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, medinfoglobal@shire.com
Scientific contact	Medical Communications, Shire Pharmaceuticals Ltd, +44 0800 0556614, medinfoglobal@shire.com

Notes:

Paediatric regulatory details

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

Withdrawal by subject	69

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. ≥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. ≥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:

An analysis across post-randomizations visits, with change from the Augmentation Baseline Visit (Visit 8) in MADRS total score as the outcome.
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.

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:

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.
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	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 (± 6.22)	1 (± 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 (± 0.74)	-4.4 (± 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 occurrences (all)	16 / 213 (7.51%) 22	25 / 211 (11.85%) 32	
Gastrointestinal disorders Dry mouth subjects affected / exposed occurrences (all)	6 / 213 (2.82%) 6	25 / 211 (11.85%) 29	
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 213 (0.47%) 1	11 / 211 (5.21%) 16	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	7 / 213 (3.29%) 7	11 / 211 (5.21%) 14	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	19 / 213 (8.92%) 20	14 / 211 (6.64%) 14	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 213 (2.35%) 5	13 / 211 (6.16%) 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