Clinical trial results:
A Phase III, Double-Blind, Placebo-Controlled, Randomised Withdrawal, Multicentre, Extension, Safety and Efficacy Study of Lisdexamfetamine Dimesylate (LDX) in Children and Adolescents Aged 6-17 with Attention-Deficit/Hyperactivity Disorder (ADHD)

Summary

EudraCT number	2008-000720-10
Trial protocol	DE FR NL SE BE GB IT HU
Global end of trial date	26 October 2011

Results information

Result version number	v1 (current)
This version publication date	21 June 2018
First version publication date	08 May 2015

Trial information

Trial identification

Sponsor protocol code	SPD489-326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00784654
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	Hampshire International Business Park, Chineham, Basingstoke; Hampshire, United Kingdom, RG24 8EP
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-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 October 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2011
Global end of trial reached?	Yes
Global end of trial date	26 October 2011
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 evaluate the long-term maintenance of efficacy of SPD489, using a composite endpoint based on the attention-deficit/hyperactivity disorder (ADHD) Rating Scale – IV (ADHD-RS-IV) and Clinical Global Impression – Severity of Illness (CGI-S) rating scale, via a randomized withdrawal design in children and adolescents diagnosed with moderately symptomatic ADHD. Children and adolescents were treated with SPD489 (30, 50, or 70mg/day) for at least 6 months prior to entering a 6-week double-blind randomized (SPD489 or placebo) withdrawal period.

Protection of trial subjects:

The subject's informed consent was mandatory for study participation and was obtained in writing. This study was conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH) principles of Good Clinical Practice (GCP), and local ethical and legal requirements, and with the principles of the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989) and 48th (South Africa 1996) World Medical Assemblies, Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2009
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: 8
Country: Number of subjects enrolled	Sweden: 49
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 95
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	276
EEA total number of subjects	236

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)	158
Adolescents (12-17 years)	118
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 41 investigational sites in the European Union (EU) and the United States (US). The following 8 EU countries participated: Germany (12 sites), Sweden (4 sites), Hungary (4 sites), Poland (4 sites), Great Britain (4 sites), France (3 sites), Italy (3 sites), and Belgium (3 sites). Four sites were located in the US.

Pre-assignment

Screening details:

Subjects who had been exposed to double-blind test product for a minimum of 4 weeks, reached Visit 4, and completed the 1-week post-treatment washout during Study SPD489-325 were evaluated for study eligibility. US children and adolescents (6-17 years of age inclusive) were also evaluated for direct entry into the study.

Period 1

Period 1 title	Open-label (Non-randomized)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Lisdexamfetamine Dimesylate (LDX)(Open-label)

Arm description:

Consisted of at least 26 weeks where subjects were titrated to an optimal dose of LDX and then maintained on their optimal dose of open-label LDX.

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

Dosage and administration details:

30, 50, or 70 mg capsule once-daily at approximately 7:00 AM +/- 2 hours

Number of subjects in period 1	Lisdexamfetamine Dimesylate (LDX)(Open-label)
Started	276
Completed	165
Not completed	111
Home situation intolerable	1
'Did not provide end of study page '	1
Mother is a drug addict	1
Protocol violation	7
ADHD-RS score too high for random phase	1
Adverse event	44
Decision of medical monitor	1

Lost to follow-up	11
Met stopping criteria for CGI-S score	1
Withdrawal by subject	22
Lack of efficacy	21

Period 2

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

Blinding implementation details:

The test (SPD489) and reference products (placebo) were over-encapsulated and appeared identical

Arms

Are arms mutually exclusive?	Yes
Arm title	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)

Arm description:

Subjects were randomized to receive their optimal dose of LDX for up to 6 weeks.

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

Dosage and administration details:

Over-encapsulated 30, 50, or 70 mg capsule once-daily at approximately 7:00 AM +/- 2 hours

Arm title	Placebo (Randomized Withdrawal)

Arm description:

Subjects were randomized to receive placebo for up to 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:

Over-encapsulated placebo capsule once-daily at approximately 7:00 AM +/- 2 hours

Number of subjects in period 2[1]	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)
Started	78	79
Completed	60	16
Not completed	18	63
Protocol violation	2	1
Did not complete a visit	1	-
Adverse event	1	1
'Met relapse criteria per investigator '	8	35
Family reasons	-	1
Lack of efficacy	5	18
Withdrawal by subject	1	7

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Eight subjects completed the original protocol design/Open-label period but were not randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Open-label (Non-randomized)
Reporting group description:	
All enrolled subjects	

Reporting group values	Open-label (Non-randomized)	Total	
Number of subjects	276	276	
Age categorical Units: Subjects			
6-12 years	191	191	
13-17 years	85	85	
Age continuous Units: years			
arithmetic mean	10.9		
standard deviation	± 2.82	-	
Gender categorical Units: Subjects			
Female	64	64	
Male	212	212	
Region of enrollment Units: Subjects			
United States	40	40	
Italy	20	20	
United Kingdom	16	16	
France	11	11	
Hungary	28	28	
Belgium	9	9	
Poland	8	8	
Germany	95	95	
Sweden	49	49	

End points

End points reporting groups

Reporting group title	Lisdexamfetamine Dimesylate (LDX)(Open-label)
Reporting group description:	
Consisted of at least 26 weeks where subjects were titrated to an optimal dose of LDX and then maintained on their optimal dose of open-label LDX.	
Reporting group title	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)
Reporting group description:	
Subjects were randomized to receive their optimal dose of LDX for up to 6 weeks.	
Reporting group title	Placebo (Randomized Withdrawal)
Reporting group description:	
Subjects were randomized to receive placebo for up to 6 weeks.	

Primary: Percent of Participants With Treatment Failures at End of the Randomized Withdrawal Period

End point title	Percent of Participants With Treatment Failures at End of the Randomized Withdrawal Period
End point description:	
Treatment failure was defined as a 50% increase (worsening) in Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS-IV) total score and >= 2 point increase (worsening) in the Clinical Global Impression-Severity of Illness (CGI-S) score observed at any visit during the randomized withdrawal period compared to the respective scores at baseline of the randomized withdrawal period. This end point was analysed using the Randomized Full Analysis Set (Randomized FAS), which included all subjects who were randomized and received at least 1 dose of investigational product during the randomized withdrawal period. Subjects without an endpoint value were classed as treatment failures.	
End point type	Primary
End point timeframe:	
Baseline of the randomized withdrawal period and its relevant endpoint	

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	77		
Units: treatment failure subjects-percent				
number (not applicable)	15.8	67.5		

Statistical analyses

Statistical analysis title	Treatment Failures at Endpoint
Comparison groups	Placebo (Randomized Withdrawal) v Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Change From Open-label Baseline in the Attention Deficit Hyperactivity Disorder Rating Scale-Fourth Edition (ADHD-RS-IV) Total Score at Endpoint (Week-26) of the Open-label Period

End point title	Change From Open-label Baseline in the Attention Deficit Hyperactivity Disorder Rating Scale-Fourth Edition (ADHD-RS-IV) Total Score at Endpoint (Week-26) of the Open-label Period

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 end point was analysed using the Open-label Full Analysis set (Open-label FAS), which included all subjects who received at least 1 dose of investigational product during the open-label period.

End point type	Secondary

End point timeframe:

Open-label baseline and Endpoint (Week-26)

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	257			
Units: scores on a scale				
arithmetic mean (standard deviation)	-26.6 (± 11.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomized Withdrawal Baseline in the ADHD-RS-IV Total Score at Endpoint of the Randomized Withdrawal Period

End point title	Change From Randomized Withdrawal Baseline in the ADHD-RS-IV Total Score at Endpoint of the Randomized Withdrawal Period

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 end point was analysed using the Randomized FAS, which included all subjects who were randomized and received at least 1 dose of investigational product during the randomized withdrawal period.

End point type	Secondary

End point timeframe:

Baseline of the randomized withdrawal period and its relevant endpoint

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	73		
Units: scores on a scale				
least squares mean (standard error)	1.2 (± 1.09)	13.8 (± 1.06)		

Statistical analyses

Statistical analysis title	Change From Baseline in ADHD-RS-IV Total Score
Comparison groups	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal) v Placebo (Randomized Withdrawal)
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-12.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	-9.8

Secondary: Percent of Participants With Clinical Global Impression - Severity of Illness (CGI-S) at Endpoint (Week-26) of the Open-label Period

End point title	Percent of Participants With Clinical Global Impression - Severity of Illness (CGI-S) at Endpoint (Week-26) of the Open-label Period

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).
This end point was analysed using the Open-label FAS, which included all subjects who received at least 1 dose of investigational product during the open-label period.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	198			
Units: percentage of subjects				
number (not applicable)				
Normal, not at all ill	39.9			
Borderline mentally ill	46.5			
Mildly ill	1.5			
Moderately ill	6.6			
Markedly ill	4.5			
Severely ill	0.5			
Among the most extremely ill	0.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants With CGI-S at Endpoint of the Randomized Withdrawal Period, LOCF

End point title	Percent of Participants With CGI-S at Endpoint of the Randomized Withdrawal Period, 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).
This end point was analysed using the Randomized FAS, which included all subjects who were randomized and received at least 1 dose of investigational product during the randomized withdrawal period.

End point type	Secondary

End point timeframe:

At endpoint of the randomized withdrawal period

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	73		
Units: percentage of subjects				
number (not applicable)				
Normal, not at all ill	40	8.2		
Borderline mentally ill	41.3	19.2		

Mildly ill	8	11		
Moderately ill	10.7	39.7		
Markedly ill	0	15.1		
Severely ill	0	6.8		
Among the most extremely ill	0	0		

Statistical analyses

Statistical analysis title	CGI-S at Endpoint of The Period
Comparison groups	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal) v Placebo (Randomized Withdrawal)
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Percent of Participants With Improvement on Clinical Global Impression - Improvement (CGI-I) at Endpoint (Week-26) of the Open-label Period

End point title	Percent of Participants With Improvement on Clinical Global Impression - Improvement (CGI-I) at Endpoint (Week-26) of the Open-label Period

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 end point was analysed using the Open-label FAS, which included all subjects who received at least 1 dose of investigational product during the open-label period.
Improvement includes CGI-I categories of very much improved and much improved. No improvement includes all other assessed categories.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	257			
Units: percentage of improved subjects				
number (not applicable)	79.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline in the Health Utilities Index-2 (HUI-2) Scores at Endpoint (Week-26) of the Open-label Period, LOCF

End point title	Change From Open-label Baseline in the Health Utilities Index-2 (HUI-2) Scores at Endpoint (Week-26) of the Open-label Period, 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.
This end point was analysed using the Open-label FAS, which included all subjects who received at least 1 dose of investigational product during the open-label period.

End point type	Secondary

End point timeframe:

At open-label baseline and endpoint (Week-26) of the open-label period

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	223			
Units: scores on a scale				
arithmetic mean (standard deviation)	0.087 (± 0.1307)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomized Withdrawal Baseline in the HUI-2 Scores at Endpoint of the Randomized Withdrawal Period

End point title	Change From Randomized Withdrawal Baseline in the HUI-2 Scores at Endpoint of the Randomized Withdrawal Period

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 end point was analysed using the Randomized FAS, which included all subjects who were randomized and received at least 1 dose of investigational product during the randomized withdrawal period.

End point type	Secondary

End point timeframe:

Baseline of the randomized withdrawal period and its relevant endpoint

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.005 (± 0.0772)	-0.046 (± 0.1098)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline in the Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP-CE:PRF) Global T-score at Endpoint (Week-26) of the Open-label Period

End point title	Change From Open-label Baseline in the Child Health and Illness Profile, Child Edition: Parent Report Form (CHIP-CE:PRF) Global T-score at Endpoint (Week-26) of the Open-label Period

End point description:

The CHIP-CE:PRF evaluates health-related quality of life. It is composed of 5 domains (satisfaction, comfort, resilience, avoidance, and achievement) consisting of a total of 76 items. The global score is an average of the scores for the 5 domains. The majority of items assess frequency of events using a 5-point response format. There is no range for a total score. Raw scale scores were used to generate T-scores. Higher scores indicate better health.
This end point was analysed using the Open-label FAS, which included all subjects who received at least 1 dose of investigational product during the open-label period.

End point type	Secondary

End point timeframe:

At open-label baseline and endpoint (Week -26) of the open-label period

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: T-scores				
arithmetic mean (standard deviation)	10.2 (± 10.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomized Withdrawal Baseline in the CHIP-CE:PRF Global T-score at Endpoint of the Randomized Withdrawal Period

End point title	Change From Randomized Withdrawal Baseline in the CHIP-CE:PRF Global T-score at Endpoint of the Randomized Withdrawal Period

End point description:

The CHIP-CE:PRF evaluates health-related quality of life. It is composed of 5 domains (satisfaction, comfort, resilience, avoidance, and achievement) consisting of a total of 76 items. The global score is an average of the scores for the 5 domains. The majority of items assess frequency of events using a 5-point response format. There is no range for a total score. Raw scale scores were used to generate T-scores. Higher scores indicate better health.
This end point was analysed using the Randomized FAS, which included all subjects who were randomized and received at least 1 dose of investigational product during the randomized withdrawal period.

End point type	Secondary

End point timeframe:

Baseline of the randomized withdrawal period and its relevant endpoint

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	60		
Units: T-scores				
least squares mean (standard error)	1.1 (± 1.17)	-5.4 (± 1.1)		

Statistical analyses

Statistical analysis title	Change From Baseline in CHIP-CE:PRF Global T-score
Comparison groups	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal) v Placebo (Randomized Withdrawal)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.5
upper limit	9.5

Secondary: Change From Open-label Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Global Score at Endpoint (Week-26) of the Open-label Period

End point title	Change From Open-label Baseline in the Weiss Functional

	Impairment Rating Scale - Parent Report (WFIRS-P) Global Score at Endpoint (Week-26) of the Open-label Period

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 end point was analysed using the Open-label FAS, which included all subjects who received at least 1 dose of investigational product during the open-label period.

End point type	Secondary

End point timeframe:

At open-label baseline and endpoint (Week-26) of the open-label period

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	223			
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.43 (± 0.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomized Withdrawal Baseline in the WFIRS-P Global Score at Endpoint of the Randomized Withdrawal Period

End point title	Change From Randomized Withdrawal Baseline in the WFIRS-P Global Score at Endpoint of the Randomized Withdrawal Period

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 end point was analysed using the Randomized FAS, which included all subjects who were randomized and received at least 1 dose of investigational product during the randomized withdrawal period.

End point type	Secondary

End point timeframe:

Baseline of the randomized withdrawal period and its relevant endpoint

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: scores on a scale				
least squares mean (standard error)	0.01 (± 0.03)	0.2 (± 0.03)		

Statistical analyses

Statistical analysis title	Change From Baseline in the WFIRS-P Global Score
Comparison groups	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal) v Placebo (Randomized Withdrawal)
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.11

Secondary: Change From Open-label Baseline in the Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Endpoint (Week-26) of the Open-label Period

End point title	Change From Open-label Baseline in the Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Endpoint (Week-26) of the Open-label Period

End point description:

The BPRS-C characterizes psychopathology. A total of 21 items were rated on a scale from 0 (not present) to 6 (extremely severe) with a total score ranging from 0 to 126. A decrease in score indicates a reduction in psychopathology.
The end point was analysed using the Open-label Safety Population, which included all subjects who received at least 1 dose of investigational product in the open-label period.

End point type	Secondary

End point timeframe:

At open-label baseline and endpoint (Week-26) of the open-label period

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: scores on a scale				
arithmetic mean (standard deviation)	-13.9 (±			

	12.58)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomized Withdrawal Baseline in the BPRS-C Total Score at Endpoint of the Randomized Withdrawal Period

End point title	Change From Randomized Withdrawal Baseline in the BPRS-C Total Score at Endpoint of the Randomized Withdrawal Period

End point description:

The BPRS-C characterizes psychopathology. A total of 21 items were 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 end point was analysed using the Randomized Safety Population, which included all subjects who received at least 1 dose of any investigational product during the randomized withdrawal period.

End point type	Secondary

End point timeframe:

Baseline of the randomized withdrawal period and its relevant endpoint

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	27		
Units: scores on a scale				
arithmetic mean (standard deviation)	-17.1 (± 11.17)	-9.1 (± 11.26)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent of Participants With CGI-S at Open-label Baseline

End point title	Percent of Participants With CGI-S at Open-label Baseline

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).
This end point was analyzed using the Open-label FAS, which included all subjects who received at least 1 dose of investigational product during the open-label period.

End point type	Other pre-specified

End point timeframe:

Open-label baseline

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	261			
Units: percentage of subjects				
number (not applicable)				
Normal, not at all ill	0			
Borderline mentally ill	0			
Mildly ill	1.5			
Moderately ill	27.2			
Markedly ill	50.2			
Severely ill	17.6			
Among the most extremely ill	3.4			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent of Participants With CGI-S at Randomized Withdrawal Baseline

End point title	Percent of Participants With CGI-S at Randomized Withdrawal Baseline

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).
This end point was analysed using the Randomized FAS, which included all subjects who were randomized and received at least 1 dose of investigational product during the randomized withdrawal period.

End point type	Other pre-specified

End point timeframe:

Randomized withdrawal baseline

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	77		
Units: percentage of subjects				
number (not applicable)				
Normal, not at all ill	50	46.8		
Borderline mentally ill	50	53.2		
Mildly ill	0	0		

Moderately ill	0	0		
Markedly ill	0	0		
Severely ill	0	0		
Among the most extremely ill	0	0		

Statistical analyses

Statistical analysis title	CGI-S at Randomized Withdrawal Baseline
Comparison groups	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal) v Placebo (Randomized Withdrawal)
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.726
Method	Cochran-Mantel-Haenszel

Other pre-specified: Columbia-Suicide Severity Rating Scale (C-SSRS) During the Open-label Period

End point title	Columbia-Suicide Severity Rating Scale (C-SSRS) During the Open-label Period

End point description:

C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviours 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 was analysed using the Open-label Safety Population, which included all subjects who received at least 1 dose of investigational product in the open-label period.

End point type	Other pre-specified

End point timeframe:

From open-label baseline to Week-26

End point values	Lisdexamfetamine Dimesylate (LDX)(Open-label)			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: subjects				
Suicidal ideation	1			
Suicidal behaviour	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: C-SSRS During the Randomized Withdrawal Period

End point title	C-SSRS During the Randomized Withdrawal Period

End point description:

C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviours 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 end point was analysed using the Randomized Safety Population, which included all subjects who received at least 1 dose of any investigational product during the randomized withdrawal period.

End point type	Other pre-specified

End point timeframe:

Baseline of the randomized withdrawal period to end of the study

End point values	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	41		
Units: subjects				
Suicidal ideation	0	0		
Suicidal behaviour	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

33 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Lisdexamfetamine Dimesylate (LDX)(Open-label)

Reporting group description:

Consisted of at least 26 weeks where subjects were titrated to an optimal dose of LDX (30, 50 or 70 mg once-daily orally at approximately 7:00 AM +/- 2 hours) and then maintained on their optimal dose of LDX (30, 50 or 70 mg once-daily orally at approximately 7:00 AM +/- 2 hours).

Reporting group title	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)

Reporting group description:

Subjects were randomized to receive their optimal dose of LDX at 30, 50, or 70 mg once-daily orally at approximately 7:00 AM +/- 2 hours for up to 6 weeks.

Reporting group title	Placebo (Randomized Withdrawal)

Reporting group description:

Subjects were randomized to receive placebo once-daily orally at approximately 7:00 AM +/- 2 hours for up to 6 weeks.

Serious adverse events	Lisdexamfetamine Dimesylate (LDX)(Open-label)	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 276 (4.35%)	0 / 78 (0.00%)	1 / 79 (1.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 276 (0.72%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			

Treatment noncompliance			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	2 / 276 (0.72%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anger			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oppositional defiant disorder			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 276 (0.00%)	0 / 78 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric infection			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 276 (0.36%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Lisdexamfetamine Dimesylate (LDX)(Open-label)	Lisdexamfetamine Dimesylate (LDX)(Randomized Withdrawal)	Placebo (Randomized Withdrawal)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	227 / 276 (82.25%)	31 / 78 (39.74%)	20 / 79 (25.32%)
Investigations			
Weight decreased			
subjects affected / exposed	46 / 276 (16.67%)	2 / 78 (2.56%)	1 / 79 (1.27%)
occurrences (all)	60	2	1
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 276 (1.09%)	2 / 78 (2.56%)	0 / 79 (0.00%)
occurrences (all)	3	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 276 (2.90%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	8	0	0
Headache			
subjects affected / exposed	58 / 276 (21.01%)	6 / 78 (7.69%)	5 / 79 (6.33%)
occurrences (all)	80	6	7

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 276 (6.52%)	1 / 78 (1.28%)	0 / 79 (0.00%)
occurrences (all)	22	1	0
Irritability			
subjects affected / exposed	13 / 276 (4.71%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	17	0	0
Pyrexia			
subjects affected / exposed	18 / 276 (6.52%)	1 / 78 (1.28%)	1 / 79 (1.27%)
occurrences (all)	25	1	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	6 / 276 (2.17%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	6	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 276 (7.25%)	2 / 78 (2.56%)	0 / 79 (0.00%)
occurrences (all)	25	2	0
Abdominal pain upper			
subjects affected / exposed	23 / 276 (8.33%)	4 / 78 (5.13%)	2 / 79 (2.53%)
occurrences (all)	25	4	2
Diarrhoea			
subjects affected / exposed	12 / 276 (4.35%)	1 / 78 (1.28%)	0 / 79 (0.00%)
occurrences (all)	12	1	0
Nausea			
subjects affected / exposed	27 / 276 (9.78%)	2 / 78 (2.56%)	0 / 79 (0.00%)
occurrences (all)	36	2	0
Vomiting			
subjects affected / exposed	32 / 276 (11.59%)	2 / 78 (2.56%)	1 / 79 (1.27%)
occurrences (all)	43	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 276 (6.88%)	2 / 78 (2.56%)	0 / 79 (0.00%)
occurrences (all)	25	2	0
Oropharyngeal pain			

subjects affected / exposed	15 / 276 (5.43%)	3 / 78 (3.85%)	4 / 79 (5.06%)
occurrences (all)	18	3	4
Psychiatric disorders			
Aggression			
subjects affected / exposed	7 / 276 (2.54%)	2 / 78 (2.56%)	0 / 79 (0.00%)
occurrences (all)	7	2	0
Anxiety			
subjects affected / exposed	9 / 276 (3.26%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	9	0	0
Attention deficit/hyperactivity disorder			
subjects affected / exposed	2 / 276 (0.72%)	0 / 78 (0.00%)	2 / 79 (2.53%)
occurrences (all)	2	0	2
Depressed mood			
subjects affected / exposed	11 / 276 (3.99%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	16	0	0
Initial insomnia			
subjects affected / exposed	20 / 276 (7.25%)	1 / 78 (1.28%)	0 / 79 (0.00%)
occurrences (all)	22	1	0
Insomnia			
subjects affected / exposed	39 / 276 (14.13%)	1 / 78 (1.28%)	1 / 79 (1.27%)
occurrences (all)	44	1	1
Tic			
subjects affected / exposed	8 / 276 (2.90%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	11	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	9 / 276 (3.26%)	1 / 78 (1.28%)	2 / 79 (2.53%)
occurrences (all)	11	1	2
Nasopharyngitis			
subjects affected / exposed	43 / 276 (15.58%)	7 / 78 (8.97%)	3 / 79 (3.80%)
occurrences (all)	64	7	3
Rhinitis			
subjects affected / exposed	1 / 276 (0.36%)	2 / 78 (2.56%)	0 / 79 (0.00%)
occurrences (all)	2	2	0
Sinusitis			

subjects affected / exposed	7 / 276 (2.54%)	1 / 78 (1.28%)	1 / 79 (1.27%)
occurrences (all)	7	1	1
Tonsillitis			
subjects affected / exposed	6 / 276 (2.17%)	1 / 78 (1.28%)	0 / 79 (0.00%)
occurrences (all)	6	2	0
Upper respiratory tract infection			
subjects affected / exposed	14 / 276 (5.07%)	1 / 78 (1.28%)	1 / 79 (1.27%)
occurrences (all)	21	1	1
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	41 / 276 (14.86%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	48	0	0
Decreased appetite			
subjects affected / exposed	76 / 276 (27.54%)	3 / 78 (3.85%)	0 / 79 (0.00%)
occurrences (all)	91	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2009	Primarily incorporated revisions associated with the change in the primary objective of the study from long-term safety to long-term maintenance of efficacy. The Fixed Dose and Randomized Withdrawal Periods were added to the study.
17 December 2009	Added the Brief Psychiatric Rating Scale for Children (BPRS-C) and Columbia-Suicide Severity Rating Scale (C-SSRS) assessments. This Amendment also referenced the inclusion of subjects from the United States (US), where necessary.
21 May 2010	Changed the safety follow-up assessment from a telephone call to a site visit as required by the European Medicines Agency Paediatric Committee, 19 Feb 2010.
29 March 2011	Primarily clarified the statistical analysis of the separate components of the primary efficacy measure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported