Clinical trial results:
A Phase 3b, Double-blind, Randomised, Active-controlled, Parallel-group Study to Compare the Time to Response of Lisdexamfetamine Dimesylate to Atomoxetine Hydrochloride in Children and Adolescents Aged 6-17 Years With Attention Deficit/Hyperactivity Disorder (ADHD) Who Have Had an Inadequate Response to Methylphenidate Therapy.

Summary

EudraCT number	2009-011745-94
Trial protocol	GB DE SE FR ES BE PL HU IT
Global end of trial date	19 July 2012

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	02 May 2015

Trial information

Trial identification

Sponsor protocol code	SPD489-317

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01106430
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	Medical Communications, Medical Communications, +44 0800055 6614, medinfoglobal@shire.com
Scientific contact	Medical Communications, Medical Communications, +44 0800055 6614, medinfoglobal@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000553-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	19 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2012
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 compare the time to response of lisdexamfetamine dimesylate (SPD489) with that of atomoxetine hydrochloride (STRATTERA) in subjects who were judged by the Investigator to have had an inadequate response to methylphenidate (MPH) treatment, where inadequate response included, but was not limited to, the presence of some residual symptoms, inadequate duration of action and/or variability of symptom control, and/or Investigator felt that the subject may have derived benefit from an alternative treatment to MPH therapy. The primary efficacy measure was time to response; where individual subject response was assessed using the Clinical Global Impressions – Global Improvement (CGI-I) Scale.

Protection of trial subjects:

The study was conducted in accordance with International Council on Harmonisation Good Clinical Practice (GCP) Guideline E6 (1996), European Union Directive 2001/20/EC (2001), and applicable regulatory requirements and guidelines.

Background therapy: -

Evidence for comparator:

STRATTERA (atomoxetine) is a nonstimulant therapy approved for the treatment of ADHD.

Actual start date of recruitment	28 June 2010
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	Poland: 1
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 138
Country: Number of subjects enrolled	Canada: 35
Worldwide total number of subjects	267
EEA total number of subjects	94

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)	179
Adolescents (12-17 years)	88
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 in this study at 51 sites in the European Union and North America.

Pre-assignment

Screening details:

The screening period lasted up to 11 days and included a washout phone call.

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	Investigator, Subject

Blinding implementation details:

Reference product was over-encapsulated and appeared identical to the test product to protect the study blind. To maintain the blind, all subjects, regardless of treatment group, who weighed >64.5kg at the Baseline Visit (Visit 0) were instructed to take 2 capsules daily. Subjects randomized to SPD489 took 1 SPD489 capsule and 1 placebo capsule. Subjects randomized to Strattera and up-titrated to 80mg took two 40mg capsules; those up-titrated to 100mg took one 40mg capsule and one 60mg capsule.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lisdexamfetamine Dimesylate

Arm description:

Lisdexamfetamine Dimesylate (LDX, Vyvanse, SPD489) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at doses of 30, 50, or 70 mg.

Arm type	Experimental
Investigational medicinal product name	Lisdexamfetamine Dimesylate
Investigational medicinal product code	
Other name	Vyvanse, LDX, SPD489
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A combination of 30, 50, or 70mg capsules once-daily for 9 weeks. The beginning dose for all subjects randomized to SPD489 was 30mg/day for the first week, with subsequent dose increases adjusted based on increments of 20mg such that at the beginning of the second week, subjects were up-titrated to 50mg/day, if required, with a further up-titration to 70mg/day, if required, at the beginning of the third week. The first dose of investigational product was to be taken the morning after the Baseline Visit (at 7:00AM ±2 hours).

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

Dosage and administration details:

One placebo capsule once daily for subjects who weighed >64.5kg at the Baseline Visit (Visit 0).

Arm title	Atomoxetine Hydrochloride

Arm description:

Atomoxetine Hydrochloride (Strattera) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at weight adjusted

doses of 10 mg to 100 mg.

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 for a total dose of 10mg to 100mg once-daily for 9 weeks. For subjects weighing <70kg at the Baseline Visit (Visit 0), Strattera dosing was based on body weight (mg/kg). The beginning dose for these subjects was 0.5mg/kg/day for the first week. At the beginning of the second week, subjects were up-titrated to a final target dose of approximately 1.2mg/kg/day, not to exceed 1.4mg/kg/day. For subjects weighing >/= 70kg at the Baseline Visit (Visit 0), the beginning dose of Strattera was 40mg/day for the first week. At the beginning of the second week, subjects were up-titrated to 80mg/day, with a further up-titration to 100mg/day, if required, at the beginning of the third week. The first dose of investigational product was to be taken the morning after the Baseline Visit (at 7:00AM ±2 hours).

Number of subjects in period 1	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride
Started	133	134
Completed	100	101
Not completed	33	33
'Previous use of marijuana '	1	-
Moved out of state	-	1
Hard time swallowing the pills	1	-
Early termination requested by sponsor	1	-
Protocol violation	7	2
'Noncompliance '	-	1
Adverse event	8	10
Lost to follow-up	5	1
Refused to take medication	-	1
Lack of efficacy	2	13
Withdrawal by subject	8	4

Baseline characteristics

Reporting groups	
Reporting group title	Lisdexamfetamine Dimesylate
Reporting group description:	
Lisdexamfetamine Dimesylate (LDX, Vyvanse, SPD489) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at doses of 30, 50, or 70 mg.	
Reporting group title	Atomoxetine Hydrochloride
Reporting group description:	
Atomoxetine Hydrochloride (Strattera) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at weight adjusted doses of 10 mg to 100 mg.	

Reporting group values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride	Total
Number of subjects	133	134	267
Age categorical			
Baseline characteristics are reported for enrolled subjects.			
Units: Subjects			
6-12 years	99	100	199
13-17 years	34	34	68
Age continuous			
Baseline characteristics are reported for enrolled subjects.			
Units: years			
arithmetic mean	10.8	10.4	
standard deviation	± 2.98	± 2.84	-
Gender categorical			
Baseline characteristics are reported for enrolled subjects.			
Units: Subjects			
Female	34	31	65
Male	99	103	202
Study enrollment by country			
Baseline characteristics are reported for enrolled subjects.			
Units: Subjects			
Canada	17	18	35
Germany	20	22	42
Hungary	10	10	20
Italy	1	0	1
Poland	0	1	1
Spain	12	10	22
Sweden	3	3	6
United States	70	68	138
Belgium	0	2	2

End points

End points reporting groups

Reporting group title	Lisdexamfetamine Dimesylate
Reporting group description:	
Lisdexamfetamine Dimesylate (LDX, Vyvanse, SPD489) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at doses of 30, 50, or 70 mg.	
Reporting group title	Atomoxetine Hydrochloride
Reporting group description:	
Atomoxetine Hydrochloride (Strattera) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at weight adjusted doses of 10 mg to 100 mg.	
Subject analysis set title	Lisdexamfetamine Dimesylate
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set includes all subjects who were randomized and who received at least 1 dose of investigational product.	
Subject analysis set title	Atomoxetine Hydrochloride
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set includes all subjects who were randomized and who received at least 1 dose of investigational product. One subject was randomized to receive Strattera but actually received SPD489. Based on the intention-to-treat principle, this subject is included in the Strattera arm for the efficacy analysis.	

Primary: Time to First Response

End point title	Time to First Response
End point description:	
Time to first response was defined as a Clinical Global Impression-Improvement (CGI-I) value of 1 (very much improved) or 2 (much improved) first recorded following first dose of investigational product. CGI-I consists of a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). This endpoint analyzed the Full Analysis Set, defined as all subjects who were randomized and who received at least 1 dose of investigational product.	
End point type	Primary
End point timeframe:	
9 weeks	

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	135		
Units: days				
median (confidence interval 95%)	12 (8 to 16)	21 (15 to 23)		

Statistical analyses

Statistical analysis title	Analysis of time to first response
Comparison groups	Lisdexamfetamine Dimesylate v Atomoxetine Hydrochloride

Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Peto-Peto-Prentice Wilcoxon Test

Secondary: Percent of Participants With Improvement on Clinical Global Impression-Improvement (CGI-I) Score - Last Observation Carried Forward (LOCF)

End point title	Percent of Participants With Improvement on Clinical Global Impression-Improvement (CGI-I) Score - Last Observation Carried Forward (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.
This endpoint analyzed the Full Analysis Set, defined as all subjects who were randomized and who received at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Week 9

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	132		
Units: percent of subjects responded				
number (not applicable)	81.7	63.6		

Statistical analyses

Statistical analysis title	Analysis of CGI-I score
Comparison groups	Lisdexamfetamine Dimesylate v Atomoxetine Hydrochloride
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percent (SPD489-Strattera)
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	28.7

Secondary: Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-Fourth Edition (ADHD-RS-IV) Total Score at Week 9- LOCF

End point title	Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-Fourth Edition (ADHD-RS-IV) Total Score at Week 9- LOCF

End point description:

ADHD-RS-IV consists of 18 items scored on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms) with total score ranging from 0 to 54. A decrease in score indicates an improvement in ADHD symptomology.
This endpoint analyzed the Full Analysis Set, defined as all subjects who were randomized and who received at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Baseline and 9 weeks

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	133		
Units: units on a scale				
least squares mean (standard error)	-26.1 (± 1.16)	-19.7 (± 1.13)		

Statistical analyses

Statistical analysis title	Analysis of ADHD-RS-IV total score
Comparison groups	Lisdexamfetamine Dimesylate v Atomoxetine Hydrochloride
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in least squares means
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	-3.6

Secondary: Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Global Score at Endpoint

End point title	Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Global Score at

	Endpoint

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.
This endpoint analyzed the Full Analysis Set, defined as all subjects who were randomized and who received at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Baseline and endpoint

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	113		
Units: units on a scale				
least squares mean (standard error)	-0.35 (± 0.034)	-0.27 (± 0.032)		

Statistical analyses

Statistical analysis title	Analysis of WFIRS-P global score
Comparison groups	Lisdexamfetamine Dimesylate v Atomoxetine Hydrochloride
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046
Method	ANCOVA
Parameter estimate	Difference in least squares means
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0

Secondary: Health Utilities Index-2 (HUI-2) Score at Endpoint

End point title	Health Utilities Index-2 (HUI-2) Score at Endpoint

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.
This endpoint analyzed the Full Analysis Set, defined as all subjects who were randomized and who received at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Endpoint

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	123		
Units: units on a scale				
arithmetic mean (standard deviation)	0.92 (± 0.0961)	0.922 (± 0.0937)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Endpoint

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

End point description:

The BPRS-C characterizes psychopathology. 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.
This endpoint analyzed the Safety Population, defined as all subjects who were randomized and who had taken at least 1 dose of investigational product.

End point type	Other pre-specified

End point timeframe:

Baseline and endpoint

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	123		
Units: units on a scale				
arithmetic mean (standard deviation)	-10.7 (± 9.27)	-7.9 (± 9.07)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 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.
This endpoint analyzed the Safety Population, defined as all subjects who were randomized and who had taken at least 1 dose of investigational product.

End point type	Other pre-specified

End point timeframe:

9 weeks

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	132		
Units: subjects				
Suicidal Ideation	0	0		
Suicidal Behavior	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Udvalg for Kliniske Undersogelser Side Effect Rating Scale - Clinician (UKU-SERS-Clin) With Side Effects Scores >=1

End point title	Udvalg for Kliniske Undersogelser Side Effect Rating Scale - Clinician (UKU-SERS-Clin) With Side Effects Scores >=1

End point description:

UKU-SERS-Clin is composed of 48 items each of which asks about a single side effect. Each side effect is rated based on a 4-point scale ranging from 0 (no or doubtful presence) to 3 (the least favorable rating). The rating is independent of whether the symptom is regarded as related to the investigational product.
This endpoint analyzed the Safety Population, defined as all subjects who were randomized and who had taken at least 1 dose of investigational product.

End point type	Other pre-specified

End point timeframe:

9 weeks

End point values	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	132		
Units: subjects				
Weight Loss	46	19		
Reduced Duration of Sleep	29	16		
Asthenia/Lassitude/Increased Fatigability	25	29		
Tension/Inner Unrest	20	22		
Nausea/Vomiting	19	26		
Sleepiness/Sedation	16	35		
Reduced Salivation	16	6		

Headache-Tension Headache	15	17		
Concentration Difficulties	75	92		
Failing Memory	10	21		
Depression	6	10		
Increased Duration of Sleep	12	12		
Increased Dream Activity	3	8		
Emotional Indifference	12	10		
Dystonia	0	1		
Rigidity	0	1		
Hypokinesia/Akinesia	1	0		
Hyperkinesia Logic	2	3		
Tremor	3	1		
Akathisia	0	2		
Paraesthesias	1	0		
Accomodation Disturbances	0	2		
Increased Salivation	1	2		
Diarrhea	6	9		
Constipation	9	5		
Micturition Disturbances	0	1		
Polyuria/Polydipsia	3	2		
Orthostatic Dizziness	10	9		
Palpitations/Tachycardia	1	5		
Increased Tendency to Sweating	3	5		
Rash-Morbiliform	0	1		
Rash-Petechial	1	0		
Rash-Urticarial	1	1		
Rash-Cannot be Classified	1	2		
Pruritus	4	7		
Weight Gain	7	8		
Headache-Migraine	2	2		
Headache-Other Forms	11	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
70 days	
Adverse event reporting additional description:	
Safety Population, defined as all subjects who were randomized and who had taken at least 1 dose of investigational product.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Lisdexamfetamine Dimesylate
Reporting group description:	
Lisdexamfetamine Dimesylate (LDX, Vyvanse, SPD489) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at doses of 30, 50, or 70 mg.	
Reporting group title	Atomoxetine Hydrochloride
Reporting group description:	
Atomoxetine Hydrochloride (Strattera) was administered orally once-daily at approximately 7:00am for 9 weeks (4-week dose optimization period and a 5-week dose maintenance period) at weight adjusted doses of 10 mg to 100 mg.	

Serious adverse events	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 128 (0.00%)	0 / 134 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Lisdexamfetamine Dimesylate	Atomoxetine Hydrochloride	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 128 (71.88%)	95 / 134 (70.90%)	
Investigations			
Weight decreased			
subjects affected / exposed	28 / 128 (21.88%)	9 / 134 (6.72%)	
occurrences (all)	30	9	
Nervous system disorders			

Headache			
subjects affected / exposed	17 / 128 (13.28%)	22 / 134 (16.42%)	
occurrences (all)	25	29	
Sedation			
subjects affected / exposed	5 / 128 (3.91%)	8 / 134 (5.97%)	
occurrences (all)	5	9	
Somnolence			
subjects affected / exposed	4 / 128 (3.13%)	16 / 134 (11.94%)	
occurrences (all)	4	23	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 128 (9.38%)	14 / 134 (10.45%)	
occurrences (all)	14	16	
Irritability			
subjects affected / exposed	8 / 128 (6.25%)	3 / 134 (2.24%)	
occurrences (all)	8	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 128 (2.34%)	8 / 134 (5.97%)	
occurrences (all)	3	10	
Abdominal pain upper			
subjects affected / exposed	3 / 128 (2.34%)	10 / 134 (7.46%)	
occurrences (all)	3	12	
Constipation			
subjects affected / exposed	8 / 128 (6.25%)	2 / 134 (1.49%)	
occurrences (all)	9	2	
Diarrhoea			
subjects affected / exposed	2 / 128 (1.56%)	9 / 134 (6.72%)	
occurrences (all)	3	11	
Dry mouth			
subjects affected / exposed	8 / 128 (6.25%)	4 / 134 (2.99%)	
occurrences (all)	8	4	
Nausea			
subjects affected / exposed	16 / 128 (12.50%)	21 / 134 (15.67%)	
occurrences (all)	16	27	
Vomiting			

subjects affected / exposed occurrences (all)	6 / 128 (4.69%) 6	13 / 134 (9.70%) 17	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 15 / 128 (11.72%) 16	 8 / 134 (5.97%) 8	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 8 / 128 (6.25%) 9 3 / 128 (2.34%) 3	 8 / 134 (5.97%) 9 8 / 134 (5.97%) 8	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 33 / 128 (25.78%) 36	 14 / 134 (10.45%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2010	Important changes to the protocol set forth by Amendment 1 include: * Australia was added. * The number of proposed sites was increased. * The number of subjects to be randomized was increased. * A fixed-block randomization was to be done within each country. * The study design was modified to a group sequential clinical trial design. * The following extensions were made to the study design: - The Double-blind Treatment Period was extended. This included a 4-week dose optimization period and a dose maintenance period that was increased; - The study period was extended; - The number of visits was increased. * The total duration of the study was increased * A definition for inadequate response to MPH therapy was added. * Secondary objectives were added: - To assess the impact of SPD489 compared to STRATTERA on the perception of health state preferences via the HUI-2. - To monitor subject safety via the BPRS-C, the C-SSRS, and the UKU-SERS-Clin. * The study schedule was modified to include the HUI-2, BPRS-C, C-SSRS, and UKU-SERS-Clin assessments and to specify at what visits these were to be performed. * A section describing the suitability of the subject to remain in the study was added. * The safety follow-up was changed from a phone call to a site visit. * Assessments performed at the Safety Follow-up Visit (Visit 10) were specified. * An upward dose titration limit of 100mg STRATTERA was added for subjects weighing >/= 70kg. * A chronic or current tic disorder or history of tics was added as an exclusion criterion. * Additional subjects were to be recruited if more than 20% of subjects were prematurely discontinued. * A window of ±2 hour was added for dosing. * The number of capsules taken per visit was specified based on subject weight. * It was specified that the ADHD-RS-IV was to be completed by a physician. * The assumed cumulative response rates for each treatment group were updated. * An external DSMB was added.

15 December 2010	Important changes to the protocol set forth by Amendment 2 include: * Australia was removed. * Randomization was to be stratified by country. * The definition of inadequate response to MPH therapy was modified. * The Screening Period was to be from Day -14 to Day -3. * Down-titration was to only occur within the first 4 weeks. * Electrocardiogram was added as a safety endpoint. * Clarification that the change from baseline in the ADHD-RS-IV Total Score was a secondary endpoint. * The following changes involved inclusion or exclusion criteria: - Subjects using a standard dose of inhaled beta-agonist were allowed study entry; - Subjects who had taken >1 MPH or who previously had intolerable side effects to 1 or more MPH treatments were excluded; - Subjects with intermittent passive suicidal ideation were not necessarily excluded; - Subjects with a known CYP2D6 poor metabolizer genotype were excluded; - Subjects with a known penicillin allergy were excluded; - Subjects with current or anticipated inpatient care were excluded; - Subjects taking medications that caused orthostatic hypotension were excluded. * An Enrolled Population was added. * Assessment scales were to be administered by the same person, as appropriate, whenever possible. * Certain assessments (ADHD-RS-IV, CGI, physical examination, BPRS-C, C-SSRS, and UKU-SERS-Clin) were to be performed by a qualified rater/individual. * The external DSMB was renamed to DMC. * The internal DMC was renamed to DRC. * Subjects who were prematurely discontinued from the study were to be censored at Visit 9. * A supportive analysis was performed on the cumulative proportion of ADHD-RS-IV responders based on LOCF rather than observed data. * HUI-2 and WFIRS-P were recategorized as a health outcome and a functional outcome, respectively. * ANCOVA for ADHD-RS-IV Total Score was to include country as a blocking factor. * The definition of a treatment-emergent AE was expanded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported