarified wording for AEs of potential interest in the event that subjects reported suspected PN-related events (including paresthesia or hypoesthesia). - Allowed pharmacokinetic assessment to be conducted starting at Week 4.
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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: