



Clinical trial results:

The SPD489-322 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	2011-003018-17
Trial protocol	ES
Global end of trial date	23 December 2013

Results information

Result version number	v1
This version publication date	23 October 2018
First version publication date	08 February 2015

Trial information

Trial identification

Sponsor protocol code	SPD489-322
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01436149
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard, Wayne, PA, United States, 19087
Public contact	Study Physician, Shire Pharmaceuticals Ltd, +1 866 842 5335,
Scientific contact	Study Physician, Shire Pharmaceuticals Ltd, +1 866 842 5335,

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	23 December 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was 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-Asberg Depression Rating Scale (MADRS) total scores.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements. The subject's informed consent was a mandatory condition for taking part in the study. It was obtained in writing at the Screening Visit (Visit 1) prior to the performance of any study-specific procedures. The subject's informed consent was documented (on an appropriate form approved by the EC) by the dated signature of the subject and the dated signature of the investigator or investigator's delegate.

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 HCl, venlafaxine HCl extended-release, and duloxetine HCl. Randomized subjects were assigned to receive either SPD489 or placebo orally once daily in addition to their assigned background product.

If not already on 1 of the 4 permitted background products at the Screening Visit (Visit 1), a subject was assigned 1 of the 4 background products, as available and provided by the sponsor, at the Lead-in Baseline Visit (Visit 2). Assignment of background product was based on investigator assessment of clinical factors, including prior antidepressant use, response, and tolerability. Investigators were to distribute background product choices equally at their site and were to have made an effort not to assign any 1 background product to more than 40% of their subjects.

Evidence for comparator: -

Actual start date of recruitment	27 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	Spain: 15
Country: Number of subjects enrolled	Canada: 83
Country: Number of subjects enrolled	Croatia: 10
Country: Number of subjects enrolled	Mexico: 58
Country: Number of subjects enrolled	United States: 1096
Worldwide total number of subjects	1262
EEA total number of subjects	25

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)	1256
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 76 sites in 5 countries (Canada, Croatia, Mexico, Spain, United States).

Pre-assignment

Screening details:

Adults (18-65 years of age, inclusive) who met all study eligibility criteria, including a primary diagnosis of non-psychotic major depressive disorder (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.

Period 1

Period 1 title	Antidepressant 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	Antidepressant + Single-blind Placebo (Lead-in Phase)
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Arm description:

Subjects received assigned, unblinded, antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended-release, or duloxetine hydrochloride) plus placebo (matching SPD489) for 8 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:

Placebo capsule once-daily

Number of subjects in period 1	Antidepressant + Single-blind Placebo (Lead-in Phase)
Started	1262
Completed	896
Not completed	366
Adverse Event	39
Lost to Follow-up	96
Not Specified	119
Withdrawal by Subject	61
Protocol Violation	29
Met BP or Pulse Withdrawal Criteria	22

Period 2

Period 2 title	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. Background product (standard antidepressant therapy) was not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Antidepressant + Single-blind Placebo (Randomized Phase)

Arm description:

Subjects received assigned, unblinded, antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended-release, or duloxetine hydrochloride) plus placebo (matching SPD489) for 8 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:

Placebo capsule once-daily

Arm title	Antidepressant + Double-blind Placebo
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Arm description:

Subjects received assigned, unblinded antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus placebo (matching SPD489) for 8 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:

Placebo capsule once-daily

Arm title	Antidepressant + Double-blind SPD489
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Arm description:

Subjects received assigned, unblinded antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus SPD489 for

8 weeks.

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

Dosage and administration details:

Over-encapsulated SPD489 capsules optimized among 20, 30, 50, or 70 mg dose once-daily

Number of subjects in period 2	Antidepressant + Single-blind Placebo (Randomized Phase)	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489
Started	492	202	202
Completed	415	164	160
Not completed	77	38	42
Lack of Efficacy	-	-	1
Adverse Event	9	10	11
Lost to Follow-up	34	5	6
Not Specified	12	5	11
Withdrawal by Subject	16	10	10
Protocol Violation	4	5	-
Met BP or Pulse Withdrawal Criteria	2	3	3

Baseline characteristics

Reporting groups

Reporting group title	Antidepressant Lead-in Phase
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Reporting group description:

Subjects received assigned, unblinded, antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended-release, or duloxetine hydrochloride) plus placebo (matching SPD489) for 8 weeks.

Reporting group values	Antidepressant Lead-in Phase	Total	
Number of subjects	1262	1262	
Age categorical Units: Subjects			
18-55 years	1125	1125	
56-65 years	137	137	
Age continuous Units: years			
arithmetic mean	39.5		
standard deviation	± 12.11	-	
Gender categorical Units: Subjects			
Female	806	806	
Male	456	456	

End points

End points reporting groups

Reporting group title	Antidepressant + Single-blind Placebo (Lead-in Phase)
Reporting group description: Subjects received assigned, unblinded, antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended-release, or duloxetine hydrochloride) plus placebo (matching SPD489) for 8 weeks.	
Reporting group title	Antidepressant + Single-blind Placebo (Randomized Phase)
Reporting group description: Subjects received assigned, unblinded, antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended-release, or duloxetine hydrochloride) plus placebo (matching SPD489) for 8 weeks.	
Reporting group title	Antidepressant + Double-blind Placebo
Reporting group description: Subjects received assigned, unblinded antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus placebo (matching SPD489) for 8 weeks.	
Reporting group title	Antidepressant + Double-blind SPD489
Reporting group description: Subjects received assigned, unblinded antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus SPD489 for 8 weeks.	

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

End point title	Mean Change From Baseline in the 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 included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: units on a scale				
least squares mean (confidence interval 95%)	-6.3 (-7.6 to -4.9)	-6.1 (-7.5 to -4.8)		

Statistical analyses

Statistical analysis title	Change From Baseline in MADRS Total Score
Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.883
Method	Mixed-effects Model for Repeat Measures
Parameter estimate	Difference in LS Mean
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.96

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

End point title	Change From Baseline in the 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 included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: units on a scale				
least squares mean (confidence interval 95%)	-4.3 (-5.3 to -3.3)	-4.7 (-5.6 to -3.7)		

Statistical analyses

Statistical analysis title	Change From Baseline in SDS Total Score
Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.576
Method	Mixed- effects Model for Repeat Measures
Parameter estimate	Difference in LS Mean
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.69

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

End point title	Percentage of Participants Achieving a 25% Response on the MADRS
End point description:	
<p>The percentage of subjects who achieved a 25% response (i.e., $\geq 25\%$ reduction in MADRS total score from Lead-in Baseline, Visit 2; Week 0). A comparison was performed at Visit 14/Early Termination (ET) (Week 16/ET).</p> <p>This end point used the Full Analysis Set, which included 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).</p>	
End point type	Secondary
End point timeframe:	
Up to 8 weeks	

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: percentage of subjects				
number (not applicable)	65	74.5		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants Achieving a 50% Response on the
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End point description:

The percentage of subjects who achieved a 50% response (i.e., $\geq 50\%$ reduction in MADRS total score from Lead-in Baseline, Visit 2; Week 0). A comparison was performed at Visit 14/ET (Week 16/ET). This end point used the Full Analysis Set, which included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: percentage of subjects				
number (not applicable)	38.5	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Remission on the MADRS

End point title

Percentage of Participants Achieving Remission on the MADRS

End point description:

MADRS remission was defined as a MADRS total score of ≤ 10 . A comparison was performed at Visit 14/ET (Week 16/ET).

This end point used the Full Analysis Set, which included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: percentage of subjects				
number (not applicable)	22.5	18.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline Over Time in the MADRS Total Score

End point title	Mean Change From Baseline Over Time in the MADRS Total Score
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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 included 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
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End point timeframe:

Baseline and up to 8 weeks

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Visit 9 (Week 9)	-2.2 (-3.1 to -1.2)	-3.4 (-4.3 to -2.4)		
Visit 10 (Week 10)	-3.8 (-4.9 to -2.7)	-4.2 (-5.3 to -3.2)		
Visit 11 (Week 11)	-6 (-7.2 to -4.8)	-5.4 (-6.6 to -4.2)		
Visit 12 (Week 12)	-6.2 (-7.4 to -5)	-5.6 (-6.8 to -4.4)		
Visit 13 (Week 14)	-7.4 (-8.7 to -6)	-7.3 (-8.6 to -6)		
Visit 14 (Week 16)	-6.3 (-7.6 to -4.9)	-6.1 (-7.5 to -4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Quick Inventory of Depressive Symptomatology - Self Report (QIDS SR)

End point title	Mean Change From Baseline in the Quick Inventory of Depressive Symptomatology - Self Report (QIDS SR)
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End point description:

The QIDS-SR is a self-administered questionnaire designed to rate depressive symptoms. The scale contains 16 items, each scored using a 4-point scale ranging from 0 (representing the most favorable response [low amount of symptoms]) to 3 (representing the least favorable response [frequent/intense symptoms]). The total score could range from 0 (no depression) to 27 (very severe depression). Higher scores represent more severe depressive symptoms.

This end point used the Full Analysis Set, which included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	185		
Units: units on a scale				
least squares mean (confidence interval 95%)	-2.6 (-3.2 to -1.9)	-2.3 (-2.9 to -1.7)		

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)
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End point description:

The SF-12V2 total score ranges from 0 (lowest level of health) to 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 included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	186		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Physical	0.69 (-0.39 to 1.77)	-0.81 (-1.89 to 0.28)		
Mental	5.59 (3.93 to 7.25)	6.5 (4.84 to 8.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Quality of Life Enjoyment Satisfaction Questionnaire Short Form (Q-LES-Q-SF)

End point title	Mean Change From Baseline in the Quality of Life Enjoyment Satisfaction Questionnaire Short Form (Q-LES-Q-SF)
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End point description:

The Q-LES-Q-SF is a 16-item self-report questionnaire that evaluates general subject satisfaction with health, mood, relationships, functioning in daily life, and the treatment being taken. The overall level of satisfaction is evaluated on a 5-point scale from 1 (very poor) to 5 (very good). The total score ranges from 14-70 (the last two items on the form are not included in the total score). A higher score indicates a better quality of life.

This end point used the Full Analysis Set, which included 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
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End point timeframe:

Up to 8 weeks

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	184		
Units: units on a scale				
least squares mean (confidence interval 95%)	7.2 (4.9 to 9.5)	7 (4.7 to 9.3)		

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)
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End point description:

Clinical Global Impression-Improvement (CGI-I) consists of a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved) or 2 (much improved) on the scale.

This end point used the Full Analysis Set, which included 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
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End point timeframe:

Up to 8 weeks

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	199		
Units: percentage of subjects				
number (not applicable)				
Improved	53.3	55.3		
Not Improved	46.2	44.7		
Not Assessed	0.5	0		

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 Full Analysis Set, which included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	201		
Units: percentage of subjects				
number (not applicable)				
≥1 Positive Suicidal Ideation	7	7		
≥1 Suicidal Attempt	0.5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Amphetamine Cessation Symptom Assessment (ACSA)

End point title	Amphetamine Cessation Symptom Assessment (ACSA)
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 Full Analysis Set, which included 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 Placebo	Antidepressant + Double-blind SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	183		
Units: units on a scale				
arithmetic mean (standard deviation)	15.1 (\pm 10.71)	14.7 (\pm 10.94)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

17 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Antidepressant + Double-blind Placebo
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Reporting group description:

Subjects received assigned oral, once-daily antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus double-blind placebo (matching SPD489) for 8 weeks.

Reporting group title	Antidepressant + Double-blind SPD489
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Reporting group description:

Subjects received assigned oral, once-daily antidepressant therapy (escitalopram oxalate, sertraline hydrochloride, venlafaxine hydrochloride extended release, or duloxetine hydrochloride) plus SPD489 for 8 weeks.

Serious adverse events	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 201 (2.49%)	3 / 201 (1.49%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 201 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 201 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Appendectomy			

subjects affected / exposed	1 / 201 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 201 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 201 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 201 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 201 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489	
Total subjects affected by non-serious adverse events subjects affected / exposed	74 / 201 (36.82%)	99 / 201 (49.25%)	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	10 / 201 (4.98%) 11 21 / 201 (10.45%) 28	9 / 201 (4.48%) 9 13 / 201 (6.47%) 14	
Gastrointestinal disorders Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	6 / 201 (2.99%) 6 10 / 201 (4.98%) 11	19 / 201 (9.45%) 19 13 / 201 (6.47%) 13	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	15 / 201 (7.46%) 16	19 / 201 (9.45%) 20	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 201 (1.99%) 4	11 / 201 (5.47%) 12	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	8 / 201 (3.98%) 8	15 / 201 (7.46%) 17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2011	<p>1-Updated information for emergency contact, MADRS, and Q-LES-Q-SF</p> <p>2-Specified that the 4 antidepressants were "as available and provided by the sponsor"</p> <p>3- Revised exclusion criteria</p> <p>4- Added that subjects with no improvement in depressive symptoms from Visit 2 to Visit 8 were to be discontinued</p> <p>5-Qualified that subjects "whose depressive symptoms have improved, but" who did not meet randomization criteria at Visit 8 were allowed to continue in the study receiving placebo</p> <p>6-Reduced the duration after the study that a subject was to use contraception.</p> <p>7- Specified that the management of blood pressure and pulse during the study were to be based on an "average of 3 readings" for each respective measurement as well as on an "average" value for each respective measurement on 2 consecutive visits</p> <p>8- Expanded permitted concomitant medications to include any medication not affecting blood pressure, heart rate, or the CNS. Antibiotics were excluded.</p> <p>9-Specified that background product was to be taken in conjunction with investigational product</p> <p>10-Defined target dose of background product</p> <p>11-Titration to a target dose of the background product was clarified to be consistent with the labeling guidelines</p> <p>12- Listed study assessments to be performed when background product was tapered or investigational product was down-titrated</p> <p>13- Dosing and re-dispensing of background and investigational products was expanded upon</p> <p>14- Specified that controlled substances were to be stored based on the label</p> <p>15-Removed the following sentence: "Continued antidepressant treatment will not be provided by the sponsor" from the section describing study procedures performed during the follow-up period</p> <p>16- Specified tapering of background product after the study</p> <p>17- Specified that any urine drug screen at Visit 2 was to be negative</p> <p>18-Listed specific items of interest on the C-SSRS for the investigator to use when evaluating a subject's suitability to remain in the study</p>

12 November 2012	1-Updated emergency contact information 2-Removed the secondary objective to evaluate the efficacy of SPD489 augmentation based on the CGI-S 3- Increased the number of subjects to be screened 4-Increased the number of planned sites 5-Revised exclusion criteria 6- Specified Visit 2 as the start for evaluation of additional randomization assessments 7- Specified intervals for QTcF and QTcB that would trigger discontinuation 8- Removed the following sentence from the analysis of secondary efficacy variables: "The CGI-S data at Visit 14 will be compared between augmentation treatment groups using the Wilcoxon rank sum test" 9- Specified Visit 2 as the time of enrolment 10- Specified that any Visit 1 assessment requiring a repeat measurement should be performed before confirming eligibility 11- Subject discontinuation based on laboratory or ECG results that would preclude treatment with SPD489 was to be agreed upon by the investigator in conjunction with the CRO Medical Monitor 12-Added that contraceptive requirements were to be reviewed at all study visits 13-The following (in "quotes") was removed regarding removal of a subject from drug or therapy: the reason for withdrawal (by the sponsor or investigator) should be "discussed where possible with the contract research organization (CRO) Medical Monitor before the subject stops investigational product" 14-Added that subjects requiring a prohibited change to their treatment must be discontinued 15-Added reasons for discontinuation under the category of Other: Change in background product required Treatment with a prohibited medication required Other reasons must be specified 16-Expanded the processes for discontinuing medications 17-Prohibited "chronic" use of an herbal treatment 18- Specified that the investigator was to contact the CRO Medical Monitor as soon as possible after unblinding 19-Added the formula for medication compliance 20- Changed reporting requirements of SAEs and pregnancies
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported