



Clinical trial results:

The SPD489-323, Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexible Dose Titration, Efficacy and Safety Study of SPD489 in Combination with an Antidepressant in the Treatment of Adults with Major Depressive Disorder with Inadequate Response to Prospective Treatment with an Antidepressant.

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2011-003006-25 |
| Trial protocol | HU PL CZ BE EE FI IT |
| Global end of trial date | 10 December 2013 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 04 September 2018 |
| First version publication date | 08 February 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | SPD489-323 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01436162 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Shire Development LLC |
| Sponsor organisation address | 725 Chesterbrook Boulevard, Wayne, United States, 19087 |
| Public contact | Medical Communications, Shire Pharmaceuticals Ltd, +44 0800 0556614, medinfo@shire.com |
| Scientific contact | Medical Communications, Shire Pharmaceuticals Ltd, +44 0800 0556614, medinfo@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? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 December 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 December 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the efficacy of SPD489 when used as augmentation therapy in the treatment of major depressive disorder (MDD) in inadequate responders following an 8-week course of treatment with an antidepressant, as measured by the mean change in Montgomery-Åsberg Depression Rating Scale (MADRS) total scores.

Protection of trial subjects:

This study was conducted in accordance with International Council of Harmonization (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy:

The background products provided for this study were the following selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants: escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride. Randomized subjects were assigned to receive either SPD489 or placebo orally once daily in addition to their assigned background product.

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 19 October 2011 |
| 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 | Romania: 14 |
| Country: Number of subjects enrolled | South Africa: 29 |
| Country: Number of subjects enrolled | Estonia: 35 |
| Country: Number of subjects enrolled | Poland: 41 |
| Country: Number of subjects enrolled | Sweden: 21 |
| Country: Number of subjects enrolled | Czech Republic: 128 |
| Country: Number of subjects enrolled | Finland: 15 |
| Country: Number of subjects enrolled | Germany: 152 |
| Country: Number of subjects enrolled | Hungary: 18 |
| Country: Number of subjects enrolled | United States: 652 |
| Worldwide total number of subjects | 1105 |
| EEA total number of subjects | 424 |

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) | 0 |
| Adults (18-64 years) | 1097 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Adults (18-65 years of age, inclusive) who met all study eligibility criteria including a primary diagnosis of non-psychiatric major depressive disorder (MDD; single or recurrent) as defined by the SCID-CT, that had lasted at least 8 weeks prior to the Screening Visit (Visit 1) were eligible for evaluation to participate in this study.

Pre-assignment

Screening details:

The screening and washout period took place on Days -28 to -7. The screening involved examination and determination of baseline clinical variables.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Single-blind Lead-in Phase |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Blinding implementation details:

Placebo capsules to match the over-encapsulated SPD489.

Arms

| | |
|------------------|---|
| Arm title | Lead-in Antidepressant + Single-blind Placebo |
|------------------|---|

Arm description:

Subjects received unblinded oral, once daily standard antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus oral, once daily placebo (matching SPD489).

| | |
|--|----------|
| 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:

Placebo was administered once daily

| Number of subjects in period 1 | Lead-in Antidepressant + Single-blind Placebo |
|---|---|
| Started | 1105 |
| Completed | 823 |
| Not completed | 282 |
| Protocol violation | 24 |
| Other | 107 |
| Adverse event | 26 |
| Met blood pressure or pulse withdrawal criteria | 13 |
| Lost to follow-up | 43 |

Period 2

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

Blinding implementation details:

SPD489 was over-encapsulated and appeared identical to placebo

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Antidepressant + Double-blind SPD489 |

Arm description:

Subjects received assigned oral, once daily antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride), plus oral, once daily SPD489 (Lisdexamfetamine dimesylate optimized among a 20, 30, 50, or 70 mg dose).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | SPD489 |
| Investigational medicinal product code | |
| Other name | Lisdexamfetamine dimesylate, Vyvanse, Venvanse, Elvanse, Tyvense |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

20, 30, 50, or 70 mg over-encapsulated capsules; the assigned number of capsules was taken once daily upon awakening together with the background product.

| | |
|------------------|---------------------------------------|
| Arm title | Antidepressant + Double-blind Placebo |
|------------------|---------------------------------------|

Arm description:

Subjects received assigned oral, once daily antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus oral, once daily, double-blind placebo (matching SPD489).

| | |
|--|----------|
| 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:

The assigned number of placebo capsules was taken once daily upon awakening together with background product.

| | |
|------------------|---------------------------------------|
| Arm title | Antidepressant + Single-blind Placebo |
|------------------|---------------------------------------|

Arm description:

Subjects received unblinded oral, once daily standard antidepressant therapy (either escitalopram

oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus oral, once daily placebo (matching SPD489).

| | |
|--|----------|
| 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:

Placebo was administered once daily together with background product.

| Number of subjects in period 2 | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | Antidepressant + Single-blind Placebo |
|--|--|--|--|
| | | | |
| Started | 212 | 214 | 397 |
| Completed | 181 | 189 | 353 |
| Not completed | 31 | 25 | 44 |
| Protocol violation | 4 | 2 | 4 |
| Not specified | 5 | 4 | 2 |
| Adverse event | 5 | 6 | 1 |
| Met blood pressure or pulse withdrawal criteria | 2 | - | 4 |
| Lost to follow-up | 5 | 4 | 17 |
| Withdrawal by subject | 9 | 8 | 16 |
| Lack of efficacy | 1 | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Lead-in Antidepressant + Single-blind Placebo |
|-----------------------|---|

Reporting group description:

Subjects received unblinded oral, once daily standard antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus oral, once daily placebo (matching SPD489).

| Reporting group values | Lead-in Antidepressant + Single-blind Placebo | Total | |
|--|---|-------|--|
| Number of subjects | 1105 | 1105 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 1097 | 1097 | |
| From 65-84 years | 8 | 8 | |
| 85 years and over | 0 | 0 | |
| Gender categorical Units: Subjects | | | |
| Female | 744 | 744 | |
| Male | 361 | 361 | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Lead-in Antidepressant + Single-blind Placebo |
| Reporting group description: Subjects received unblinded oral, once daily standard antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus oral, once daily placebo (matching SPD489). | |
| Reporting group title | Antidepressant + Double-blind SPD489 |
| Reporting group description: Subjects received assigned oral, once daily antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride), plus oral, once daily SPD489 (Lisdexamfetamine dimesylate optimized among a 20, 30, 50, or 70 mg dose). | |
| Reporting group title | Antidepressant + Double-blind Placebo |
| Reporting group description: Subjects received assigned oral, once daily antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus oral, once daily, double-blind placebo (matching SPD489). | |
| Reporting group title | Antidepressant + Single-blind Placebo |
| Reporting group description: Subjects received unblinded oral, once daily standard antidepressant therapy (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus oral, once daily placebo (matching SPD489). | |

Primary: Mean Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at 8 Weeks

| | |
|--|---|
| End point title | Mean Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at 8 Weeks |
| End point description: MADRS is a validated, 10-item rating scale with each item being scored on a scale from 0-6 with a total score ranging from 0-60. Lower scores indicate a decreased severity of depression. This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8). | |
| End point type | Primary |
| End point timeframe: 8 weeks | |

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 213 | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -7.3 (-8.6 to -6) | -6.8 (-8.1 to -5.5) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Mean Change from Baseline in MADRS Total Score |
| Comparison groups | Antidepressant + Double-blind SPD489 v Antidepressant + Double-blind Placebo |
| Number of subjects included in analysis | 422 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.583 |
| Method | Mixed-effects Model for Repeat Measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 1.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.92 |

Secondary: Mean Change from Baseline in Sheehan Disability Scale (SDS) Total Score at 8 Weeks

| | |
|-----------------|--|
| End point title | Mean Change from Baseline in Sheehan Disability Scale (SDS) Total Score at 8 Weeks |
|-----------------|--|

End point description:

SDS is designed to evaluate the extent to which illness symptoms impact a subject's life in 3 areas: work/school, social, and family/home. Each area is scored on a scale from 0 (no impairment) to 10 (highly impaired) with a total score ranging from 0 (unimpaired) to 30 (highly impaired). Lower scores translate into less impairment.

This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 8 weeks | |

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 213 | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -4.9 (-5.8 to -4) | -4.3 (-5.2 to -3.4) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Mean Change from Baseline in SDS Total Score |
| Comparison groups | Antidepressant + Double-blind SPD489 v Antidepressant + Double-blind Placebo |
| Number of subjects included in analysis | 422 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.354 |
| Method | Mixed-effects Model for Repeat Measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 0.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.65 |

Secondary: Percentage of Subjects Achieving a 25% Response on the MADRS

| | |
|---|--|
| End point title | Percentage of Subjects Achieving a 25% Response on the MADRS |
| End point description: | |
| The percentage of subjects who achieved a 25% response (i.e. $\geq 25\%$ reduction in MADRS total score from the Lead-in Baseline, Visit 2). This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8). | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 8 weeks | |

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|-------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 213 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 68.9 | 74.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving a 50% Response on the MADRS

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving a 50% Response on the MADRS |
|-----------------|--|

End point description:

The percentage of subjects who achieved a 50% response (i.e. $\geq 50\%$ reduction in MADRS total score from the Lead-in Baseline, Visit 2).

This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

End point type Secondary

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|-------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 213 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 41.6 | 37.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects Achieving Remission on the MADRS

End point title Percent of Subjects Achieving Remission on the MADRS

End point description:

MADRS remission was defined as a MADRS total score of ≤ 10 .

This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

End point type Secondary

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|-------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 213 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 23 | 17.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline Over Time in MADRS Total Score

| | |
|---|--|
| End point title | Mean Change from Baseline Over Time in MADRS Total Score |
| End point description: | |
| <p>An analysis across post-randomizations visits, with change from the Augmentation Baseline Visit (Visit 8) in MADRS total score as the outcome.</p> <p>This end point used the Full Analysis Set (FAS), which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of MADRS total score after the Augmentation Baseline Visit (Visit 8). The sample size (n) of MADRS total score at each visit differed from sample size (N) of the FAS.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 8 weeks | |

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 213 | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 9 (Visit 9) | -2.9 (-3.9 to -2) | -2.1 (-3 to -1.1) | | |
| Week 10 (Visit 10) | -4.4 (-5.5 to -3.3) | -4.3 (-5.4 to -3.2) | | |
| Week 11 (Visit 11) | -5.9 (-7.1 to -4.7) | -5 (-6.2 to -3.8) | | |
| Week 12 (Visit 12) | -6.3 (-7.6 to -5.1) | -5.3 (-6.5 to -4.1) | | |
| Week 14 (Visit 13) | -6.9 (-8.2 to -5.5) | -6.4 (-7.7 to -5.1) | | |
| Week 16 (Visit 14) | -7.3 (-8.6 to -6) | -6.8 (-8.1 to -5.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Abbreviated Brief Assessment of Cognition Affective Disorders (ABAC-A) Composite T-Scores

| | |
|--|--|
| End point title | Mean Change from Baseline in Abbreviated Brief Assessment of Cognition Affective Disorders (ABAC-A) Composite T-Scores |
| End point description: | |
| <p>The ABAC-A is a rater-administered series of activities designed to be sensitive to the critical cognitive deficits in affective disorders and schizophrenia. There are 6 subtests of the ABAC-A: List Learning (verbal memory); Digit Sequencing Task (working memory); Token Motor Task (motor speed); Verbal Fluency; Symbol Coding (attention and processing speed); and Tower of London Test (executive functions). The ABAC-A Composite T-score change from Augmentation Baseline Visit (Visit 8; Week 8) at Visit 14/Early Termination (ET) (Week 16/ET) was analyzed.</p> <p>This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of</p> | |

randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 194 | 198 | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | 3 (2.1 to 4) | 2.5 (1.5 to 3.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the Short Form-12 Health Survey V2 (SF-12V2)

| | |
|-----------------|---|
| End point title | Mean Change from Baseline in the Short Form-12 Health Survey V2 (SF-12V2) |
|-----------------|---|

End point description:

The SF-12V2 total score ranges from 0 (lowest level of health) - 100 (highest level of health) on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability (i.e. a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability). Higher scores are associated with better quality of life.

This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196 | 205 | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Physical | 1.07 (0.04 to 2.1) | 0.9 (-0.11 to 1.91) | | |
| Mental | 6.63 (5.03 to 8.23) | 5.16 (3.6 to 6.73) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Sexual Functioning Questionnaire - 14 Item Scale (CSFQ-14) Total Score Male

| | |
|-----------------|--|
| End point title | Mean Change in Sexual Functioning Questionnaire - 14 Item Scale (CSFQ-14) Total Score Male |
|-----------------|--|

End point description:

The CSFQ-14 is a short-form interview/questionnaire that measures illness- and medication-related changes in sexual functioning. A 5-point Likert scale is used ranging from 1 (never) to 5 (always). The CSFQ-14 total score can range from 14 to 70, with lower scores being associated with worsened sexual functioning.

This end point used the Full Analysis Set, which was defined as male subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--------------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 67 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 2.1 (\pm 6.22) | 1 (\pm 6.02) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Sexual Functioning Questionnaire - 14 Item Scale (CSFQ-14) Total Score Female

| | |
|-----------------|--|
| End point title | Mean Change in Sexual Functioning Questionnaire - 14 Item Scale (CSFQ-14) Total Score Female |
|-----------------|--|

End point description:

The CSFQ-14 is a short-form interview/questionnaire that measures illness- and medication-related changes in sexual functioning. A 5-point Likert scale is used ranging from 1 (never) to 5 (always). The CSFQ-14 total score can range from 14 to 70, with lower scores being associated with worsened sexual functioning.

This end point used the Full Analysis Set, which was defined as female subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--------------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 125 | 133 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 3 (± 7.11) | 1.9 (± 5.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions - Global Improvement (CGI-I)

End point title Clinical Global Impressions - Global Improvement (CGI-I)

End point description:

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 used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

End point type Secondary

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|-------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 209 | 213 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Improved | 56.9 | 53.5 | | |
| Not improved | 43.1 | 46.5 | | |
| Not assessed | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the Multidimensional Assessment of

Fatigue (MAF) Global Fatigue Index (GFI)

| | |
|-----------------|--|
| End point title | Mean Change from Baseline in the Multidimensional Assessment of Fatigue (MAF) Global Fatigue Index (GFI) |
|-----------------|--|

End point description:

MAF contains 16 items scored on a scale from 1 (not at all) to 10 (a great deal). Answers are converted to a GFI with total scores ranging from 1 (no fatigue) to 50 (severe fatigue). Lower scores indicate less fatigue.

This end point used the Full Analysis Set, which was defined as subjects who took at least 1 dose of randomized investigational product and who had at least 1 valid primary efficacy measurement of the MADRS total score after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|-------------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 205 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -6.6 (\pm 0.74) | -4.4 (\pm 0.73) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Columbia Suicide Severity Rating Scale (C-SSRS)

| | |
|-----------------|---|
| End point title | Columbia Suicide Severity Rating Scale (C-SSRS) |
|-----------------|---|

End point description:

C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The assessment is done by the nature of the responses, not by a numbered scale.

This end point used the Safety Analysis Set, which was defined as all subjects who took at least 1 dose of randomized investigational product and who had at least 1 safety assessment (e.g., coming back for any visit, reporting of an adverse event [AE], or reporting the absence of AEs) after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|-------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 211 | 213 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |

| | | | | |
|-------------------------------|---|-----|--|--|
| ≥1 positive suicidal ideation | 9 | 9.4 | | |
| ≥1 suicidal attempt | 0 | 0.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Amphetamine Cessation Symptom Assessment (ACSA) - Total Aggregate Score

| | |
|-----------------|---|
| End point title | Amphetamine Cessation Symptom Assessment (ACSA) - Total Aggregate Score |
|-----------------|---|

End point description:

The ACSA scale has 16 symptom items rated on a scale from 0 (not at all) to 4 (extremely) with a possible total score range of 0 to 64. Higher scores indicate greater withdrawal symptom severity. This end point used the Safety Analysis Set, which was defined as all subjects who took at least 1 dose of randomized investigational product and who had at least 1 safety assessment (e.g., coming back for any visit, reporting of an adverse event [AE], or reporting the absence of AEs) after the Augmentation Baseline Visit (Visit 8).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

8 weeks

| End point values | Antidepressant + Double-blind SPD489 | Antidepressant + Double-blind Placebo | | |
|--------------------------------------|--------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 194 | 199 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 17 (± 10.8) | 17.2 (± 10.56) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

8 weeks

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Antidepressant + Placebo: Antidepressant (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release or duloxetine hydrochloride) oral, once daily + Double-blind Placebo (oral, once daily) for 8 weeks. AEs are reported for the Safety Analysis Set, defined as all subjects who took at least 1 dose of randomized investigational product and who had at least 1 safety assessment (e.g., coming back for any visit, reporting of an adverse event [AE], or reporting the absence of AEs) after the Augmentation Baseline Visit (Visit 8).

| | |
|-----------------------|--------|
| Reporting group title | SPD489 |
|-----------------------|--------|

Reporting group description:

Antidepressant + SPD489 (Lisdexamfetamine dimesylate): Antidepressant (either escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release or duloxetine hydrochloride) oral, once daily + Double-blind SPD489 (oral, 20, 30, 50 or 70 mg, once daily) for 8 weeks. AEs are reported for the Safety Analysis Set, defined as all subjects who took at least 1 dose of randomized investigational product and who had at least 1 safety assessment (e.g., coming back for any visit, reporting of an adverse event [AE], or reporting the absence of AEs) after the Augmentation Baseline Visit (Visit 8).

| Serious adverse events | Placebo | SPD489 | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 213 (0.47%) | 1 / 211 (0.47%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Accelerated hypertension | | | |
| subjects affected / exposed | 0 / 213 (0.00%) | 1 / 211 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 213 (0.47%) | 0 / 211 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | SPD489 | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 213 (21.60%) | 72 / 211 (34.12%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 16 / 213 (7.51%) | 25 / 211 (11.85%) | |
| occurrences (all) | 22 | 32 | |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 6 / 213 (2.82%) | 25 / 211 (11.85%) | |
| occurrences (all) | 6 | 29 | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 213 (0.47%) | 11 / 211 (5.21%) | |
| occurrences (all) | 1 | 16 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 7 / 213 (3.29%) | 11 / 211 (5.21%) | |
| occurrences (all) | 7 | 14 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 19 / 213 (8.92%) | 14 / 211 (6.64%) | |
| occurrences (all) | 20 | 14 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 213 (2.35%) | 13 / 211 (6.16%) | |
| occurrences (all) | 5 | 14 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 11 November 2011 | Important changes to the protocol set forth by this amendment include: 1-The contact information was updated; 2-Further clarification was provided on removal of those subjects who show no improvement, or who have worsening of depressive symptoms, based on the total MADRS score at the Augmentation Baseline Visit (Visit 8); 3-Information was clarified regarding the background product, randomization criteria, marketing of SPD489, readings for vital signs, assessments to be carried out upon tapering or down-titration, label descriptions, storage of investigational product, and the requirement for tapering for subjects who terminate early; 4-Revised definitions were provided for vital signs, randomization, target dose of the background product, eligible subjects, subjects not randomized, and the required results of urine tests; 5-The exclusion and inclusion criteria were modified; 6-Updated criteria were provided for C-SSRS responses for suitability to remain in the study; 7-Assessment types were added to Table 4 for clarification; 8-The MADRS version and date were updated, and the reference to "acute 1-week recall" was removed from the SF-12V2; 9-"product" was removed when referencing the package insert; 10-A clarification was made that changes in packaging refer to investigational product only; 11-The post-study contraception duration was reduced from 30 days after last dose of investigational product to the time of follow-up as specified in Section 7.1.6; 12-Information was updated to reflect current status of clinical studies; 13-NRP104 was added to indicate the previous nomenclature of SPD489; 14-Clarification was provided that background products will be supplied by the Sponsor in manageable counts; 15-A reference was removed to index scores for the secondary measure EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire; and 16-The EuroQol Questionnaire and scores were modified. |
| 12 November 2012 | Important changes to the protocol set forth by this amendment include: 1-The emergency contact information was updated; 2-The secondary objectives were modified; 3-The number of subjects to be screened and planned sites was increased; 4-The exclusion criteria were revised; 5-The visit for additional randomization assessments was modified; 6-Specified requirements of testing at Visit 1; 7-A requirement to review contraceptive requirements was added; 8-The criteria for the removal of subjects was modified; 9-The processes for discontinuing certain other concomitant medications was expanded; 10-The requirements for communications in case of unblinding were modified; 11-Reporting requirements for pregnancies and serious adverse events were modified; 12-Visit 2 was specified as the point in time of enrollment into the study; 13-Specified that the Investigator's decision to discontinue a subject due to clinical or ECG results should be made in conjunction with the contract research organization's Medical Monitor. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported