Clinical trial results:
A Phase 3, Double-Blind, Placebo-Controlled, Multicentre, Randomised-Withdrawal, Long-Term Maintenance of Efficacy and Safety Study of Extended-Release Guanfacine Hydrochloride in Children and Adolescents Aged 6-17 with Attention-deficit/Hyperactivity Disorder

Summary

EudraCT number	2009-018161-12
Trial protocol	GB DE NL ES SE BE IT
Global end of trial date	09 July 2013

Results information

Result version number	v2 (current)
This version publication date	04 September 2018
First version publication date	07 December 2014
Version creation reason	• Correction of full data set Need to correct PIP information.

Trial information

Trial identification

Sponsor protocol code	SPD503-315

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01081145
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard, 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	11 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the long-term maintenance of efficacy of SPD503 in children and adolescents (6-17 years) with attention-deficit/hyperactivity disorder (ADHD) who respond to an initial open label, short-term treatment with SPD503.

Protection of trial subjects:

The role of the DMC was to protect the interests of subjects in the study and of potential subjects, by review of accumulating safety and tolerability data as it was generated. This study was conducted in accordance with International Conference on Harmonisation of good clinical practice (GCP), 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	11 May 2010
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	Netherlands: 29
Country: Number of subjects enrolled	Spain: 68
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	United States: 280
Worldwide total number of subjects	528
EEA total number of subjects	218

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	334
Adolescents (12-17 years)	194
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 67 investigative sites in Belgium, Canada, France, Italy, Germany, the Netherlands, Spain, Sweden, the United Kingdom, and the United States from 11 May 2010 to 9 July 2013.

Pre-assignment

Screening details:

Children and adolescents aged 6-17 with attention-deficit/hyperactivity disorder were enrolled in 1 of 2 [guanfacine hydrochloride 1-7 mg once daily (QD); placebo QD] treatment groups.

Period 1

Period 1 title	Open-Label Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Guanfacine Hydrochloride

Arm description: -

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:

Administered as a once-daily oral dose between 1-7mg/day depending on age and weight

Number of subjects in period 1	Guanfacine Hydrochloride
Started	528
Completed	316
Not completed	212
Response criteria not met	46
Not specified	12
Adverse event	42
Lost to follow-up	11
Protocol deviation	4
Lack of efficacy	56
Withdrawal by subject	41

Period 2

Period 2 title	Double-Blind Randomized-Withdrawal Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The actual treatment given to individual subjects during the Double-Blind Randomized-Withdrawal Phase was determined by a randomization schedule. The associated treatment assignments giving details of individual subject treatment were automatically assigned by the interactive response technology (IRT).

Arms

Are arms mutually exclusive?	Yes
Arm title	Guanfacine Hydrochloride

Arm description: -

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:

Administered as a once-daily oral dose between 1-7mg/day depending on age and weight

Arm title	Placebo

Arm description: -

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:

Administered as a once-daily oral dose

Number of subjects in period 2	Guanfacine Hydrochloride	Placebo
Started	157	159
Completed	76	53
Not completed	81	106
Treatment failure criteria met	47	71
Not specified	4	3
Adverse event	3	2
Lost to follow-up	3	2
Withdrawal by subject	10	8
Lack of efficacy	13	20
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Open-Label Phase

Reporting group description: -

Reporting group values	Open-Label Phase	Total	
Number of subjects	528	528	
Age categorical Units: Subjects			
6-12 years	393	393	
13-17 years	135	135	
Gender categorical Units: Subjects			
Female	131	131	
Male	397	397	
Region of enrollment Units: Subjects			
Belgium	19	19	
Canada	30	30	
France	14	14	
Germany	27	27	
Italy	31	31	
Netherlands	29	29	
Spain	68	68	
Sweden	5	5	
United Kingdom	25	25	
United States	280	280	

End points

End points reporting groups	
Reporting group title	Guanfacine Hydrochloride
Reporting group description: -	
Reporting group title	Guanfacine Hydrochloride
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Percentage of Subjects With Treatment Failures During the Double-Blind Randomized-Withdrawal Phase	
End point title	Percentage of Subjects With Treatment Failures During the Double-Blind Randomized-Withdrawal Phase
End point description:	
Treatment failure was defined as >= 50% increase (worsening) in ADHD-RS-IV total score and a >= 2 point increase (worsening) in CGI-S score compared with the respective scores at the Double-Blind Randomized-Withdrawal Baseline Visit at 2 consecutive Double-Blind Randomized-Withdrawal Phase visits. Subjects meeting these criteria were regarded as treatment failures regardless of whether or not they were withdrawn. All subjects who discontinued the study for any reason were regarded as treatment failures for the primary analysis.	
End point type	Primary
End point timeframe:	
26 weeks	

End point values	Guanfacine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	151		
Units: percentage of treatment failures				
number (confidence interval 95%)	49.3 (41.3 to 57.3)	64.9 (57.3 to 72.5)		

Statistical analyses

Statistical analysis title	Treatment Failures
Comparison groups	Guanfacine Hydrochloride v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Treatment Failures
Point estimate	-15.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.6
upper limit	-4.5

Secondary: Time to Treatment Failure During the Double-Blind Randomized-Withdrawal Phase

End point title	Time to Treatment Failure During the Double-Blind Randomized-Withdrawal Phase

End point description:

Treatment failure was defined as >= 50% increase (worsening) in ADHD-RS-IV total score and a >= 2 point increase (worsening) in CGI-S score compared with the respective scores at the Double-Blind Randomized-Withdrawal Baseline Visit at 2 consecutive Double-Blind Randomized-Withdrawal Phase visits. Subjects meeting these criteria were regarded as treatment failures regardless of whether or not they were withdrawn. All subjects who discontinued the study for any reason were regarded as treatment failures for the primary analysis.

End point type	Secondary

End point timeframe:

26 weeks

End point values	Guanfacine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	151		
Units: Days	218	56		

Statistical analyses

Statistical analysis title	Time to Treatment Failure
Comparison groups	Placebo v Guanfacine Hydrochloride
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Logrank

Secondary: Change From Double-Blind Randomized-Withdrawal Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 26 of the Double-Blind Randomized-Withdrawal Phase - Last Observation Carried Forward (LOCF)

End point title	Change From Double-Blind Randomized-Withdrawal Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 26 of the Double-Blind Randomized-Withdrawal Phase - 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.

End point type	Secondary

End point timeframe:

Baseline and week 26

End point values	Guanfacine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	151		
Units: units on a scale				
least squares mean (standard error)	9.64 (± 1.21)	15.89 (± 1.225)		

Statistical analyses

Statistical analysis title	Change From Baseline in ADHD-RS-IV Score Week 26
Comparison groups	Guanfacine Hydrochloride v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	ANCOVA
Parameter estimate	Difference in Least Squares Mean
Point estimate	-6.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.01
upper limit	-3.48

Notes:

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

Secondary: Percent of Subjects With an Assessment of Normal/Borderline Mentally Ill on the Clinical Global Impression-Severity of Illness (CGI-S) Scale During the Double-Blind Randomized-Withdrawal Phase - LOCF

End point title	Percent of Subjects With an Assessment of Normal/Borderline Mentally Ill on the Clinical Global Impression-Severity of Illness (CGI-S) Scale During the Double-Blind Randomized-Withdrawal Phase - LOCF

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)

End point type	Secondary

End point timeframe:

26 weeks

End point values	Guanfacine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	151		
Units: percentage of subjects				
number (not applicable)	50	32.5		

Statistical analyses

Statistical analysis title	Clinical Global Impressions - Severity
Comparison groups	Guanfacine Hydrochloride v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Percent of Subjects
Point estimate	17.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	28.5

Notes:

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

Secondary: Change From Double-Blind Randomized-Withdrawal Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Global Score at Week 26 of the Double-Blind Randomized-Withdrawal Phase - LOCF

End point title	Change From Double-Blind Randomized-Withdrawal Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Global Score at Week 26 of the Double-Blind Randomized-Withdrawal Phase - LOCF

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.

End point type	Secondary

End point timeframe:

Baseline and week 26

End point values	Guanfacine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	151		
Units: units on a scale				
least squares mean (standard error)	0.16 (± 0.035)	0.23 (± 0.036)		

Statistical analyses

Statistical analysis title	Change from Baseline WFIRS-P Global Score Week 26
Comparison groups	Guanfacine Hydrochloride v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.118 [3]
Method	ANCOVA
Parameter estimate	Difference in Least Squares Mean
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.02

Notes:

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

Secondary: Health Utilities Index-2/3 (HUI 2/3) Scores During the Double-Blind Randomized-Withdrawal Phase - LOCF

End point title	Health Utilities Index-2/3 (HUI 2/3) Scores During the Double-Blind Randomized-Withdrawal Phase - 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.

End point type	Secondary

End point timeframe:

26 weeks

End point values	Guanfacine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	142		
Units: units on a scale				
arithmetic mean (standard deviation)	0.9 (± 0.1229)	0.899 (± 0.1272)		

Statistical analyses

No statistical analyses for this end point

Secondary: Columbia-Suicide Severity Rating Scale During the Double-Blind Randomized-Withdrawal Phase

End point title	Columbia-Suicide Severity Rating Scale During the Double-Blind Randomized-Withdrawal Phase

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.

End point type	Secondary

End point timeframe:

26 weeks

End point values	Guanfacine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	158		
Units: subjects				
Suicidal Ideation	2	2		
Suicidal Behavior	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-Label Baseline in ADHD-RS-IV Total Score at Week 13 of the Open-Label Phase - LOCF

End point title	Change From Open-Label Baseline in ADHD-RS-IV Total Score at Week 13 of the Open-Label Phase - 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.

End point type	Secondary

End point timeframe:

Baseline and 13 weeks

End point values	Guanfacine Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	497			
Units: units on a scale				
arithmetic mean (standard deviation)	-25.2 (± 11.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders in the Open-Label Phase - LOCF

End point title	Percentage of Responders in the Open-Label Phase - LOCF

End point description:

Response is defined as a percentage decrease (improvement) from Baseline in the ADHD-RS-IV total score of >=30% and a CGI-S score of 1 or 2.

End point type	Secondary

End point timeframe:

13 Weeks

End point values	Guanfacine Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	497			
Units: percentage of participants				
number (not applicable)	68.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Scores During the Open-Label Phase - LOCF

End point title	Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Scores During the Open-Label Phase - LOCF

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.

End point type	Secondary

End point timeframe:

13 Weeks

End point values	Guanfacine Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	497			
Units: percentage of participants				
number (not applicable)	76.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With an Assessment of Normal/Borderline Mentally Ill on the CGI-S Scale During the Open-Label Phase - LOCF

End point title	Percent of Subjects With an Assessment of Normal/Borderline Mentally Ill on the CGI-S Scale During the Open-Label Phase - LOCF

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).

End point type	Secondary

End point timeframe:

13 Weeks

End point values	Guanfacine Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	503			
Units: percentage of participants				
number (not applicable)	68.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-Label Baseline in the WFIRS-P Global Score at Week 13 of the Open-Label Phase - LOCF

End point title	Change From Open-Label Baseline in the WFIRS-P Global Score at Week 13 of the Open-Label Phase - LOCF

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.

End point type	Secondary

End point timeframe:

Baseline and week 13

End point values	Guanfacine Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	405			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.35 (± 0.414)			

Statistical analyses

No statistical analyses for this end point

Secondary: HUI 2/3 Scores During the Open-Label Phase - LOCF

End point title	HUI 2/3 Scores During the Open-Label Phase - 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.

End point type	Secondary

End point timeframe:

13 weeks

End point values	Guanfacine Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	417			
Units: units on a scale				
arithmetic mean (standard deviation)	0.892 (± 0.123)			

Statistical analyses

No statistical analyses for this end point

Secondary: Columbia-Suicide Severity Rating Scale During the Open-Label Phase

End point title	Columbia-Suicide Severity Rating Scale During the Open-Label

	Phase

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.

End point type	Secondary

End point timeframe:

13 weeks

End point values	Guanfacine Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	526			
Units: subjects				
Suicidal Ideation	1			
Suicidal Behavior	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 42 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	Guanfacine Hydrochloride (Open-Label Phase)
Reporting group description: -	
Reporting group title	Placebo (Randomized-Withdrawal Phase)
Reporting group description: -	
Reporting group title	Guanfacine Hydrochloride (Randomized-Withdrawal Phase)
Reporting group description: -	

Serious adverse events	Guanfacine Hydrochloride (Open-Label Phase)	Placebo (Randomized-Withdrawal Phase)	Guanfacine Hydrochloride (Randomized-Withdrawal Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 526 (0.95%)	4 / 158 (2.53%)	2 / 157 (1.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 526 (0.19%)	0 / 158 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	0 / 526 (0.00%)	0 / 158 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 526 (0.19%)	0 / 158 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	2 / 526 (0.38%)	1 / 158 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Family stress			
subjects affected / exposed	0 / 526 (0.00%)	1 / 158 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 526 (0.00%)	1 / 158 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 526 (0.19%)	1 / 158 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conduct disorder			
subjects affected / exposed	0 / 526 (0.00%)	0 / 158 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 526 (0.00%)	1 / 158 (0.63%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	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	Guanfacine Hydrochloride (Open-Label Phase)	Placebo (Randomized-Withdrawal Phase)	Guanfacine Hydrochloride (Randomized-Withdrawal Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	423 / 526 (80.42%)	51 / 158 (32.28%)	65 / 157 (41.40%)

Vascular disorders			
Hypotension			
subjects affected / exposed	29 / 526 (5.51%)	0 / 158 (0.00%)	1 / 157 (0.64%)
occurrences (all)	32	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	50 / 526 (9.51%)	2 / 158 (1.27%)	3 / 157 (1.91%)
occurrences (all)	62	2	3
Headache			
subjects affected / exposed	144 / 526 (27.38%)	18 / 158 (11.39%)	25 / 157 (15.92%)
occurrences (all)	242	24	34
Sedation			
subjects affected / exposed	47 / 526 (8.94%)	0 / 158 (0.00%)	2 / 157 (1.27%)
occurrences (all)	61	0	2
Somnolence			
subjects affected / exposed	254 / 526 (48.29%)	0 / 158 (0.00%)	19 / 157 (12.10%)
occurrences (all)	386	0	27
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	130 / 526 (24.71%)	2 / 158 (1.27%)	8 / 157 (5.10%)
occurrences (all)	186	2	11
Irritability			
subjects affected / exposed	37 / 526 (7.03%)	3 / 158 (1.90%)	2 / 157 (1.27%)
occurrences (all)	41	3	2
Pyrexia			
subjects affected / exposed	22 / 526 (4.18%)	5 / 158 (3.16%)	10 / 157 (6.37%)
occurrences (all)	28	5	10
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	60 / 526 (11.41%)	8 / 158 (5.06%)	3 / 157 (1.91%)
occurrences (all)	70	10	4
Constipation			
subjects affected / exposed	31 / 526 (5.89%)	3 / 158 (1.90%)	5 / 157 (3.18%)
occurrences (all)	38	3	5
Diarrhoea			

subjects affected / exposed	37 / 526 (7.03%)	3 / 158 (1.90%)	4 / 157 (2.55%)
occurrences (all)	46	4	5
Nausea			
subjects affected / exposed	33 / 526 (6.27%)	4 / 158 (2.53%)	5 / 157 (3.18%)
occurrences (all)	42	4	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 526 (2.66%)	9 / 158 (5.70%)	5 / 157 (3.18%)
occurrences (all)	14	11	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	36 / 526 (6.84%)	13 / 158 (8.23%)	11 / 157 (7.01%)
occurrences (all)	39	14	14
Upper respiratory tract infection			
subjects affected / exposed	31 / 526 (5.89%)	10 / 158 (6.33%)	8 / 157 (5.10%)
occurrences (all)	33	10	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 526 (5.70%)	0 / 158 (0.00%)	0 / 157 (0.00%)
occurrences (all)	32	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2010	*The maximum dose allowed was reduced from 8mg to 7mg. Text relating to dose titration in certain adolescent weight groups was updated to remove the 2mg starting dose and to reflect the reduced maximum dose. *Inclusion Criterion #10 was added to exclude subjects with a supine and standing blood pressure measurement within the 95th percentile for age, gender, and height. *Instructions to assess the suitability of subjects to remain in the study were added.
17 June 2010	*Inclusion Criterion #3 was updated to allow for inclusion of inattentive subtype of ADHD. *Exclusion Criterion #5 wording was updated for clarification that only clinically significant electrocardiograms were exclusionary. *Exclusion Criterion #15 wording was changed to specifically exclude past or present active suicidal ideation and to clarify that intermittent passive suicidal ideation was not necessarily exclusionary. *Exclusion Criterion #17 wording was updated to exclude those with a presence of a serious tic disorder. *Exclusion Criterion #18 was added to exclude subjects if another member of the same household was currently participating in the study. *Body mass index was deleted from Visits 13 and 23. *Follow-up contact was changed to follow-up visit. *Added that the subject's lifetime non-pharmacological interventions (behavioral therapy) for ADHD were to be collected. *Added that a subject could have continued participation in behavioral therapy, provided they had been receiving the therapy for at least 1 month at the time of Enrollment/Visit 2/Week 0 and that the behavioral therapy must have remained stable throughout the study. *The fasting requirement was removed for biochemistry samples and it was clarified that samples could have been drawn with the subject in a fasting or non-fasting state. *The Prior Psychoactive Medication Questionnaire and the Oppositional subscale of the CPRS-R:L were added and study assessments and statistical methods sections were updated accordingly.
01 March 2011	Following responses from the Ethics Committees in Spain, Germany, and The Netherlands, Exclusion Criterion #2 was added to exclude subjects who were well-controlled on their current ADHD medication with acceptable tolerability and the parent/caregiver did not object to the current ADHD medication.
27 November 2012	*Time to treatment failure was added as a key secondary endpoint. Statistical methods sections were updated accordingly. Time to treatment failure is the key secondary objective as defined in the final SAP (Version 3.0 dated 23 May 2013). *"Temperature" or "oral temperature" was changed to "temperature (oral or tympanic)" to clarify that a subject's temperature could have been obtained via oral or tympanic readings. *The sentence "Medical history will be summarized by treatment group using the number of observations and percentages of subjects reporting each category" was deleted, as medical history was not being coded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported