



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, medinfo@global@shire.com |
| Scientific contact | Medical Communications, Shire Pharmaceutical Development Ltd., +44 8000556614, medinfo@global@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 | | | |
| <p>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.</p> <p>Safety set.</p> | | | |
| 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.

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 | <ol style="list-style-type: none">1. Increased number of sites from 55 to approximately 65 to support study recruitment2. Replaced World Health Organization body mass index (BMI) values with Centers for Disease Control and Prevention (CDC) BMI values3. Revision of reporting instructions for the treatment assignment to be unblinded as soon as possible after the investigator was unblinded4. 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 washout5. Clarification that the washout telephone call was applicable to all subjects. Modified washout telephone call procedures6. Modification that subjects accepted to participate in the pharmacogenomic substudy signed the pharmacogenomic informed consent and assent7. Revision to include provision for additional care of subjects after the study. |
| 04 January 2013 | <ol style="list-style-type: none">1. Addition of Europe and Canada to support study recruitment2. Addition of text indicating randomization would be stratified by geographic region3. Revision of text regarding Shire's serious adverse event (SAE) reporting information4. 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 study6. Removal of Exclusion Criterion that disqualified subjects who were well-controlled on their current ADHD medication with acceptable tolerability7. Increased the number of sites from 65 to approximately 80 to account for the addition of Europe and Canada8. Inclusion of updated information regarding the definition, period of observation, and recording of AEs9. Addition of text to indicate that a change in a vital sign or ECG value could represent an AE if clinically relevant10. 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