Clinical trial results:
A phase 3, randomised, double-blind, multicentre, parallel-group, placebo- and active-reference, dose-optimisation efficacy and safety study of extended-release Guanfacine Hydrochloride in children and adolescents aged 6-17 years with Attention-Deficit/Hyperactivity Disorder

Summary

EudraCT number	2010-018579-12
Trial protocol	GB DE NL FR ES SE IE AT BG IT
Global end of trial date	01 May 2013

Results information

Result version number	v1
This version publication date	28 August 2018
First version publication date	01 May 2015

Trial information

Trial identification

Sponsor protocol code	SPD503-316

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01244490
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	Shire Development LLC, Study Physician, +1 866 842 5335 ,
Scientific contact	Shire Development LLC, Study Physician, +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	01 May 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 May 2013
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 assess the efficacy of once daily dosing with optimised SPD503 compared to placebo in the treatment of children and adolescents aged 6-17 years with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) as measured by the ADHD Rating Scale-IV (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. The subject's informed consent and assent (as applicable) were mandatory for taking part in the study. It was obtained in writing prior to the performance of any study-specific procedures.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	17 January 2011
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	Poland: 37
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Spain: 51
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 68
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Ukraine: 54
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	338
EEA total number of subjects	208

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)	204
Adolescents (12-17 years)	134
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited to participate at 1 of 58 sites, including 11 sites in the United States (US), 2 sites in Canada, and 45 sites in Europe (Austria, France, Germany, Ireland, Italy, Poland, Romania, Spain, Sweden, Ukraine, and United Kingdom).

Pre-assignment

Screening details:

This study consisted of a screening/washout period that lasted for 35 days. Following successful screening, the subject discontinued any current psychoactive medication (if any) for the Washout Period. The washout for all prohibited medications was at least a minimum of 5 times the half-life of the medication.

Period 1

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

Blinding implementation details:

Capsules were overencapsulated to protect the blind between the active product and the placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.

Arm type	Placebo
Investigational medicinal product name	SPD503 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were to take 1 matching placebo tablet once daily if optimized to a dose of 1-4mg SPD503 or 2 matching placebo tablets once daily if optimized to a dose of 5-7mg SPD503.

Investigational medicinal product name	Strattera Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects optimized to a dose requiring a daily dose higher than 60mg of STRATTERA took 2 matching placebo capsules once daily. Subjects at all other optimized doses (</= 60mg/day) took 1 matching placebo capsule once daily.

Arm title	Guanfacine Hydrochloride

Arm description:

Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.

Arm type	Experimental

Investigational medicinal product name	Guanfacine Hydrochloride
Investigational medicinal product code	
Other name	SPD503, Intuniv
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A combination of 1, 2, 3, and 4mg tablets for a total dosage of 1mg to 7mg based on age and weight. Subjects were to take either 1 SPD503 tablet once daily if optimized to a dose of 1-4mg or 2 SPD503 tablets once daily if optimized to a dose of 5-7mg.

Investigational medicinal product name	Strattera Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects optimized to a dose requiring a daily dose higher than 60mg of STRATTERA took 2 matching placebo capsules once daily. Subjects at all other optimized doses (</= 60mg/day) took 1 matching placebo capsule once daily.

Arm title	Atomoxetine Hydrochloride

Arm description:

Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo.

Arm type	Active comparator
Investigational medicinal product name	Atomoxetine Hydrochloride
Investigational medicinal product code	
Other name	Strattera
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A combination of 10, 18, 25, 40, or 60mg capsules, once daily, at the optimised dose (10mg to 100mg based on weight). The maximum dose was 4mg/day for children aged 6-12 years and 4-7mg/day for adolescents aged 13-17 years, depending on the subject's weight. Subjects optimized to a dose requiring a daily dose higher than 60mg took 2 STRATTERA capsules. Subjects at all other optimized doses (</= 60mg/day) took 1 STRATTERA capsule.

Investigational medicinal product name	SPD503 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were to take 1 matching placebo tablet once daily if optimized to a dose of 1-4mg SPD503 or 2 matching placebo tablets once daily if optimized to a dose of 5-7mg SPD503.

Number of subjects in period 1	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride
Started	111	115	112
Completed	92	91	89
Not completed	19	24	23
Not specified	-	-	1
Adverse event	1	9	5
Lost to follow-up	-	6	3

Lack of efficacy	14	5	5
Withdrawal by subject	4	4	9

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.	
Reporting group title	Guanfacine Hydrochloride
Reporting group description:	
Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.	
Reporting group title	Atomoxetine Hydrochloride
Reporting group description:	
Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo.	

Reporting group values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride
Number of subjects	111	115	112
Age categorical Units: Subjects			
6-12 years	79	81	82
13-17 years	32	34	30
Age continuous Units: years			
arithmetic mean	11	10.9	10.5
standard deviation	± 2.76	± 2.78	± 2.81
Gender categorical Units: Subjects			
Female	25	38	25
Male	86	77	87
Region of enrollment Units: Subjects			
Austria	2	4	5
Canada	6	7	6
France	2	2	2
Germany	23	23	22
Ireland	0	1	1
Italy	5	4	4
Poland	11	14	12
Romania	5	3	6
Spain	16	18	17
Sweden	1	1	2
Ukraine	21	18	15
United Kingdom	1	0	1
United States	18	20	19

Reporting group values	Total		
Number of subjects	338		
Age categorical Units: Subjects			
6-12 years	242		

13-17 years	96		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	88		
Male	250		
Region of enrollment Units: Subjects			
Austria	11		
Canada	19		
France	6		
Germany	68		
Ireland	2		
Italy	13		
Poland	37		
Romania	14		
Spain	51		
Sweden	4		
Ukraine	54		
United Kingdom	2		
United States	57		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.	
Reporting group title	Guanfacine Hydrochloride
Reporting group description:	
Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.	
Reporting group title	Atomoxetine Hydrochloride
Reporting group description:	
Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo.	

Primary: Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 10/13 - Last Observation Carried Forward (LOCF)

End point title	Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 10/13 - Last Observation Carried Forward (LOCF)

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. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 20% of the items used for summing a score were missing, the score was set to missing.

End point type	Primary

End point timeframe:

Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	112	112	
Units: units on a scale				
least squares mean (standard error)	-15 (± 1.1612)	-23.9 (± 1.1531)	-18.8 (± 1.1549)	

Statistical analyses

Statistical analysis title	Analysis of ADHD-RS-IV total score
Comparison groups	Placebo v Guanfacine Hydrochloride

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	-5.8

Statistical analysis title	Analysis of ADHD-RS-IV total score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	-0.7

Secondary: Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Score

End point title	Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Score

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. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. Not all subjects in the FAS population had data for this outcome.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	112	112	
Units: percent of subjects				
number (not applicable)	44.1	67.9	56.3	

Statistical analyses

Statistical analysis title	Analysis of CGI-I score
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage improvement
Point estimate	23.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	36.4

Statistical analysis title	Analysis of CGI-I score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage improvement
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	25.1

Secondary: Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Learning and School Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Learning and School Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Learning in School Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	103	100	
Units: units on a scale				
least squares mean (standard error)	-0.419 (± 0.0537)	-0.636 (± 0.0527)	-0.581 (± 0.0534)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P learning domain score
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.217
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.358
upper limit	-0.076

Statistical analysis title	Analysis of WFIRS-P learning domain score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.162
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.305
upper limit	-0.019

Secondary: Change From Baseline in the WFIRS-P Family Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Family Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Family Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	109	105	
Units: units on a scale				
least squares mean (standard error)	-0.409 (± 0.0568)	-0.617 (± 0.0558)	-0.499 (± 0.0566)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P family domain score
Comparison groups	Placebo v Guanfacine Hydrochloride

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.358
upper limit	-0.059

Statistical analysis title	Analysis of WFIRS-P family domain score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.242
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.241
upper limit	-0.061

Secondary: Clinical Global Impression-Severity of Illness (CGI-S) - LOCF

End point title	Clinical Global Impression-Severity of Illness (CGI-S) - LOCF

End point description:

CGI-S assesses the severity of the subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. Not all subjects in the FAS population had data for this outcome.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	112	112	
Units: percent of subjects				
number (not applicable)				
1 (Normal, not at all ill)	9.9	14.3	6.3	
2 (Borderline mentally ill)	15.3	23.2	19.6	
3 (Mildly ill)	20.7	31.3	32.1	
4 (Moderately ill)	20.7	22.3	19.6	
5 (Markedly ill)	25.2	5.4	13.4	
6 (Severely ill)	6.3	3.6	7.1	
7 (Among the most extremely ill)	1.8	0	1.8	

Statistical analyses

Statistical analysis title	Analysis of CGI-S
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of CGI-S #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.196 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Nominal p-value uncorrected for multiplicity.

Secondary: Health Utilities Index-2/3 (HUI 2/3) Scores - LOCF

End point title	Health Utilities Index-2/3 (HUI 2/3) Scores - LOCF

End point description:

HUI is used to describe health status and to obtain utility scores by collecting data using one or more questionnaires in formats selected to match the specific study design criteria. Scoring ranges from 0.00 (dead) to 1.00 (perfect health). Higher scores represent better health status. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. Not all subjects in the FAS population had data for this outcome.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	110	106	
Units: units on a scale				
arithmetic mean (standard deviation)	0.927 (± 0.095)	0.922 (± 0.0908)	0.913 (± 0.1052)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the WFIRS-P Global Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Global Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Global Score is the mean of 50 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	110	104	
Units: units on a scale				
least squares mean (standard error)	-0.321 (± 0.0387)	-0.487 (± 0.0374)	-0.425 (± 0.0384)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P global score
Comparison groups	Placebo v Guanfacine Hydrochloride

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.266
upper limit	-0.064

Notes:

[3] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of WFIRS-P global score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.207
upper limit	-0.001

Notes:

[4] - Nominal p-value uncorrected for multiplicity.

Secondary: Change From Baseline in the WFIRS-P Academic Performance Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Academic Performance Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Academic Performance Domain is the mean of 4 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	103	101	
Units: units on a scale				
least squares mean (standard error)	-0.555 (± 0.0784)	-0.766 (± 0.0757)	-0.681 (± 0.0759)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P academic performance score
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [5]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.416
upper limit	-0.007

Notes:

[5] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of WFIRS-P academic performance score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.231 [6]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.331
upper limit	0.08

Notes:

[6] - Nominal p-value uncorrected for multiplicity.

Secondary: Change From Baseline in the WFIRS-P Behavior in School Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Behavior in School Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Behavior in School Domain is the mean of 6 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	103	100	
Units: units on a scale				
least squares mean (standard error)	-0.363 (± 0.0512)	-0.592 (± 0.0502)	-0.544 (± 0.0509)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P school behavior score
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.229
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.364
upper limit	-0.094

Notes:

[7] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of WFIRS-P school behavior score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [8]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.181

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.317
upper limit	-0.045

Notes:

[8] - Nominal p-value uncorrected for multiplicity.

Secondary: Change From Baseline in the WFIRS-P Life Skills Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Life Skills Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Life Skills Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	110	104	
Units: units on a scale				
least squares mean (standard error)	-0.383 (± 0.0422)	-0.477 (± 0.0411)	-0.45 (± 0.0422)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P life skills domain score
Comparison groups	Guanfacine Hydrochloride v Placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [9]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.204
upper limit	0.017

Notes:

[9] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of WFIRS-P life skills domain score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.242 [10]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.046

Notes:

[10] - Nominal p-value uncorrected for multiplicity.

Secondary: Change From Baseline in the WFIRS-P Child Self-Concept Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Child Self-Concept Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Child Self-Concept Domain is the mean of 3 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	108	103	
Units: units on a scale				
least squares mean (standard error)	-0.312 (± 0.0544)	-0.361 (± 0.0528)	-0.39 (± 0.0536)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P self-concept domain score
Comparison groups	Placebo v Guanfacine Hydrochloride

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5 [11]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.191
upper limit	0.094

Notes:

[11] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of WFIRS-P self-concept domain score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.288 [12]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.222
upper limit	0.066

Notes:

[12] - Nominal p-value uncorrected for multiplicity.

Secondary: Change From Baseline in the WFIRS-P Social Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Social Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Social Domain is the mean of 7 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	110	104	
Units: units on a scale				
least squares mean (standard error)	-0.322 (± 0.0537)	-0.555 (± 0.0519)	-0.434 (± 0.0532)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P social domain score
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [13]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.233
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.374
upper limit	-0.092

Notes:

[13] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of WFIRS-P social domain score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124 [14]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.253
upper limit	0.031

Notes:

[14] - Nominal p-value uncorrected for multiplicity.

Secondary: Change From Baseline in the WFIRS-P Risk Domain Score at Week 10/13 - LOCF

End point title	Change From Baseline in the WFIRS-P Risk Domain Score at Week 10/13 - LOCF

End point description:

The WFIRS-P Risk Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

End point type	Secondary

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	105	97	
Units: units on a scale				
least squares mean (standard error)	-0.134 (± 0.0284)	-0.19 (± 0.0275)	-0.173 (± 0.0285)	

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P risk domain score
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139 [15]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.131
upper limit	0.018

Notes:

[15] - Nominal p-value uncorrected for multiplicity.

Statistical analysis title	Analysis of WFIRS-P risk domain score #2
Comparison groups	Placebo v Atomoxetine Hydrochloride
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.315 [16]
Method	ANCOVA
Parameter estimate	Difference in least squares mean
Point estimate	-0.039

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.115
upper limit	0.037

Notes:

[16] - Nominal p-value uncorrected for multiplicity.

Secondary: Change From Baseline in Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Weeks 10/13 - LOCF

End point title	Change From Baseline in Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Weeks 10/13 - LOCF

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. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.
This endpoint analyzed the Safety Population, defined as of randomized subjects who took at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Baseline and up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	101	99	
Units: units on a scale				
arithmetic mean (standard deviation)	-5.6 (± 8.82)	-8.3 (± 8.4)	-6.5 (± 9.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Structure Side-Effect Questionnaire

End point title	Structure Side-Effect Questionnaire

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' on the checklist for each of the events listed. Outcome measure is at 12 weeks for ages 6-12 years and at 15 weeks for ages 13-17 years.
This endpoint analyzed the Safety Population, defined as of randomized subjects who took at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Up to 12 weeks for children aged 6-12 years and up to 15 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	112	112	
Units: participants				
Nausea	19	30	39	
Vomiting	11	7	25	
Diarrhea	15	18	8	
Abdominal Pain	26	45	42	
Decreased Appetite	25	31	48	
Increased Appetite	30	40	25	
Headache	35	52	34	
Dizziness	16	28	23	
Fatigue	30	55	35	
Nervousness/Anxiety	25	37	34	
Insomnia	19	32	24	
Somnolence	26	57	38	
Depression	7	7	9	
Itching	7	13	10	
Rash	4	9	8	
Missed Menses	0	1	0	

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.
Outcome measure is at 12 weeks for ages 6-12 years and at 15 weeks for ages 13-17 years.
This endpoint analyzed the Safety Population, defined as of randomized subjects who took at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Up to 12 weeks for children aged 6-12 years and up to 15 weeks for adolescents aged 13-17 years

End point values	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	112	112	
Units: participants				
Suicidal Ideation	2	3	5	
Suicidal Behaviour	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 13 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.	
Reporting group title	Guanfacine Hydrochloride
Reporting group description: Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.	
Reporting group title	Atomoxetine Hydrochloride
Reporting group description: Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo.	

Serious adverse events	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	0 / 112 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Guanfacine Hydrochloride	Atomoxetine Hydrochloride
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 111 (55.86%)	79 / 114 (69.30%)	67 / 112 (59.82%)
Nervous system disorders			
Dizziness			

subjects affected / exposed	9 / 111 (8.11%)	14 / 114 (12.28%)	17 / 112 (15.18%)
occurrences (all)	9	18	24
Headache			
subjects affected / exposed	27 / 111 (24.32%)	30 / 114 (26.32%)	22 / 112 (19.64%)
occurrences (all)	46	51	36
Somnolence			
subjects affected / exposed	16 / 111 (14.41%)	50 / 114 (43.86%)	20 / 112 (17.86%)
occurrences (all)	18	94	32
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 111 (18.02%)	29 / 114 (25.44%)	24 / 112 (21.43%)
occurrences (all)	22	45	32
Pyrexia			
subjects affected / exposed	4 / 111 (3.60%)	7 / 114 (6.14%)	3 / 112 (2.68%)
occurrences (all)	4	9	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 111 (18.02%)	19 / 114 (16.67%)	19 / 112 (16.96%)
occurrences (all)	32	29	31
Abdominal pain upper			
subjects affected / exposed	6 / 111 (5.41%)	7 / 114 (6.14%)	2 / 112 (1.79%)
occurrences (all)	6	7	3
Diarrhoea			
subjects affected / exposed	15 / 111 (13.51%)	10 / 114 (8.77%)	2 / 112 (1.79%)
occurrences (all)	18	16	3
Nausea			
subjects affected / exposed	11 / 111 (9.91%)	18 / 114 (15.79%)	30 / 112 (26.79%)
occurrences (all)	13	19	54
Vomiting			
subjects affected / exposed	8 / 111 (7.21%)	6 / 114 (5.26%)	18 / 112 (16.07%)
occurrences (all)	9	8	29
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 111 (7.21%)	9 / 114 (7.89%)	7 / 112 (6.25%)
occurrences (all)	15	16	18
Insomnia			

subjects affected / exposed	7 / 111 (6.31%)	13 / 114 (11.40%)	8 / 112 (7.14%)
occurrences (all)	7	21	10
Nervousness			
subjects affected / exposed	6 / 111 (5.41%)	6 / 114 (5.26%)	6 / 112 (5.36%)
occurrences (all)	7	7	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 111 (5.41%)	6 / 114 (5.26%)	3 / 112 (2.68%)
occurrences (all)	7	7	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 111 (10.81%)	15 / 114 (13.16%)	31 / 112 (27.68%)
occurrences (all)	23	20	44
Increased appetite			
subjects affected / exposed	9 / 111 (8.11%)	12 / 114 (10.53%)	4 / 112 (3.57%)
occurrences (all)	11	15	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2011	The following changes to study inclusion criteria and procedures were made based on communications with country-specific Ethics Committees: *Following responses from the Ethics Committees in Spain, Germany, and The Netherlands, an Exclusion Criterion (#2) was added: "Subject is well-controlled on their current ADHD medication, with acceptable tolerability and the parent/caregiver does not object to the current medication." *Following a request from the French Ethics Committee, all CYP2D6 inhibitors were prohibited from use during the study, without exception and Exclusion Criterion (#10) that details use of prohibited medications was modified to include CYP2D6 inhibitors. In addition, the washout schedule for CYP2D6 inhibitors was modified such that all CYP2D6 inhibitors were required to have a 30-day washout period prior to the Baseline Visit (Visit 2/Week 0). Additional text was inserted as a prompt that these medications may have signaled the presence of an exclusionary diagnosis (Exclusion Criterion #10). Other changes included: *Neutrophil band analysis was removed. *Screening for methylphenidate was removed from drug and alcohol screen. * Appendix 2.5 presenting stature-for-age percentiles was inserted.
15 February 2012	In the context of the challenges with recruitment and enrollment in the study, the statistical power of the study was decreased to 80% and the numbers of subjects required was decreased accordingly. Approximately 333 subjects (111 per treatment arm) was changed to approximately 252 subjects (84 per treatment arm). The number of subjects assessed for the primary efficacy was decreased according to the decreased power of the study. Approximately 210 subjects (105 subjects in each of the SPD503 and placebo groups) was changed to approximately 158 subjects (79 subjects in each of the SPD503 and placebo groups).
24 July 2012	The approximate number of subjects to be randomized was increased back to the original target number (ie, 333). The increase was in response to a higher than anticipated recruitment rate. Approximately 252 subjects (84 per treatment arm) was changed to approximately 333 subjects (111 per treatment arm). The numbers of subject assessed for primary efficacy was increased as enrollment rates had improved and the statistical power of the study was increased from 80% (as per Amendment 3) to the original 90%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported