Clinical trial results:
A Phase 3, Open-label, Multicentre Study to Provide Access to Guanfacine Hydrochloride Extended-release for European Subjects with Attention-deficit/Hyperactivity Disorder (ADHD) who Participated in Study SPD503-315 or SPD503-316

Summary

EudraCT number	2011-004668-31
Trial protocol	GB DE SE AT ES IE BE IT NL PL
Global end of trial date	15 September 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	SPD503-318

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01500694
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Pharmaceutical Development Ltd.
Sponsor organisation address	Hampshire International Business Park Chineham, Basingstoke, Hampshire, United Kingdom, RG24 8EP
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	15 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term safety and tolerability of SPD503.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Ukraine: 41
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	215
EEA total number of subjects	174

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)	110
Adolescents (12-17 years)	100
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 52 sites in 11 countries in Europe: Austria, Belgium, France, Germany, Italy, The Netherlands, Poland, Romania, Spain, Ukraine, and United Kingdom.

Pre-assignment

Screening details:

Of 218 subjects screened, 215 subjects were enrolled:131 subjects aged 6-12 years and 84 subjects aged 13-18 years. Among them 214 subjects received treatment, of which 133 subjects completed the study. The first subject's consent was obtained on 20 March 2012 and the last subject assessment took place on 15 September 2015.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SPD503 (6-12 years)

Arm description:

Subjects aged 6-12 years received extended-release guanfacine hydrochloride (SPD503) one tablet (1 x 1 milligram [mg] or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.

Arm type	Experimental
Investigational medicinal product name	Extended-release guanfacine hydrochloride
Investigational medicinal product code	SPD503
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received extended-release guanfacine hydrochloride (SPD503) one tablet (1-4mg) or two tablets (5-7 mg) once daily.

Arm title	SPD503 (13-18 years)

Arm description:

Subjects aged 13-18 years received extended-release Guanfacine hydrochloride (SPD503) one tablet (1 x 1 mg or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.

Arm type	Experimental
Investigational medicinal product name	Extended-release guanfacine hydrochloride
Investigational medicinal product code	SPD503
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received extended-release guanfacine hydrochloride (SPD503) one tablet (1-4mg) or two tablets (5-7 mg) once daily.

Number of subjects in period 1[1]	SPD503 (6-12 years)	SPD503 (13-18 years)
Started	131	83
Subjects Received Treatment	131	83
Completed	79	54
Not completed	52	29
Consent withdrawn by subject	23	14
Protocol violation	-	1
Adverse event	4	3
Unspecified	9	3
Lost to follow-up	2	3
Lack of efficacy	14	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all the subjects reported in the baseline period were treated with the study drug, that is the reason the worldwide number enrolled is not the same as the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	SPD503 (6-12 years)
Reporting group description:	
Subjects aged 6-12 years received extended-release guanfacine hydrochloride (SPD503) one tablet (1 x 1 milligram [mg] or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.	
Reporting group title	SPD503 (13-18 years)
Reporting group description:	
Subjects aged 13-18 years received extended-release Guanfacine hydrochloride (SPD503) one tablet (1 x 1 mg or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.	

Reporting group values	SPD503 (6-12 years)	SPD503 (13-18 years)	Total
Number of subjects	131	83	214
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	9.8	14.7	
standard deviation	± 1.56	± 1.49	-
Gender, Male/Female Units: subjects			
Female	26	30	56
Male	105	53	158

End points

End points reporting groups

Reporting group title	SPD503 (6-12 years)
Reporting group description:	
Subjects aged 6-12 years received extended-release guanfacine hydrochloride (SPD503) one tablet (1 x 1 milligram [mg] or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.	
Reporting group title	SPD503 (13-18 years)
Reporting group description:	
Subjects aged 13-18 years received extended-release Guanfacine hydrochloride (SPD503) one tablet (1 x 1 mg or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.	

Primary: Change from Baseline in Mean Systolic Blood Pressure at Final Assessment

End point title	Change from Baseline in Mean Systolic Blood Pressure at Final Assessment[1]
End point description:	
Systolic Blood pressure was measured at supine and standing position and mean supine systolic blood pressure was reported here. Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ Early Terminatino [ET]/Day 714). Safety Analysis Set includes all enrolled subjects who took at least 1 dose of SPD503. Here, n = number of subjects analysed for the specific categories for each arm respectively.	
End point type	Primary
End point timeframe:	
Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)	

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: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	83		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n = 131, 83)	107.5 (± 8.73)	113.5 (± 9.23)		
Change at Final Assessment (n = 130, 82)	0.9 (± 9.35)	0.3 (± 9.32)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Mean Diastolic Blood Pressure at Final Assessment

End point title	Change From Baseline in Mean Diastolic Blood Pressure at Final Assessment[2]

End point description:

Diastolic Blood pressure was measured at supine and standing position and mean supine diastolic blood pressure was reported here. Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714). Safety Analysis Set includes all enrolled subjects who took at least 1 dose of SPD503. Here, n = number of subjects analysed for the specific categories for each arm respectively.

End point type	Primary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

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: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	83		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=131, 83)	64.3 (± 8.12)	66.8 (± 9.14)		
Change at Final Assessment (n = 130, 82)	0.2 (± 8.96)	0.1 (± 9.55)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Mean Supine Pulse at Final Assessment

End point title	Change From Baseline in Mean Supine Pulse at Final Assessment[3]

End point description:

Pulse was measured at supine and standing position and mean supine pulse was reported here. Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714). Safety Analysis Set includes all enrolled subjects who took at least 1 dose of SPD503. Here, n = number of subjects analysed for the specific categories for each arm respectively.

End point type	Primary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

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: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	83		
Units: beats per minute(bpm)				
arithmetic mean (standard deviation)				
Baseline (n = 131, 83)	79.3 (± 11.17)	72.1 (± 9.91)		
Change at Final Assessment (n=130, 82)	-7.1 (± 13.52)	-2.9 (± 11.71)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Mean Height at Final Assessment

End point title	Change From Baseline in Mean Height at Final Assessment[4]

End point description:

Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714). Safety Analysis Set included all enrolled subjects who took at least 1 dose of SPD503. Here, n = number of subjects analysed for the specific categories for each arm respectively.

End point type	Primary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

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: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	83		
Units: centimeter (cm)				
arithmetic mean (standard deviation)				
Baseline (n = 131, 83)	142.03 (± 10.916)	166.32 (± 9.274)		
Change at Final Assessment (n = 128, 79)	8.8 (± 5.075)	5.54 (± 5.491)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Mean Weight at Final Assessment

End point title	Change From Baseline in Mean Weight at Final Assessment[5]

End point description:

Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714). Safety Analysis Set included all enrolled subjects who took at least 1 dose of SPD503. Here, n = number of subjects analysed for the specific categories for each arm respectively.

End point type	Primary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

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: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	83		
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline (n = 131, 83)	37.29 (± 9.256)	58.53 (± 11.478)		
Change at Final Assessment (n = 128, 79)	8.96 (± 5.886)	6.74 (± 5.859)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Electrocardiogram Result (QRS interval) at Final Assessment

End point title	Change From Baseline in Electrocardiogram Result (QRS interval) at Final Assessment[6]

End point description:

Safety Analysis Set included all enrolled subjects who took at least 1 dose of SPD503. Here, n = number of subjects analysed for the specific categories for each arm respectively. Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714).

End point type	Primary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

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: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	83		
Units: millisecond (ms)				
arithmetic mean (standard deviation)				
Baseline (n=131, 83)	84.9 (± 7.72)	89.7 (± 6.22)		
Change at Final Assessment (n=127, 77)	1.8 (± 6)	1.8 (± 6.16)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Electrocardiogram Result (QT interval) at Final Assessment

End point title	Change From Baseline in Electrocardiogram Result (QT interval) at Final Assessment[7]

End point description:

Safety Analysis Set included all enrolled subjects who took at least 1 dose of SPD503. Here, n = number of subjects analysed for the specific categories (Visit 19/ET/Day 714). Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication. Here, n = number of subjects analysed for the specific categories for each arm respectively.

End point type	Primary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	83		
Units: millisecond (ms)				
arithmetic mean (standard deviation)				
Baseline (n = 131, 83)	361.4 (± 21.4)	375.9 (± 24.93)		
Change at Final Assessment (n = 127, 77)	16.9 (± 27.87)	9.5 (± 29.93)		

Statistical analyses

No statistical analyses for this end point

Primary: Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Columbia-Suicide Severity Rating Scale (C-SSRS)[8]

End point description:

C-SSRS is a semi-structured interview that captures the occurrence, severity and frequency of suicide-related thoughts and behaviours during the assessment period.There is a maximum of 19 items to be completed: 7 that are required, 10 potential additional items if there is a positive response to a required item and 2 items for suicide/suicide behaviour present during the interview. Final Assessment is last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714). Safety Analysis Set included all enrolled subjects who took at least 1 dose of SPD503 with number of subjects evaluable for this end point only. One subject aged 6-12 years responded "yes" to the suicidal ideation category of "wish to be dead" while not on treatment (at the end of treatment visit, after his last dose).

End point type	Primary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

Notes:

[8] - 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: Only descriptive analysis were performed, inferential statistics were not performed.

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	82		
Units: subjects				
number (not applicable)				
Suicidal Ideation: Wish to Dead	2	1		
Suicidal Ideation: Non-specific Suicidal Thoughts	2	0		
Suicidal Behaviour: Non-suicidal Self-injurious	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Attention deficit and Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV)- Total Score at Final Assessment

End point title	Change From Baseline in Attention deficit and Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV)- Total Score at Final Assessment

End point description:

ADHD-RS-IV was developed to measure the behaviours of children with ADHD with 18 items. Each item is scored from a range of 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0-54. The 18 items may be grouped into 2 sub-scales: hyperactivity/impulsivity (even numbered items 2-18) and inattentiveness (odd numbered items 1-17) with possible score range from 0 (no symptoms) to 27 (most severe symptoms). The ADHD-RS-IV possible total scores range from 0 (no symptoms) to 54 (most severe symptoms). Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714). Full Analysis Set included enrolled subjects who took at least 1 dose of SPD503, excluding subjects from site 403. Here, n = number of subjects analysed for the specific categories for each arm respectively.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	81		
Units: units on a scale				
arithmetic mean (standard error)				
Baseline (n = 127, 81)	40 (± 0.78)	31.2 (± 1.19)		
Change at Final Assessment (n = 126, 80)	-20.2 (± 1.1)	-19.3 (± 1.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects assessed with Clinical Global Impression - Severity of Illness (CGI-S) Scale

End point title	Number of subjects assessed with Clinical Global Impression - Severity of Illness (CGI-S) Scale

End point description:

The CGI-S evaluate each subject's severity and improvement over time. The severity of a subject's condition is rated on a 7-point scale ranging from 1 to 7. The scale measures 0= Not assessed, 1 = Normal, not at all ill, 2 = Borderline mentally ill (BL-MI), 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Among the most extremely ill subjects. Final Assessment is the last valid assessment obtained after Baseline (Visit 2/Day 0) whilst on investigational product and before first dose taper medication (Visit 19/ET/Day 714). Full Analysis Set included enrolled subjects who took at least 1 dose of SPD503, excluding subjects from site 403. Here, n = number of subjects analysed for the specific categories for each arm respectively.

End point type	Secondary

End point timeframe:

Baseline (Day 0) and Final Assessment (last non missing data/up to Day 714)

End point values	SPD503 (6-12 years)	SPD503 (13-18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	81		
Units: subjects				
number (not applicable)				
Baseline: Normal/BL-MI (n=127, 81)	0	2		
Baseline: Mildly ill or greater (n=127, 81)	127	79		
Final assessment:Normal/BL-MI(n=127,80)	45	51		
Final Asesment:Mildly ill or greater(n=127,80)	82	29		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of the study drug administration up to 10 days after the last dose of study drug administration

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	SPD503 (6-12 years)

Reporting group description:

Subjects aged 6-12 years received extended-release guanfacine hydrochloride (SPD503) one tablet (1 x 1 mg or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.

Reporting group title	SPD503 (13-18 years)

Reporting group description:

Subjects aged 13-18 years received extended-release guanfacine hydrochloride (SPD503) one tablet (1 x 1 mg or 2 mg or 3 mg or 4mg) or two tablets (1 x 2+3 mg or 1 x 2+4 mg, 1 x 3+4 mg) once daily for up to 2 years.

Serious adverse events	SPD503 (6-12 years)	SPD503 (13-18 years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 131 (6.11%)	2 / 83 (2.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	2 / 131 (1.53%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 131 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius fracture			
subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 131 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 131 (0.76%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 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	SPD503 (6-12 years)	SPD503 (13-18 years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 131 (77.86%)	55 / 83 (66.27%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 131 (9.16%)	9 / 83 (10.84%)	
occurrences (all)	16	10	
Headache			
subjects affected / exposed	38 / 131 (29.01%)	23 / 83 (27.71%)	
occurrences (all)	91	43	
Somnolence			
subjects affected / exposed	50 / 131 (38.17%)	27 / 83 (32.53%)	
occurrences (all)	81	37	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 131 (22.90%)	13 / 83 (15.66%)	
occurrences (all)	43	15	
Pyrexia			
subjects affected / exposed	8 / 131 (6.11%)	2 / 83 (2.41%)	
occurrences (all)	9	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 131 (6.87%)	4 / 83 (4.82%)	
occurrences (all)	11	4	
Abdominal pain upper			
subjects affected / exposed	8 / 131 (6.11%)	2 / 83 (2.41%)	
occurrences (all)	11	2	
Diarrhoea			

subjects affected / exposed	7 / 131 (5.34%)	3 / 83 (3.61%)	
occurrences (all)	8	3	
Nausea			
subjects affected / exposed	12 / 131 (9.16%)	2 / 83 (2.41%)	
occurrences (all)	15	2	
Vomiting			
subjects affected / exposed	8 / 131 (6.11%)	3 / 83 (3.61%)	
occurrences (all)	12	4	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	7 / 131 (5.34%)	4 / 83 (4.82%)	
occurrences (all)	8	5	
Psychiatric disorders			
Aggression			
subjects affected / exposed	7 / 131 (5.34%)	2 / 83 (2.41%)	
occurrences (all)	7	2	
Insomnia			
subjects affected / exposed	10 / 131 (7.63%)	6 / 83 (7.23%)	
occurrences (all)	10	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 131 (5.34%)	18 / 83 (21.69%)	
occurrences (all)	14	24	
Rhinitis			
subjects affected / exposed	8 / 131 (6.11%)	3 / 83 (3.61%)	
occurrences (all)	11	3	
Upper respiratory tract infection			
subjects affected / exposed	9 / 131 (6.87%)	4 / 83 (4.82%)	
occurrences (all)	16	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2011	-It was clarified that adolescent subjects aged greater than equal (>=) 13 years enrolling from Study SPD503-316 (2010-018579-12) must have completed 13 weeks of double-blind treatment in study SPD503-316 (2010-018579-12). -Sentences that limited dose reduction to only 1 reduction during the study were removed.
10 January 2012	-The primary and secondary objectives were revised. -The rationale and study design were clarified to align with the revised primary and secondary objectives. -Text was added to clarify visit windows for Visits 18 and 19 (Schedule of Assessments). -The number of days between Visit 18 and Visit 19 was revised to 98 days to be consistent with the 14 weeks between these visits. -The total days listed for Visits 20 and 21 was revised. -Urine pregnancy test for all female subjects of childbearing potential at Visit 6 and Visits 10-18 was added. -Bands were removed from hematology assessments. -The days provided in Table 6 (dose tapering schedule) were revised from Days 700-714 to Days 714-728.
29 January 2013	-Serious adverse events (SAE), pregnancy, and product quality complaint reporting language was updated. -The number of expected sites was updated. -It was clarified when the screening visit for this study could occur in relation to the antecedent study. -Inclusion criteria were revised for subjects enrolling from antecedent study SPD503-315 (2009-018161-12) and SPD503-316 (2010-018579-12). -Wash period of 30 days was deleted from Investigational compounds. -A minimum washout" was deleted from Investigational compounds to be consistent with the rest of the table. -With the exception of investigational product taken in Study SPD503-315 (2009-018161-12) which only required a 7-day washout prior to the baseline visit (Visit 2)" was deleted from alpha (α) 2-adrenergic agonists. -Electrocardiogram (ECGs) was deleted from screening visit. -Information on the planned data cut for regulatory authority submission purposes was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported