Clinical trial results:
A Phase 2, Open-label, Multicentre, Extension Safety and Tolerability Study for Transfusionally Iron Overloaded Children, Adolescents and Adults Using SSP-004184 (SPD602)

Summary

EudraCT number	2011-006322-25
Trial protocol	GB IT
Global end of trial date	24 April 2014

Results information

Result version number	v1 (current)
This version publication date	03 October 2018
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	SPD602-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01671111
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, 1 866-842-5335,
Scientific contact	Study Physician, Shire, 1 866-842-5335,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To measure the extent and durability of SSP-004184AQ (SPD602) treatment effects
2. To assess the safety, tolerability and efficacy of SSP-004184AQ in subjects who received SSP-004184AQ in a prior SSP-004184AQ study
3. To allow access and assess response to SSP-004184AQ in subjects randomized to another chelation therapy in a prior SSP-004184AQ study.

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 August 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	Canada: 7
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	30
EEA total number of subjects	15

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)	2

Adolescents (12-17 years)	8
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects received SSP-004184AQ with last available data during end of treatment visit in feeder studies SPD602-201(NCT01186419), SPD602-202(NCT01363908) and SPD602-203(NCT01604941), those not transitioned but fulfilled screening criteria in their respective feeder studies, and who had normal liver iron/serum ferritin levels, were included.

Pre-assignment

Screening details:

A total of 30 subjects were enrolled to this open-label extension study (24 subjects transferred directly from feeder studies SPD602-201 [NCT01186419], SPD602-202 [NCT01363908], and SPD602-203 [NCT01604941] and 6 subjects did not transfer directly and received a chelator other than SSP-004184 after discontinuation from a feeder study).

Period 1

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

Arms

Arm title	SSP-004184AQ

Arm description:

Subjects received SSP-004184AQ (magnesium salt of free acid or active form, that is, SSP-004184 [SPD602, FBS0701]) capsules orally at a total daily dose of 8-75 milligram per kilogram per day (mg/kg/day) (equivalent to SSP-004184 7-68 mg/kg/day) either once daily or twice daily at the discretion of investigator for up to a maximum of 3 years or until the sponsor decided to stop the study.

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

Dosage and administration details:

Subjects received SSP-004184AQ (magnesium salt of free acid or active form, that is, SSP-004184 [SPD602, FBS0701]) capsules orally at a total daily dose of 8-75 mg/kg/day (equivalent to SSP-004184 7-68 mg/kg/day) either once daily or twice daily at the discretion of investigator for up to a maximum of 3 years or until the sponsor decided to stop the study.

Number of subjects in period 1	SSP-004184AQ
Started	30
Completed	0
Not completed	30
Physician decision	1
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Unspecified	24
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	SSP-004184AQ

Reporting group description:

Subjects received SSP-004184AQ (magnesium salt of free acid or active form, that is, SSP-004184 [SPD602, FBS0701]) capsules orally at a total daily dose of 8-75 milligram per kilogram per day (mg/kg/day) (equivalent to SSP-004184 7-68 mg/kg/day) either once daily or twice daily at the discretion of investigator for up to a maximum of 3 years or until the sponsor decided to stop the study.

Reporting group values	SSP-004184AQ	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 25.5 ± 11.38	 -	
Gender Units: Subjects			
Female	17	17	
Male	13	13	

End points

End points reporting groups

Reporting group title	SSP-004184AQ

Reporting group description:

Subjects received SSP-004184AQ (magnesium salt of free acid or active form, that is, SSP-004184 [SPD602, FBS0701]) capsules orally at a total daily dose of 8-75 milligram per kilogram per day (mg/kg/day) (equivalent to SSP-004184 7-68 mg/kg/day) either once daily or twice daily at the discretion of investigator for up to a maximum of 3 years or until the sponsor decided to stop the study.

Primary: Change From Baseline in Ferriscan® R2 Liver Iron Concentrations (LIC) at Week 24 (Cycle 1)

End point title	Change From Baseline in Ferriscan® R2 Liver Iron Concentrations (LIC) at Week 24 (Cycle 1)[1]

End point description:

Efficacy of SSP-004184 was assessed by determining LIC. Abdominal magnetic resonance imaging (MRI) data were collected by using FerriScan R2 standard procedures and used to determine LIC. A negative change from baseline indicates that LIC decreased. A cycle consisted of 8 standard 6-weekly visits and the cycles were repeated each year for the duration of the study.
Full analysis set (FAS) included all subjects in the Safety set (all subjects who had taken at least 1 dose of study drug) who had at least 1 post-baseline primary efficacy assessment. Here, 'n' signifies the number of FAS subjects evaluable for the respective time points.

End point type	Primary

End point timeframe:

Baseline, Week 24 (Cycle 1)

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: EudraCT database does not allow reporting statistical analysis for a single reporting group. Due to this format constraint, charts have been uploaded with the accurate details of statistical analysis for this endpoint. Please find the statistical analysis in the attachment below.

End point values	SSP-004184AQ			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: milligram per gram (mg/g) dry tissue				
arithmetic mean (standard deviation)				
Baseline (n=23)	9.9 (± 8.1)			
Change at Week 24 (Cycle 1) (n=13)	-1.1 (± 1.86)			

Attachments (see zip file)	Statistical Analyses_Primary_LIC_W24 (C1)/SPD602-

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Ferriscan® R2 Liver Iron Concentrations (LIC) at Week 48 (Cycle 1)

End point title	Change From Baseline in Ferriscan® R2 Liver Iron

	Concentrations (LIC) at Week 48 (Cycle 1)[2]

End point description:

Efficacy of SSP-004184 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. A cycle consisted of 8 standard 6-weekly visits and the cycles were repeated each year for the duration of the study.
FAS subjects evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 48 (Cycle 1)

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: EudraCT database does not allow reporting statistical analysis for a single reporting group. Due to this format constraint, charts have been uploaded with the accurate details of statistical analysis for this endpoint. Please find the statistical analysis in the attachment below.

End point values	SSP-004184AQ			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: mg/g dry tissue				
arithmetic mean (standard deviation)	-1 (± 1.68)			

Attachments (see zip file)	Statistical Analyses_Primary_LIC_W48 (C1)/SPD602-

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Ferriscan® R2 Liver Iron Concentrations (LIC) at Week 24 (Cycle 2)

End point title	Change From Baseline in Ferriscan® R2 Liver Iron Concentrations (LIC) at Week 24 (Cycle 2)[3]

End point description:

Efficacy of SSP-004184 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. A cycle consisted of 8 standard 6-weekly visits and the cycles were repeated each year for the duration of the study.
FAS subjects evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 24 (Cycle 2)

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: EudraCT database does not allow reporting statistical analysis for a single reporting group. Due to this format constraint, charts have been uploaded with the accurate details of statistical analysis for this endpoint. Please find the statistical analysis in the attachment below.

End point values	SSP-004184AQ			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mg/g dry tissue				
arithmetic mean (standard deviation)	-1.5 (± 2.23)			

Attachments (see zip file)	Statistical Analyses_Primary_LIC_W24 (C2)/SPD602-

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Cardiac T2* Values at Week 24 (Cycle 1)

End point title	Change From Baseline in Cardiac T2* Values at Week 24 (Cycle 1)[4]

End point description:

The efficacy of SSP-004184 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. A cycle consisted of 8 standard 6-weekly visits and the cycles were repeated each year for the duration of the study.
FAS. Here, 'n' signifies the number of FAS subjects evaluable for the respective time points.

End point type	Primary

End point timeframe:

Baseline, Week 24 (Cycle 1)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT database does not allow reporting statistical analysis for a single reporting group. Due to this format constraint, charts have been uploaded with the accurate details of statistical analysis for this endpoint. Please find the statistical analysis in the attachment below.

End point values	SSP-004184AQ			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: milliseconds				
arithmetic mean (standard deviation)				
Baseline (n=23)	35.14 (± 12.242)			
Change at Week 24 (Cycle 1) (n=14)	-0.41 (± 8.069)			

Attachments (see zip file)	Statistical Analyses_Primary_Cardiac_W24 (C1)/SPD602-

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Cardiac T2* Values at Week 48 (Cycle 1)

End point title	Change From Baseline in Cardiac T2* Values at Week 48 (Cycle 1)[5]

End point description:

The efficacy of SSP-004184 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. A cycle consisted of 8 standard 6-weekly visits and the cycles were repeated each year for the duration of the study.
FAS subjects evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 48 (Cycle 1)

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: EudraCT database does not allow reporting statistical analysis for a single reporting group. Due to this format constraint, charts have been uploaded with the accurate details of statistical analysis for this endpoint. Please find the statistical analysis in the attachment below.

End point values	SSP-004184AQ			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: milliseconds				
arithmetic mean (standard deviation)	-3.47 (± 9.619)			

Attachments (see zip file)	Statistical Analyses_Primary_Cardiac_W48 (C1)/SPD602-

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Cardiac T2* Values at Week 24 (Cycle 2)

End point title	Change From Baseline in Cardiac T2* Values at Week 24 (Cycle 2)[6]

End point description:

The efficacy of SSP-004184 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. A cycle consisted of 8 standard 6-weekly visits and the cycles were repeated each year for the duration of the study.
FAS subjects evaluable for this outcome.

End point type	Primary

End point timeframe:

Baseline, Week 24 (Cycle 2)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT database does not allow reporting statistical analysis for a single reporting group. Due to this format constraint, charts have been uploaded with the accurate details of statistical analysis for this endpoint. Please find the statistical analysis in the attachment below.

End point values	SSP-004184AQ			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: milliseconds				
arithmetic mean (standard deviation)	-3.91 (± 5.551)			

Attachments (see zip file)	Statistical Analyses_Primary_Cardiac_W24 (C2)/SPD602-

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Serum Ferritin Values at Specified Visits

End point title	Change from Baseline in Serum Ferritin Values at Specified Visits

End point description:

A negative change from baseline indicates that serum ferritin decreased. A cycle consisted of 8 standard 6-weekly visits and the cycles were repeated each year for the duration of the study.
FAS. Here, 'n' signifies the number of FAS subjects evaluable for the respective time points.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24 and 48 of Cycle 1, Week 24 of Cycle 2

End point values	SSP-004184AQ			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: nanogram per milliliter				
arithmetic mean (standard deviation)				
Baseline (n=23)	5353.38 (± 4588.423)			
Change at Week 24 (Cycle 1) (n=12)	-395.82 (± 569.305)			
Change at Week 48 (Cycle 1) (n=9)	-250.87 (± 452.327)			
Change at Week 24 (Cycle 2) (n=7)	-384.03 (± 649.99)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to the end of study (1 week after the end of treatment)

Adverse event reporting additional description:

An adverse event (AE) that occurred during the study was considered a treatment-emergent AE (TEAE) if it had a start date and time on or after the study treatment or if it had a start date before the date and time of the study treatment but increased in intensity on or after the date and time of the study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	SSP-004184AQ

Reporting group description:

Subjects received SSP-004184AQ (magnesium salt of free acid or active form, that is, SSP-004184 [SPD602, FBS0701]) capsules orally at a total daily dose of 8-75 mg/kg/day (equivalent to SSP-004184 7-68 mg/kg/day) either once daily or twice daily at the discretion of investigator for up to a maximum of 3 years or until the sponsor decided to stop the study.

Serious adverse events	SSP-004184AQ		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SSP-004184AQ		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 30 (83.33%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Asthenia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	5		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 6 2 / 30 (6.67%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3 5 / 30 (16.67%) 6 2 / 30 (6.67%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2012	Due to an error in the study phase numbering, the study phase was amended from Phase 3 to Phase 2.
30 April 2013	1. SPD602-301 replaces FBS0701-CTP-15 2. Updated selection of study population, study assessments 3. Updated the description of the study design to allow entry (further to meeting all qualification criteria) of subjects who were unable to transition directly into this extension study due to administrative reasons, and who had initiated treatment with a chelator other than SSP-004184 4. Replaced glucose intolerance test with fasting glucose test 5. Added pharmacokinetic parameters to the study objectives 6. Updated the description of the study period and timelines 7. Added information regarding adverse events (AEs) of particular interest including paresthesia and hypoesthesia and extended neurological examinations 8. Updated Inclusion and exclusion criteria for subjects who did not transition directly from their feeder protocol 9. Updated the description of the study period and timelines to include timelines for qualification for subjects who did not transition directly from their feeder protocol and who had initiated treatment with a chelator other than SSP-004184 10. Qualified that the measurable data demonstrating qualification into the extension study were to be taken from the end of treatment visit from the feeder protocol for those subjects who transitioned directly from their feeder protocol only 11. Updated the follow-up period from 30 days to 7 days 12. Added withdrawal criteria: Cardiac left ventricular ejection fraction (LVEF) <50% 13. Updated the management of study toxicities section 14. Inserted endocrine laboratory tests for subjects 10 years and over who enrolled in their feeder protocol <18-years old, visual acuity test and eye examination for all subjects 15. Amended the timing of AE and serious AE collection to detail that AEs were to be recorded from the time of signed informed consent until 7 days after the last dosing 16. Added data monitoring committee

22 October 2013	1. Clarified that echocardiography was acceptable for LVEF if MRI information was not available 2. To replace extended neurological examinations with total neuropathy score nurse (TNSn) assessments at Qualification and Enrolment, Visits 4, 8, and end of treatment/early discontinuation 3. Subjects who had either completed 1 of the previous feeder studies or who discontinued (with agreement from the investigator and Shire physician) and who met qualification criteria were permitted to enrol subjects who had either completed a previous SSP-004184AQ study or prematurely discontinued 1 of the SSP-004184AQ studies (with agreement from the investigator and Shire physician) were permitted to enrol 4. Subjects who had either completed a previous SSP-004184AQ study or prematurely discontinued 1 of the SSP-004184AQ studies (with agreement from the investigator and Shire physician) were permitted to enrol 5. Excluded subjects with cardiac T2* MRI <10.0 milliseconds (from <8msec), LVEF below the locally determined normal range or LVEF <50% at baseline testing by MRI or echocardiography 6. "Chronic cholecystitis" was no longer exclusionary 7. Subjects were to be withdrawn from the study and classified as treatment failures if they continued to accumulate iron based on cardiac iron concentration determined by MRI 8. Replaced previous AE severity assessment with those reflecting National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 criteria 9. Added statement indicating that Qualification and Enrollment physical examination, TNSn and ECG are required if assessment was not completed at the last feeder study visit (as well as for subjects who did not transition directly from their feeder protocol)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 March 2014	The SPD-602 development program was placed on clinical hold in March 2014. This clinical hold was a result of data from a 104-week rat carcinogenicity study that demonstrated an increased incidence of renal tubular adenomas and carcinomas in male rats. The relevance of these finding to humans, if any, was unknown. However, Shire continued to take appropriate measures to further assess these results. Investigators and relevant regulatory authorities were informed and a comprehensive surveillance program was implemented to monitor safety in subjects who participated in SPD602 studies. Because of the interruption in treatment with SPD602 and the inability at the time to draw definitive conclusions regarding the relevance of the rat findings to humans, ongoing clinical studies were terminated in July 2014.	-

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 due to non-clinical safety results. Not all subjects completed the study. The available efficacy data were analyzed as specified in the statistical analysis plan; however, no efficacy conclusions were drawn.

Notes: