EU Clinical Trials Register

Clinical trial results:
A Phase 3, Double-blind, Randomized, Multi-center, Placebo controlled, Dose-optimization Study Evaluating the Safety, Efficacy, and Tolerability of Once daily Dosing with Extended-release Guanfacine Hydrochloride in Adolescents Aged 13-17 years Diagnosed With Attention-deficit/Hyperactivity Disorder (ADHD)

Summary

EudraCT number	2011-002221-21
Trial protocol	Outside EU/EEA
Global end of trial date	16 May 2013

Results information

Result version number	v2 (current)
This version publication date	25 November 2018
First version publication date	06 December 2014
Version creation reason	• Correction of full data set Update actual start date of recruitment

Trial information

Trial identification

Sponsor protocol code	SPD503-312

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01081132
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Blvd., Wayne, United States, 19087
Public contact	Study Physician, Shire Development LLC, +1 866-842-5335 ,
Scientific contact	Study Physician, Shire Development LLC, +1 866-842-5335 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000745-PIP01-09
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	16 May 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2013
Global end of trial reached?	Yes
Global end of trial date	16 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of once daily dosing with optimized SPD503 compared with placebo in the treatment of adolescents aged 13-17 years with a diagnosis of ADHD as measured by the Attention deficit/Hyperactivity Disorder Rating Scale (ADHD-RS-IV).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation of 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	19 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 314
Worldwide total number of subjects	314
EEA total number of subjects	0

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)	314
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	314
Number of subjects completed	314

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Orally administered a once-daily dose

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Orally administered a once-daily dose

Arm title	SPD503

Arm description:

Orally administered a once-daily optimal dose between 0.05 mg/kg/day - 0.12 mg/kg/day (up to 7 mg/day depending on weight).

Arm type	Experimental
Investigational medicinal product name	Guanfacine Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Orally administered a once-daily optimal dose between 0.05 mg/kg/day - 0.12 mg/kg/day (up to 7 mg/day depending on weight).

Number of subjects in period 1	Placebo	SPD503
Started	157	157
Completed	102	105
Not completed	55	52
Patient did not complete wk 14 and 15	-	1
Consent withdrawn by subject	13	16
Missed visits	1	1
Adverse event, non-fatal	3	9
Non-compliance	4	3
Stopped taking meds	2	-
Lost to follow-up	4	11
Declined taper phase	-	1
Lack of efficacy	25	9
Protocol deviation	3	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Orally administered a once-daily dose	
Reporting group title	SPD503
Reporting group description:	
Orally administered a once-daily optimal dose between 0.05 mg/kg/day - 0.12 mg/kg/day (up to 7 mg/day depending on weight).	

Reporting group values	Placebo	SPD503	Total
Number of subjects	157	157	314
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	157	157	314
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	14.6	14.5	
standard deviation	± 1.44	± 1.35	-
Gender categorical			
Units: Subjects			
Female	57	54	111
Male	100	103	203

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Orally administered a once-daily dose	
Reporting group title	SPD503
Reporting group description:	
Orally administered a once-daily optimal dose between 0.05 mg/kg/day - 0.12 mg/kg/day (up to 7 mg/day depending on weight).	

Primary: Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 13

End point title	Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 13
End point description:	
The ADHD-RS-IV consists of 18 items scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms) with total score ranging from 0 to 54. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.	
End point type	Primary
End point timeframe:	
Baseline through week 13	

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	109		
Units: Units on a scale				
least squares mean (standard error)	-18.527 (± 1.0841)	-24.552 (± 1.0625)		

Statistical analyses

Statistical analysis title	Change From Baseline in ADHD-RS-IV Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.865
upper limit	-3.187

Secondary: Subjects With an Assessment of Normal/Borderline Mentally Ill on Clinical Global Impression-Severity of Illness (CGI-S) Scale at the Last On-Treatment Assessment

End point title	Subjects With an Assessment of Normal/Borderline Mentally Ill on Clinical Global Impression-Severity of Illness (CGI-S) Scale at the Last On-Treatment Assessment

End point description:

CGI-S assesses the severity of the subject's condition on a 7-point scale: 1 (normal, not at all ill), 2 (borderline mentally ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), 7 (among the most extremely ill). The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline through 13 weeks

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: Subjects	56	78		

Statistical analyses

Statistical analysis title	Clinical Global Impressions - Severity
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Cochran-Mantel-Haenszel

Secondary: Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Learning and School Domain Scores at Week 13

End point title	Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Learning and School Domain Scores at Week 13

End point description:

The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). The Learning and School Domain consists of 10-items. Mean scores range from 0 to 3. Higher

scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary
End point timeframe:	
Baseline and week 13	

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	97		
Units: Units on a scale				
least squares mean (standard error)	-0.457 (± 0.058)	-0.572 (± 0.058)		

Statistical analyses

Statistical analysis title	WFIRS-P Learning and School Domain
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.254
upper limit	0.024

Secondary: Change From Baseline in the WFIRS-P Family Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Family Domain Score at Week 13
End point description:	

The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). The Family Domain consists of 10-items. Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary
End point timeframe:	
Baseline and week 13	

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	105		
Units: Units on a scale				
least squares mean (standard error)	-0.314 (± 0.055)	-0.371 (± 0.054)		

Statistical analyses

Statistical analysis title	Change From Baseline in the WFIRS-P Family Domain
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.408
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.192
upper limit	0.078

Secondary: Change From Baseline in the WFIRS-P Behavior in School Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Behavior in School Domain Score at Week 13

End point description:

The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	97		
Units: Units on a scale				
least squares mean (standard error)	-0.376 (± 0.051)	-0.459 (± 0.05)		

Statistical analyses

Statistical analysis title	WFIRS-P Behavior in School Domain Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.176
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.203
upper limit	0.037

Secondary: Change From Baseline in the WFIRS-P Global Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Global Domain Score at Week 13

End point description:

The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	108		
Units: Units on a scale				
least squares mean (standard error)	-0.296 (± 0.036)	-0.347 (± 0.035)		

Statistical analyses

Statistical analysis title	WFIRS-P Global Domain Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.253
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	-0.036

Secondary: Change From Baseline in the WFIRS-P Risk Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Risk Domain Score at Week 13

End point description:

The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). The Risk Domain consists of 10-items. Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	107		
Units: Units on a scale				
least squares mean (standard error)	-0.194 (± 0.027)	-0.191 (± 0.026)		

Statistical analyses

Statistical analysis title	WFIRS-P Risk Domain Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.912
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.004

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.068

Secondary: Change From Baseline in the WFIRS-P Social Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Social Domain Score at Week 13

End point description:

The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). The Social Domain consists of 7-items. Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	108		
Units: Units on a scale				
least squares mean (standard error)	-0.234 (± 0.046)	-0.263 (± 0.045)		

Statistical analyses

Statistical analysis title	WFIRS-P Social Domain Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.606
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.139
upper limit	0.081

Secondary: Change From Baseline in the WFIRS-P Child Self-Concept Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Child Self-Concept Domain Score at Week 13
End point description:	
The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). The Child Self-Concept Domain consists of 3-items. Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.	
End point type	Secondary
End point timeframe:	
Baseline and week 13	

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	106		
Units: Units on a scale				
least squares mean (standard error)	-0.376 (± 0.067)	-0.275 (± 0.066)		

Statistical analyses

Statistical analysis title	WFIRS-P Child Self-Concept Domain Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.228
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.064
upper limit	0.268

Secondary: Change From Baseline in the WFIRS-P Life Skills Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Life Skills Domain Score at Week 13
End point description:	
The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). The Life Skills Domain consists of 10-items. Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.	

End point type	Secondary
End point timeframe:	
Baseline and week 13	

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	107		
Units: Units on a scale				
least squares mean (standard error)	-0.328 (± 0.046)	-0.375 (± 0.045)		

Statistical analyses

Statistical analysis title	WFIRS-P Life Skills Domain Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.159
upper limit	0.065

Secondary: Change From Baseline in the WFIRS-P Academic Performance Domain Score at Week 13

End point title	Change From Baseline in the WFIRS-P Academic Performance Domain Score at Week 13
End point description:	

The WFIRS-P is a 50-item scale with each item scored from 0 (never/not at all) to 3 (very often/very much). Mean scores range from 0 to 3. Higher scores indicate greater functional impairment. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary
End point timeframe:	
Baseline and week 13	

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	96		
Units: Units on a scale				
least squares mean (standard error)	-0.632 (± 0.096)	-0.841 (± 0.096)		

Statistical analyses

Statistical analysis title	WFIRS-P Academic Performance Domain Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.443
upper limit	0.026

Secondary: Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Scores at the Last On-Treatment Assessment

End point title	Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Scores at the Last On-Treatment Assessment

End point description:

Clinical Global Impression-Improvement (CGI-I) consists of a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved) or 2 (much improved) on the scale. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

weeks 1 through 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: Subjects	71	104		

Statistical analyses

Statistical analysis title	Clinical Global Impression-Improvement Scores
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Changes From Baseline in Behavior Rating Inventory of Executive Function (BRIEF) Scores at Week 13

End point title	Changes From Baseline in Behavior Rating Inventory of Executive Function (BRIEF) Scores at Week 13

End point description:

Behavior Rating Inventory of Executive Function (BRIEF) is an 86-item questionnaire composed of three indices (Global Executive Composite, Behavioral Regulation Index, and Metacognition Index). Items are rated 1 (never), 2 (sometimes), and 3 (often). Lower scores reflect better functioning. The Full Analysis Set, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	88		
Units: Units on a scale				
least squares mean (standard error)				
Global Executive Composite	-10.6 (± 1.23)	-12.9 (± 1.19)		
Behavioral Regulation Index	-11.5 (± 1.29)	-12.4 (± 1.25)		
Metacognition Index	-8.9 (± 1.18)	-11.6 (± 1.14)		

Statistical analyses

Statistical analysis title	Global Executive Composite
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	0.7

Statistical analysis title	Behavioral Regulation Index
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.579
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	2.3

Statistical analysis title	Metacognition Index
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	0.2

Secondary: Change From Baseline in Pediatric Daytime Sleepiness Scale (PDSS) Total Score at Week 13

End point title	Change From Baseline in Pediatric Daytime Sleepiness Scale (PDSS) Total Score at Week 13

End point description:

The Pediatric Daytime Sleepiness Scale (PDSS) is an 8 item questionnaire scored on a scale from 0 (never) to 4 (always/very often). Total scores range from 0 to 32, with increasing score reflecting greater sleepiness. The Safety Population, which consisted of all randomized subjects who took at least 1 dose of

investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	108		
Units: Units on a scale				
least squares mean (standard error)	-3.7 (± 0.52)	-4.2 (± 0.51)		

Statistical analyses

Statistical analysis title	Pediatric Daytime Sleepiness Scale Total Score
Comparison groups	Placebo v SPD503
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.8

Secondary: Change From Baseline in Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Last On-Treatment Assessment

End point title	Change From Baseline in Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Last On-Treatment Assessment

End point description:

The BPRS-C characterizes childhood behavioral and emotional symptomatology. A total of 21 items are rated on a scale from 0 (not present) to 6 (extremely severe) with a total score ranging from 0 to 126. A decrease in score indicates a reduction in psychopathology. The Safety Population, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	151		
Units: Units on a scale				
arithmetic mean (standard deviation)	-7 (± 9.85)	-9.1 (± 8.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Structure Side-Effect Questionnaire (SSEQ)

End point title	Structure Side-Effect Questionnaire (SSEQ)

End point description:

The Structured Side-effect Questionnaire is a simple checklist of 17 side effects. The subject indicates whether a side effect has occurred since the last visit by marking 'yes' or 'no' on the
checklist for each of the events listed. The Safety Population, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Through week 16

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Subjects				
Nausea	33	37		
Vomiting	17	18		
Diarrhea	24	29		
Abdominal pain	28	30		
Decreased Appetite	42	48		
Increased Appetite	47	42		
Headache	53	76		
Dizziness	31	49		
Fatigue	43	65		
Nervousness/anxiety	23	30		
Insomnia	25	28		
Somnolence	26	41		
Depression	17	14		
Itching	9	11		
Rash	7	6		
Missed menses	1	4		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

C-SSRS is a semi-structured interview that captures the occurence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behaviour occurred. The assessment is done by the nature of the responses, not by a numbered scale. The Safety Population, which consisted of all randomized subjects who took at least 1 dose of investigational product, was used for this end point.

End point type	Secondary

End point timeframe:

Through week 16

End point values	Placebo	SPD503		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: Subjects				
Suicidal ideation	4	5		
Suicidal behavior	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
16 weeks	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Orally administered a once-daily dose	
Reporting group title	SPD503
Reporting group description:	
Orally administered a once-daily optimal dose between 0.05 mg/kg/day - 0.12 mg/kg/day (up to 7 mg/day depending on weight).	

Serious adverse events	Placebo	SPD503	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 155 (1.29%)	4 / 157 (2.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 155 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 155 (0.65%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Withdrawal hypertension			

subjects affected / exposed	0 / 155 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders

Loss of consciousness

subjects affected / exposed	0 / 155 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders

Abdominal pain

subjects affected / exposed	0 / 155 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting

subjects affected / exposed	0 / 155 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders

Ovarian cyst ruptured

subjects affected / exposed	1 / 155 (0.65%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders

Cholecystitis chronic

subjects affected / exposed	0 / 155 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders

Homicidal ideation

subjects affected / exposed	0 / 155 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	SPD503	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 155 (77.42%)	147 / 157 (93.63%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 155 (10.32%)	25 / 157 (15.92%)	
occurrences (all)	17	32	
Dizziness postural			
subjects affected / exposed	3 / 155 (1.94%)	8 / 157 (5.10%)	
occurrences (all)	3	8	
Headache			
subjects affected / exposed	28 / 155 (18.06%)	42 / 157 (26.75%)	
occurrences (all)	43	64	
Sedation			
subjects affected / exposed	3 / 155 (1.94%)	18 / 157 (11.46%)	
occurrences (all)	3	21	
Somnolence			
subjects affected / exposed	33 / 155 (21.29%)	69 / 157 (43.95%)	
occurrences (all)	39	102	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 155 (12.26%)	35 / 157 (22.29%)	
occurrences (all)	21	41	
Irritability			
subjects affected / exposed	6 / 155 (3.87%)	11 / 157 (7.01%)	
occurrences (all)	6	13	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 155 (3.87%)	9 / 157 (5.73%)	
occurrences (all)	7	10	
Abdominal pain upper			
subjects affected / exposed	7 / 155 (4.52%)	10 / 157 (6.37%)	
occurrences (all)	7	11	
Diarrhoea			
subjects affected / exposed	13 / 155 (8.39%)	12 / 157 (7.64%)	
occurrences (all)	15	17	

Dry mouth			
subjects affected / exposed	0 / 155 (0.00%)	12 / 157 (7.64%)	
occurrences (all)	0	12	
Nausea			
subjects affected / exposed	21 / 155 (13.55%)	19 / 157 (12.10%)	
occurrences (all)	22	22	
Vomiting			
subjects affected / exposed	10 / 155 (6.45%)	9 / 157 (5.73%)	
occurrences (all)	12	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 155 (5.16%)	3 / 157 (1.91%)	
occurrences (all)	8	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 155 (3.87%)	14 / 157 (8.92%)	
occurrences (all)	7	16	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 155 (5.81%)	18 / 157 (11.46%)	
occurrences (all)	9	20	
Upper respiratory tract infection			
subjects affected / exposed	12 / 155 (7.74%)	14 / 157 (8.92%)	
occurrences (all)	14	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 155 (13.55%)	23 / 157 (14.65%)	
occurrences (all)	24	27	
Increased appetite			
subjects affected / exposed	13 / 155 (8.39%)	14 / 157 (8.92%)	
occurrences (all)	15	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?   No

Interruptions (globally)

Were there any global interruptions to the trial?   No

Limitations and caveats

 None reported