



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 | 25.5 | | |
| standard deviation | ± 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 |
|-----------------|--|

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 | | |

| | | | |
|---|------------------|--|--|
| 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) | 4 / 30 (13.33%) 6 | | |
| Cough subjects affected / exposed occurrences (all) | 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) | 3 / 30 (10.00%) 3 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 30 (16.67%) 6 | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 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 | <ol style="list-style-type: none">1. SPD602-301 replaces FBS0701-CTP-152. Updated selection of study population, study assessments3. 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-0041844. Replaced glucose intolerance test with fasting glucose test5. Added pharmacokinetic parameters to the study objectives6. Updated the description of the study period and timelines7. Added information regarding adverse events (AEs) of particular interest including paresthesia and hypoesthesia and extended neurological examinations8. Updated Inclusion and exclusion criteria for subjects who did not transition directly from their feeder protocol9. 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-00418410. 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 only11. Updated the follow-up period from 30 days to 7 days12. Added withdrawal criteria: Cardiac left ventricular ejection fraction (LVEF) <50%13. Updated the management of study toxicities section14. 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 subjects15. 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 dosing16. Added data monitoring committee |

| | |
|-----------------|--|
| 22 October 2013 | <ol style="list-style-type: none"> 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:

