Clinical trial results:
A Phase 4, Randomized, Double-blind, Multicenter, Parallel-group, Active-controlled, Forced-dose Titration, Safety and Efficacy Study of SPD489 (VYVANSE®) Compared With OROS-MPH (CONCERTA®) With a Placebo Reference Arm, in Adolescents Aged 13-17 Years With Attention-deficit/Hyperactivity Disorder (ADHD)

Summary

EudraCT number	2011-005452-34
Trial protocol	DE IT HU SE
Global end of trial date	22 May 2014

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	20 March 2015

Trial information

Trial identification

Sponsor protocol code	SPD489-406

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01552902
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard, Wayne, Pennsylvania, United States, 19087
Public contact	Medical Communications, Shire Pharmaceutical Development Ltd., +44 8000556614, medinfoglobal@shire.com
Scientific contact	Medical Communications, Shire Pharmaceutical Development Ltd., +44 8000556614, medinfoglobal@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lisdexamfetamine dimesylate 70 milligram (mg) compared with osmotic controlled oral release delivery system-methylphenidate (OROS-MPH) 72 mg in adolescents (13-17 years of age, inclusive) with ADHD.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 493
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	European Union: 31
Worldwide total number of subjects	549
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	549
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 77 sites in the United States, Canada, and Europe.

Pre-assignment

Screening details:

Of the 778 screened subjects, 229 were screen failures and 549 were randomized to treatment. A total of 547 subjects were treated and the reasons for 2 'randomized but not treated' subjects included withdrawal by 1 subject in the Methylphenidate group and 1 subject with a protocol violation in the Lisdexamfetamine group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

2 placebo over encapsulated capsules once daily orally for 6 weeks.

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

Dosage and administration details:

2 placebo over encapsulated capsules once daily orally for 6 weeks.

Arm title	Lisdexamfetamine dimesylate

Arm description:

Lisdexamfetamine dimesylate (LDX, Vyvanse®, SPD489) 30 to 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 4 weeks (forced dose titration), followed by LDX 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 2 weeks (dose maintenance).

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

Dosage and administration details:

2 placebo over encapsulated capsules once daily orally for 6 weeks.

Investigational medicinal product name	Lisdexamfetamine dimesylate
Investigational medicinal product code	SPD489
Other name	Elvanse, Tyvense, Vyvanse, LDX
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lisdexamfetamine dimesylate (LDX, Vyvanse®, SPD489) 30 to 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 4 weeks (forced dose titration), followed by LDX 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 2 weeks (dose maintenance).

Arm title	Methylphenidate

Arm description:

Methylphenidate (Concerta, OROS-MPH) 18 to 72 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule (no placebo administered when methylphenidate 72 mg [2*36 mg capsules] was administered) for 4 weeks (forced dose titration), followed by methylphenidate 72 mg (2*36 mg capsules) over encapsulated capsule once daily orally for 2 weeks (dose maintenance).

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

Dosage and administration details:

2 placebo over encapsulated capsules once daily orally for 6 weeks.

Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	
Other name	Concerta, OROS-MPH
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Methylphenidate (Concerta, OROS-MPH) 18 to 72 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule (no placebo administered when methylphenidate 72 mg [2*36 mg capsules] was administered) for 4 weeks (forced dose titration), followed by methylphenidate 72 mg (2*36 mg capsules) over encapsulated capsule once daily orally for 2 weeks (dose maintenance).

Number of subjects in period 1[1]	Placebo	Lisdexamfetamine dimesylate	Methylphenidate
Started	110	218	219
Completed	97	181	186
Not completed	13	37	33
Consent withdrawn by subject	1	9	6
Protocol violation	3	3	3
Adverse event	1	15	14
Unspecified	3	4	3
Lost to follow-up	1	3	6
Lack of efficacy	4	3	1

Notes:

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

in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
2 placebo over encapsulated capsules once daily orally for 6 weeks.	
Reporting group title	Lisdexamfetamine dimesylate
Reporting group description:	
Lisdexamfetamine dimesylate (LDX, Vyvanse®, SPD489) 30 to 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 4 weeks (forced dose titration), followed by LDX 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 2 weeks (dose maintenance).	
Reporting group title	Methylphenidate
Reporting group description:	
Methylphenidate (Concerta, OROS-MPH) 18 to 72 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule (no placebo administered when methylphenidate 72 mg [2*36 mg capsules] was administered) for 4 weeks (forced dose titration), followed by methylphenidate 72 mg (2*36 mg capsules) over encapsulated capsule once daily orally for 2 weeks (dose maintenance).	

Reporting group values	Placebo	Lisdexamfetamine dimesylate	Methylphenidate
Number of subjects	110	218	219
Age categorical			
Age was calculated as the difference between date of birth and date of informed consent. The Safety set consisted of all subjects in the Randomized set (all screened subjects for whom a randomization number was generated) who took at least 1 dose of investigational product.			
Units: Subjects			
Less Than or Equal to 18 Years	110	218	219
Between 18 and 65 Years	0	0	0
Greater Than or Equal to 65 Years	0	0	0
Age continuous			
Age was calculated as the difference between date of birth and date of informed consent. Safety set.			
Units: years			
arithmetic mean	14.7	14.6	14.7
standard deviation	± 1.37	± 1.38	± 1.42
Gender categorical			
Safety set.			
Units: Subjects			
Female	34	83	69
Male	76	135	150
ADHD Subtype			
Safety set.			
Units: Subjects			
Predominantly Inattentive	40	70	71
Predominantly Hyperactive/Impulsive	2	2	4
Combined Subtype	68	146	144
Clinical Global Impressions – Severity of Illness (CGI-S)			
The Clinical Global Impressions Scale permits a global evaluation of the subject's severity of illness and improvement over time. The scale includes a severity of illness item and a global improvement item. The investigator performed the CGI-S to rate the severity of a 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; or 7=extremely ill). Safety set.			
Units: Subjects			
Borderline mentally ill	1	0	0
Mildly ill	2	4	1
Moderately ill	60	93	115
Markedly ill	41	106	90
Severely ill	6	15	13
Attention-deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) Total Score			
The ADHD-RS-IV was developed to measure the behaviors of children with ADHD and is commonly used in clinical studies of ADHD. The ADHD-RS-IV consisted of 18 items designed to reflect current symptomatology of ADHD based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-Text Revision (DSM-IV-TR) criteria. Each item was scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0-54, Higher score = more severe symptoms. Safety set.			
Units: Units on a scale			
arithmetic mean	36.1	37.2	36.9
standard deviation	± 5.91	± 6.46	± 6.42

Reporting group values	Total		
Number of subjects	547		
Age categorical			
Age was calculated as the difference between date of birth and date of informed consent. The Safety set consisted of all subjects in the Randomized set (all screened subjects for whom a randomization number was generated) who took at least 1 dose of investigational product.			
Units: Subjects			
Less Than or Equal to 18 Years	547		
Between 18 and 65 Years	0		
Greater Than or Equal to 65 Years	0		
Age continuous			
Age was calculated as the difference between date of birth and date of informed consent. Safety set.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Safety set.			
Units: Subjects			
Female	186		
Male	361		
ADHD Subtype			
Safety set.			
Units: Subjects			
Predominantly Inattentive	181		
Predominantly Hyperactive/Impulsive	8		
Combined Subtype	358		
Clinical Global Impressions – Severity of Illness (CGI-S)			
The Clinical Global Impressions Scale permits a global evaluation of the subject's severity of illness and improvement over time. The scale includes a severity of illness item and a global improvement item. The investigator performed the CGI-S to rate the severity of a 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; or 7=extremely ill). Safety set.			
Units: Subjects			
Borderline mentally ill	1		
Mildly ill	7		
Moderately ill	268		
Markedly ill	237		
Severely ill	34		
Attention-deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) Total Score			
The ADHD-RS-IV was developed to measure the behaviors of children with ADHD and is commonly used in clinical studies of ADHD. The ADHD-RS-IV consisted of 18 items designed to reflect current symptomatology of ADHD based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-Text Revision (DSM-IV-TR) criteria. Each item was scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0-54, Higher score = more severe symptoms. Safety set.			
Units: Units on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

2 placebo over encapsulated capsules once daily orally for 6 weeks.

Reporting group title	Lisdexamfetamine dimesylate

Reporting group description:

Lisdexamfetamine dimesylate (LDX, Vyvanse®, SPD489) 30 to 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 4 weeks (forced dose titration), followed by LDX 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 2 weeks (dose maintenance).

Reporting group title	Methylphenidate

Reporting group description:

Methylphenidate (Concerta, OROS-MPH) 18 to 72 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule (no placebo administered when methylphenidate 72 mg [2*36 mg capsules] was administered) for 4 weeks (forced dose titration), followed by methylphenidate 72 mg (2*36 mg capsules) over encapsulated capsule once daily orally for 2 weeks (dose maintenance).

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS consisted of a total of 532 subjects (106 in placebo, 210 in Lisdexamfetamine dimesylate, and 216 in Methylphenidate) which was defined as all subjects in the Safety set who had at least 1 post-baseline measurement of the ADHD-RS-IV.

Primary: Change From Baseline in Attention-Deficit/Hyperactivity Disorder Rating Scale, Fourth Edition (ADHD-RS-IV) Total Score at Week 6

End point title	Change From Baseline in Attention-Deficit/Hyperactivity Disorder Rating Scale, Fourth Edition (ADHD-RS-IV) Total Score at Week 6

End point description:

The ADHD-RS-IV was developed to measure the behaviors of children with ADHD and is commonly used in clinical studies of ADHD. The ADHD-RS-IV consisted of 18 items designed to reflect current symptomatology of ADHD based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-Text Revision (DSM-IV-TR) criteria. Each item was scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0-54, Higher score = more severe symptoms.
FAS.

End point type	Primary

End point timeframe:

Baseline, Week 6

End point values	Placebo	Lisdexamfetamine dimesylate	Methylphenidate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93[1]	175[2]	181[3]	
Units: Units on a scale				
least squares mean (standard error)	-17 (± 1.03)	-25.4 (± 0.74)	-22.1 (± 0.73)	

Notes:

[1] - Not all FAS subjects were evaluable for this endpoint.

[2] - Not all FAS subjects were evaluable for this endpoint.

[3] - Not all FAS subjects were evaluable for this endpoint.

Statistical analyses

Statistical analysis title	Lisdexamfetamine versus Methylphenidate

Statistical analysis description:

The least squares mean (LSM), the difference in LSM and its 95% confidence interval (CI), and the p-value were from a mixed effects model for repeated measures that included treatment group, visit, interaction of the treatment group with the visit as factors, baseline score as a covariate, and an adjustment for the interaction of the baseline score with the visit. The model was based on Restricted maximum likelihood (REML) method of estimation and utilized an unstructured covariance.

Comparison groups	Lisdexamfetamine dimesylate v Methylphenidate
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Mixed models analysis
Parameter estimate	Difference in LSM
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	-1.3

Statistical analysis title	Methylphenidate versus Placebo

Statistical analysis description:

The LSM, the difference in LSM and its 95% CI, and the p-value were from a mixed effects model for repeated measures that includes treatment group, visit, interaction of the treatment group with the visit as factors, baseline score as a covariate, and an adjustment for the interaction of the baseline score with the visit. The model was based on REML method of estimation and utilized an unstructured covariance.

Comparison groups	Methylphenidate v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference in LSM
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	-2.6

Statistical analysis title	Lisdexamfetamine versus Placebo

Statistical analysis description:

The LSM, the difference in LSM and its 95% CI, and the p-value were from a mixed effects model for repeated measures that included treatment group, visit, interaction of the treatment group with the visit as factors, baseline score as a covariate, and an adjustment for the interaction of the baseline score with the visit. The model was based on REML method of estimation and utilized an unstructured covariance.

Comparison groups	Lisdexamfetamine dimesylate v Placebo
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference in LSM
Point estimate	-8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	-6

Secondary: Percentage of Subjects With an Improved Measurement in the Clinical Global Impression - Global Improvement (CGI-I) at Week 6

End point title	Percentage of Subjects With an Improved Measurement in the Clinical Global Impression - Global Improvement (CGI-I) at Week 6

End point description:

The Clinical Global Impressions Scale permits a global evaluation of the subject's severity of illness and improvement over time. The scale included a severity of illness item and a global improvement item. The investigator performed the CGI-I to rate the improvement of a subject's ADHD symptoms based on a 7-point scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; or 7=very much worse.). Percentage of subjects with an improved measurement (response of very much improved and much improved) is reported.
FAS.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	Lisdexamfetamine dimesylate	Methylphenidate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	106	210	216	
Units: Percentage of subjects				
number (not applicable)	50	81.4	71.3	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation subject administered as a pharmaceutical product that did not necessarily have a causal relationship with this treatment. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs were events between first dose of double-blind investigational product and up to 3 days after last dose that were absent before treatment or that worsened relative to pretreatment state.
Safety set.

End point type	Other pre-specified

End point timeframe:

Baseline up to 3 days after last dose (last dose at Week 6)

End point values	Placebo	Lisdexamfetamine dimesylate	Methylphenidate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	218	219	
Units: Subjects				
Subjects with TEAEs	49	145	129	
Subjects with serious TEAEs	1	1	1	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Blood Pressure at Week 6

End point title	Change From Baseline in Blood Pressure at Week 6

End point description:

Safety set.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 6

End point values	Placebo	Lisdexamfetamine dimesylate	Methylphenidate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93[4]	175[5]	181[6]	
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic blood pressure	-1 (± 9.88)	1.5 (± 9.56)	2.4 (± 9.97)	
Diastolic blood pressure	-0.1 (± 8.1)	3.4 (± 8.15)	3.5 (± 8.59)	

Notes:

[4] - Not all Safety set subjects were evaluable for this endpoint.

[5] - Not all Safety set subjects were evaluable for this endpoint.

[6] - Not all Safety set subjects were evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Pulse Rate at Week 6

End point title	Change from Baseline in Pulse Rate at Week 6
End point description: Safety set.	
End point type	Other pre-specified
End point timeframe: Baseline, Week 6	

End point values	Placebo	Lisdexamfetamine dimesylate	Methylphenidate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	93[7]	175[8]	181[9]	
Units: Beats per minute				
arithmetic mean (standard deviation)	2.4 (± 10.81)	6.7 (± 12.46)	8.2 (± 12.7)	

Notes:

[7] - Not all Safety set subjects were evaluable for this endpoint.

[8] - Not all Safety set subjects were evaluable for this endpoint.

[9] - Not all Safety set subjects were evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 3 days after last dose (last dose at Week 6)

Adverse event reporting additional description:

AEs occurred during the double-blind evaluation phase were considered as TEAEs if AEs had a start date on or after the first dose of double-blind study drug or a start date before the date of the first dose of double-blind study drug, but increased in severity on or after the date of the first dose of double-blind study drug.
Safety set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

2 placebo over encapsulated capsules once daily orally for 6 weeks.

Reporting group title	Methylphenidate

Reporting group description:

Methylphenidate (Concerta, OROS-MPH) 18 to 72 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule (no placebo administered when methylphenidate 72 mg [2*36 mg capsules] was administered) for 4 weeks (forced dose titration), followed by methylphenidate 72 mg (2*36 mg capsules) over encapsulated capsule once daily orally for 2 weeks (dose maintenance).

Reporting group title	Lisdexamfetamine dimesylate

Reporting group description:

Lisdexamfetamine dimesylate (LDX, Vyvanse®, SPD489) 30 to 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 4 weeks (forced dose titration), followed by LDX 70 mg over encapsulated capsule once daily orally along with placebo over encapsulated capsule for 2 weeks (dose maintenance).

Serious adverse events	Placebo	Methylphenidate	Lisdexamfetamine dimesylate
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 110 (0.91%)	1 / 219 (0.46%)	1 / 218 (0.46%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 110 (0.00%)	0 / 219 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic episode			

subjects affected / exposed	1 / 110 (0.91%)	0 / 219 (0.00%)	0 / 218 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 219 (0.46%)	0 / 218 (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	Placebo	Methylphenidate	Lisdexamfetamine dimesylate
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 110 (29.09%)	99 / 219 (45.21%)	113 / 218 (51.83%)
Investigations			
Weight decreased			
subjects affected / exposed	0 / 110 (0.00%)	11 / 219 (5.02%)	23 / 218 (10.55%)
occurrences (all)	0	11	23
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 110 (8.18%)	35 / 219 (15.98%)	33 / 218 (15.14%)
occurrences (all)	13	40	45
Dizziness			
subjects affected / exposed	0 / 110 (0.00%)	11 / 219 (5.02%)	12 / 218 (5.50%)
occurrences (all)	0	11	12
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	7 / 110 (6.36%)	15 / 219 (6.85%)	11 / 218 (5.05%)
occurrences (all)	7	16	11
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	1 / 110 (0.91%)	7 / 219 (3.20%)	16 / 218 (7.34%)
occurrences (all)	1	7	18
Nausea			
subjects affected / exposed	3 / 110 (2.73%)	11 / 219 (5.02%)	11 / 218 (5.05%)
occurrences (all)	3	11	12

Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2	8 / 219 (3.65%) 8	11 / 218 (5.05%) 11
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 110 (2.73%) 3	17 / 219 (7.76%) 20	17 / 218 (7.80%) 17
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	11 / 110 (10.00%) 11	51 / 219 (23.29%) 52	69 / 218 (31.65%) 74

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2012	Revision of Inclusion Criterion at the request of the Institutional Review Board to indicate that blood pressure measurements should not exceed the 90th percentile.
26 August 2012	1. Increased number of sites from 55 to approximately 65 to support study recruitment 2. Replaced World Health Organization body mass index (BMI) values with Centers for Disease Control and Prevention (CDC) BMI values 3. Revision of reporting instructions for the treatment assignment to be unblinded as soon as possible after the investigator was unblinded 4. Changed the start of the screening and washout phase from 7-28 days to 3-28 days prior to the baseline visit (Visit 0) to address day of enrolment for subjects who did not require a medication washout 5. Clarification that the washout telephone call was applicable to all subjects. Modified washout telephone call procedures 6. Modification that subjects accepted to participate in the pharmacogenomic substudy signed the pharmacogenomic informed consent and assent 7. Revision to include provision for additional care of subjects after the study.
04 January 2013	1. Addition of Europe and Canada to support study recruitment 2. Addition of text indicating randomization would be stratified by geographic region 3. Revision of text regarding Shire's serious adverse event (SAE) reporting information 4. Clarification that timeframe for reporting SAEs was 24 hours (rather than 1 business day) to comply with Medicines and Healthcare Products Regulatory Agency (United Kingdom) 5. Addition of Inclusion Criterion to allow subjects not completely satisfied with aspects of their current ADHD therapy to participate in the study 6. Removal of Exclusion Criterion that disqualified subjects who were well-controlled on their current ADHD medication with acceptable tolerability 7. Increased the number of sites from 65 to approximately 80 to account for the addition of Europe and Canada 8. Inclusion of updated information regarding the definition, period of observation, and recording of AEs 9. Addition of text to indicate that a change in a vital sign or ECG value could represent an AE if clinically relevant 10. Specification of information related to inpatient hospitalization or prolongation of existing hospitalization for SAEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported