Clinical trial results:
A Phase 2, Multicenter, Double-blind, Parallel-group, Randomized, Placebo-controlled, Forced-dose Titration, Dose-ranging 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	2011-003615-28
Trial protocol	GB
Global end of trial date	17 January 2014

Results information

Result version number	v1 (current)
This version publication date	23 October 2018
First version publication date	25 March 2015

Trial information

Trial identification

Sponsor protocol code	SPD489-209

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01435759
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	Study Physician, Shire Development LLC, +1 866 842 5335, medinfoglobal@shire.com
Scientific contact	Study Physician, Shire Development LLC, +1 866 842 5335, 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	17 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the dose-response relationship of SPD489 (10, 30, 50, and 70mg) and placebo 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 Montgomery-Asberg Depression Rating Scale (MADRS) total score, using a pre-specified set of candidate dose-response curves.

Protection of trial subjects:

The study protocol, any protocol amendments, the final approved informed consent document, relevant supporting information, and all types of subject recruitment information were submitted by the investigator to the ethics committee (EC) and approved by the EC and regulatory agency (as appropriate) prior to study initiation. This study was conducted in accordance with International Conference on Harmonisation's principles of 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 used in this study were provided as commercially available (in manageable container counts) by the sponsor. Investigators were responsible for dispensing the assigned background product to each subject at each visit as well as for monitoring drug accountability. The background products used in this study were Escitalopram oxalate (a selective serotonin reuptake inhibitor) and Venlafaxine HCl extended-release (a serotonin-norepinephrine reuptake inhibitor). Background product strengths may have varied based on commercial availability and was managed according to applicable requirements. Subjects either entered the study on 1 of the 2 allowed background products or were assigned 1 of the 2 allowed background products at study entry. For subjects who were assigned a background product at study entry, dosing began at the lowest allowed dose level. All subjects took a single dose of background product on the morning following the Lead-in Baseline Visit (Week 0). The background product was subsequently titrated to a target dose (i.e., the maximum tolerated dose) by the end of the fourth week of treatment (i.e., by Visit 6); dose adjustments of background product were not permitted after Week 4. For all subjects, weekly dose increases were made by the clinician according to the labeled guidelines for their respective background product. If a subject required a dose decrease in their respective background product or if the subject needed to be discontinued from their respective background product, the dose was tapered according to the labeled guidelines; individualized tapering was permitted. Assessments of vital signs (blood pressure, pulse, and respiratory rate), adverse events, and Columbia-Suicide Severity Rating Scale were made in conjunction with dose decreases in background product.

Evidence for comparator: -

Actual start date of recruitment	31 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 36
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Chile: 81
Country: Number of subjects enrolled	United States: 1058
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	1197
EEA total number of subjects	3

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)	1191
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted globally at 76 sites in 5 countries (United States, Argentina, Chile, Australia, and United Kingdom).

Pre-assignment

Screening details:

Adults (18-65 years of age, inclusive [or age of majority if >18 years of age, as defined by local regulations]) who met all study eligibility criteria including a primary diagnosis of non-psychotic MDD (single or recurrent), as defined by the SCID-CT, that had lasted at least 8 weeks prior to screening were eligible 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

Arms

Arm title	Lead-in Antidepressant + Single-blind Placebo

Arm description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily (QD) 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 capsules QD upon awakening at approximately 07:00 (±2 hours) in conjunction with reference product, for 8 weeks

Number of subjects in period 1	Lead-in Antidepressant + Single-blind Placebo
Started	1197
Completed	855
Not completed	342
Adverse Event	40
Lost to Follow-up	83
Not Specified	119
Withdrawal by Subject	74
Protocol Violation	16
Met BP or Pulse Withdrawal Criteria	10

Period 2

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

Blinding implementation details:

SPD489 was over-encapsulated and appeared identical to matching placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Antidepressant + Single-blind Placebo

Arm description:

Subjects whose depressive symptoms improved but who did not meet the randomization criteria were not randomized and continued to receive unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily (QD) single-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:

Placebo capsules QD upon awakening at approximately 07:00 (±2 hours) in conjunction with reference product, for 8 weeks

Arm title	Antidepressant + Double-blind Placebo

Arm description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD 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 capsules QD upon awakening at approximately 07:00 (±2 hours) in conjunction with reference product, for 8 weeks

Arm title	Antidepressant + Double-blind SPD489 10mg

Arm description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 10mg dose.

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:

One over-encapsulated SPD489 capsule, 10mg, QD upon awakening at approximately 07:00 (±2 hours) in conjunction with reference product, for 8 weeks

Arm title	Antidepressant + Double-blind SPD489 30mg

Arm description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 30mg dose.

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:

One over-encapsulated SPD489 capsule, 30mg, QD upon awakening at approximately 07:00 (±2 hours) in conjunction with reference product, for 8 weeks

Arm title	Antidepressant + Double-blind SPD489 50mg

Arm description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 50mg dose.

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:

One over-encapsulated SPD489 capsule, 50mg, QD upon awakening at approximately 07:00 (±2 hours) in conjunction with reference product, for 8 weeks

Arm title	Antidepressant + Double-blind SPD489 70mg

Arm description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 70mg dose.

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:

One over-encapsulated SPD489 capsule, 70mg, QD upon awakening at approximately 07:00 (±2 hours) in conjunction with reference product, for 8 weeks

Number of subjects in period 2	Antidepressant + Single-blind Placebo	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489 10mg
Started	463	78	78
Completed	397	71	71
Not completed	66	7	7
Adverse Event	7	-	1
Lost to Follow-up	31	1	2
Not Specified	8	2	-
Withdrawal by Subject	17	4	3
Protocol Violation	2	-	1
Met BP or Pulse Withdrawal Criteria	1	-	-

Number of subjects in period 2	Antidepressant + Double-blind SPD489 30mg	Antidepressant + Double-blind SPD489 50mg	Antidepressant + Double-blind SPD489 70mg
Started	78	78	80
Completed	69	69	71
Not completed	9	9	9
Adverse Event	1	1	3
Lost to Follow-up	-	3	3
Not Specified	2	-	-
Withdrawal by Subject	4	2	2
Protocol Violation	2	-	1
Met BP or Pulse Withdrawal Criteria	-	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Lead-in Antidepressant + Single-blind Placebo
Reporting group description:	
Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily (QD) placebo (matching SPD489).	

Reporting group values	Lead-in Antidepressant + Single-blind Placebo	Total	
Number of subjects	1197	1197	
Age categorical Units: Subjects			
18-55 years	1053	1053	
56-65 years	144	144	
Age continuous Units: years			
arithmetic mean	40.6		
standard deviation	± 11.81	-	
Gender categorical Units: Subjects			
Female	790	790	
Male	407	407	
Region of Enrollment Units: Subjects			
United States	1058	1058	
United Kingdom	3	3	
Chile	81	81	
Argentina	36	36	
Australia	19	19	

End points

End points reporting groups

Reporting group title	Lead-in Antidepressant + Single-blind Placebo
Reporting group description:	
Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily (QD) placebo (matching SPD489).	
Reporting group title	Antidepressant + Single-blind Placebo
Reporting group description:	
Subjects whose depressive symptoms improved but who did not meet the randomization criteria were not randomized and continued to receive unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily (QD) single-blind placebo (matching SPD489).	
Reporting group title	Antidepressant + Double-blind Placebo
Reporting group description:	
Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD placebo (matching SPD489).	
Reporting group title	Antidepressant + Double-blind SPD489 10mg
Reporting group description:	
Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 10mg dose.	
Reporting group title	Antidepressant + Double-blind SPD489 30mg
Reporting group description:	
Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 30mg dose.	
Reporting group title	Antidepressant + Double-blind SPD489 50mg
Reporting group description:	
Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 50mg dose.	
Reporting group title	Antidepressant + Double-blind SPD489 70mg
Reporting group description:	
Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, QD over-encapsulated SPD489 as a 70mg dose.	

Primary: Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score From Augmentation Baseline (Week 8) to Week 16 (Double-blind Phase, Dose Response Evaluable Set)

End point title	Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score From Augmentation Baseline (Week 8) to Week 16 (Double-blind Phase, Dose Response Evaluable Set)
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. Change in MADRS total score in Augmentsion Baseline to Week 16. This end point used the Dose Response Evaluable Set (DRES), which included all randomized subjects who had at least 1 valid primary efficacy measurement (MADRS total score) during the Dose Maintenance Period (Weeks 11-16) while on the target dose level of investigational product.	
End point type	Primary

End point timeframe:

Augmentation baseline (Week 8) to Week 16

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489 10mg	Antidepressant + Double-blind SPD489 30mg	Antidepressant + Double-blind SPD489 50mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	71	69	66
Units: units on a scale				
least squares mean (confidence interval 90%)	-5.4 (-7.2 to -3.5)	-6.7 (-8.6 to -4.9)	-5.3 (-7.1 to -3.4)	-6.1 (-8.1 to -4.1)

End point values	Antidepressant + Double-blind SPD489 70mg			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: units on a scale				
least squares mean (confidence interval 90%)	-6.3 (-8.2 to -4.4)			

Statistical analyses

Statistical analysis title	Dose Response Analysis-MADRS

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg v Antidepressant + Double-blind Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 1 [2]
Method	MCP-Mod Analysis Method

Notes:

[1] - For the method of estimation, the t-statistic used for this analysis, 0.10, was based on MCP-Mod Analysis from the linear contrast using optimal coefficients for the pre-specified candidate model Betamod.

[2] - The adjusted p-value was based on a critical value of 2.02 from a multivariate-t distribution with 341 degrees of freedom. Any p-value <=0.10 indicates successful establishment of dose-response relationship.

Statistical analysis title	Dose Response Analysis-MADRS #2

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 70mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 10mg

	v Antidepressant + Double-blind Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.942 [4]
Method	MCP-Mod Analysis

Notes:

[3] - For the method of estimation, the t-statistic used for this analysis, 0.41, was based on MCP-Mod Analysis from the linear contrast using optimal coefficients for the pre-specified candidate model Emax.
[4] - The adjusted p-value is based on a critical value of 2.02 from a multivariate-t distribution with 341 degrees of freedom. Any p-value <=0.10 indicates successful establishment of dose-response relationship.

Statistical analysis title	Dose Response Analysis-MADRS #3

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg v Antidepressant + Double-blind Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.995 [6]
Method	MCP-Mod Analysis

Notes:

[5] - For the method of estimation, the t-statistic used for this analysis, 0.20, was based on MCP-Mod Analysis from the linear contrast using optimal coefficients for the pre-specified candidate model Linear.
[6] - The adjusted p-value is based on a critical value of 2.02 from a multivariate-t distribution with 341 degrees of freedom. Any p-value <=0.10 indicates successful establishment of dose-response relationship.

Statistical analysis title	Dose Response Analysis-MADRS #4

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg v Antidepressant + Double-blind Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.978 [8]
Method	MCP-Mod Analysis

Notes:

[7] - For the method of estimation, the t-statistic used for this analysis, 0.30, was based on MCP-Mod Analysis from the linear contrast using optimal coefficients for the pre-specified candidate model Logistic.
[8] - The adjusted p-value is based on a critical value of 2.02 from a multivariate-t distribution with 341 degrees of freedom. Any p-value <=0.10 indicates successful establishment of dose-response relationship.

Secondary: Change in Average Systolic Blood Pressure From Augmentation Baseline (Week 8) to Week 16

End point title	Change in Average Systolic Blood Pressure From Augmentation Baseline (Week 8) to Week 16

End point description:

This end point used the Vital Signs Evaluable Set, which included all randomized subjects who had at least 1 valid vital signs measurement during the Dose Maintenance Period while on the target dose level of investigational product.

End point type	Secondary

End point timeframe:

From Augmentation Baseline (Week 8) to Week 16

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489 10mg	Antidepressant + Double-blind SPD489 30mg	Antidepressant + Double-blind SPD489 50mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	68	65	51
Units: mmHg				
arithmetic mean (standard deviation)	-0.2 (± 9.55)	0.2 (± 8.58)	0.5 (± 9.17)	3.5 (± 7.82)

End point values	Antidepressant + Double-blind SPD489 70mg			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: mmHg				
arithmetic mean (standard deviation)	2.6 (± 10.55)			

Statistical analyses

Statistical analysis title	Dose Response Analysis-Systolic Blood Pressure

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.004 [10]
Method	MCP-Mod Analysis

Notes:

[9] - For the method of estimation, the t-statistic used for this analysis, 3.14, was based on MCP-Mod Analysis for the candidate model EMax.
[10] - The systolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Systolic Blood Pressure #2

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant +

	Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.032 [12]
Method	MCP-Mod Analysis

Notes:

[11] - For the method of estimation, the t-statistic used for this analysis, 2.48, was based on MCP-Mod Analysis for the candidate model Exponential.
[12] - The systolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Systolic Blood Pressure #3

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.003 [14]
Method	MCP-Mod Analysis

Notes:

[13] - For the method of estimation, the t-statistic used for this analysis, 3.26 was based on MCP-Mod Analysis for the candidate model Linear.
[14] - The systolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Systolic Blood Pressure #4

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.01 [16]
Method	MCP-Mod Analysis

Notes:

[15] - For the method of estimation, the t-statistic used for this analysis, 2.88, was based on MCP-Mod Analysis for the candidate model Logistic1.
[16] - The systolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom

Statistical analysis title	Dose Response Analysis-Systolic Blood Pressure #5

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.005 [18]
Method	MCP-Mod Analysis

Notes:

[17] - For the method of estimation, the t-statistic used for this analysis, 3.12, was based on MCP-Mod Analysis for the candidate model Logistic2.
[18] - The systolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Secondary: Change in Average Diastolic Blood Pressure From Augmentation Baseline (Week 8) to Week 16

End point title	Change in Average Diastolic Blood Pressure From Augmentation Baseline (Week 8) to Week 16

End point description:

This endpoint used the Vital Signs Evaluable Set, which included all randomized subjects who had at least 1 valid vital signs measurement during the Dose Maintenance Period while on the target dose level of investigational product.

End point type	Secondary

End point timeframe:

From Augmentation Baseline (Week 8) to Week 16

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489 10mg	Antidepressant + Double-blind SPD489 30mg	Antidepressant + Double-blind SPD489 50mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	68	65	51
Units: mmHg				
arithmetic mean (standard deviation)	-0.1 (± 6.69)	-0.9 (± 6.64)	-0.1 (± 7.39)	2.8 (± 6.58)

End point values	Antidepressant + Double-blind SPD489 70mg			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: mmHg				
arithmetic mean (standard deviation)	1.9 (± 7.45)			

Statistical analyses

Statistical analysis title	Dose Response Analysis-Diastolic Blood Pressure

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.011 [20]
Method	MCP-Mod Analysis

Notes:

[19] - For the method of estimation, the t-statistic used for this analysis, 2.86 was based on MCP-Mod Analysis for the candidate model Emax
[20] - The diastolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Diastolic Blood Pressure #2

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.023 [22]
Method	MCP-Mod Analysis

Notes:

[21] - For the method of estimation, the t-statistic used for this analysis, 2.59, was based on MCP-Mod Analysis for the candidate model Exponential.
[22] - The diastolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Diastolic Blood Pressure #3

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.003 [24]
Method	MCP-Mod Analysis

Notes:

[23] - For the method of estimation, the t-statistic used for this analysis, 3.28, was based on MCP-Mod Analysis for the candidate model Linear.
[24] - The diastolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Diastolic Blood Pressure #4

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.009 [26]
Method	MCP-Mod Analysis

Notes:

[25] - For the method of estimation, the t-statistic used for this analysis, 2.93, was based on MCP-Mod Analysis for the candidate model Logistic1.
[26] - The diastolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Diastolic Blood Pressure #5

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.005 [28]
Method	MCP-Mod Analysis

Notes:

[27] - For the method of estimation, the t-statistic used for this analysis, 3.13, was based on MCP-Mod Analysis for the candidate model Logistic2.
[28] - The diastolic blood pressure p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Secondary: Change in Average Pulse Rate From Augmentation Baseline (Week 8) to Week 16

End point title	Change in Average Pulse Rate From Augmentation Baseline (Week 8) to Week 16

End point description:

This end point used the Vital Signs Evaluable Set, which included all randomized subjects who had at least 1 valid vital signs measurement during the Dose Maintenance Period while on the target dose level of investigational product.

End point type	Secondary

End point timeframe:

From Augmentation Baseline (Week 8) to Week 16

End point values	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489 10mg	Antidepressant + Double-blind SPD489 30mg	Antidepressant + Double-blind SPD489 50mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	68	65	51
Units: bpm				
arithmetic mean (standard deviation)	-0.8 (± 9.95)	0.8 (± 7.32)	5.3 (± 8.08)	4 (± 9.8)

End point values	Antidepressant + Double-blind			

	SPD489 70mg			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: bpm				
arithmetic mean (standard deviation)	6 (± 11.25)			

Statistical analyses

Statistical analysis title	Dose Response Analysis-Pulse

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	< 0.001 [30]
Method	MCP-Mod Analysis

Notes:

[29] - For the method of estimation, the t-statistic used for this analysis, 4.24, was based on MCP-Mod Analysis for the candidate model Emax
[30] - The pulse p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Pulse #2

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.002 [32]
Method	MCP-Mod Analysis

Notes:

[31] - For the method of estimation, the t-statistic used for this analysis, 3.36, was based on MCP-Mod Analysis for the candidate model Expontential.
[32] - The pulse p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Pulse #3

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.001 [34]
Method	MCP-Mod Analysis

Notes:

[33] - For the method of estimation, the t-statistic used for this analysis, 4.10, was based on MCP-Mod Analysis for the candidate model Linear.
[34] - The pulse p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Pulse #4

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	< 0.001 [36]
Method	MCP-Mod Analysis

Notes:

[35] - For the method of estimation, the t-statistic used for this analysis, 4.39, was based on MCP-Mod Analysis for the candidate model Logistic1.
[36] - The pulse p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Statistical analysis title	Dose Response Analysis-Pulse #5

Statistical analysis description:

Analysis of Dose Response Using the MCP-Mod Analysis Method

Comparison groups	Antidepressant + Double-blind Placebo v Antidepressant + Double-blind SPD489 10mg v Antidepressant + Double-blind SPD489 30mg v Antidepressant + Double-blind SPD489 50mg v Antidepressant + Double-blind SPD489 70mg
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.001 [38]
Method	MCP-Mod Analysis

Notes:

[37] - For the method of estimation, the t-statistic used for this analysis, 4.39 was based on MCP-Mod Analysis for the candidate model Logistic2.
[38] - The pulse p-value was based on a critical value of 1.99 from a multivariate-t distribution with 341 degrees of freedom.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 21 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Antidepressant + Double-blind Placebo

Reporting group description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily double-blind placebo (matching SPD489).

Reporting group title	Antidepressant + Double-blind SPD489 10mg

Reporting group description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily over-encapsulated SPD489 as a 10mg dose.

Reporting group title	Antidepressant + Double-blind SPD489 30mg

Reporting group description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily over-encapsulated SPD489 as a 30mg dose.

Reporting group title	Antidepressant + Double-blind SPD489 50mg

Reporting group description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily over-encapsulated SPD489 as a 50mg dose.

Reporting group title	Antidepressant + Double-blind SPD489 70mg

Reporting group description:

Subjects received unblinded standard antidepressant therapy (either escitalopram oxalate or venlafaxine hydrochloride extended-release titrated to the maximum tolerated dose) plus oral, once daily over-encapsulated SPD489 as a 70mg dose.

Serious adverse events	Antidepressant + Double-blind Placebo	Antidepressant + Double-blind SPD489 10mg	Antidepressant + Double-blind SPD489 30mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Antidepressant + Double-blind SPD489 50mg	Antidepressant + Double-blind SPD489 70mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 78 (0.00%)	1 / 80 (1.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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 10mg	Antidepressant + Double-blind SPD489 30mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 78 (25.64%)	30 / 77 (38.96%)	29 / 76 (38.16%)
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 78 (2.56%)	2 / 77 (2.60%)	2 / 76 (2.63%)
occurrences (all)	2	2	2
Headache			
subjects affected / exposed	10 / 78 (12.82%)	7 / 77 (9.09%)	5 / 76 (6.58%)
occurrences (all)	12	8	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 78 (5.13%)	2 / 77 (2.60%)	3 / 76 (3.95%)
occurrences (all)	5	2	3

Dry mouth			
subjects affected / exposed	1 / 78 (1.28%)	2 / 77 (2.60%)	2 / 76 (2.63%)
occurrences (all)	1	2	2
Nausea			
subjects affected / exposed	1 / 78 (1.28%)	5 / 77 (6.49%)	6 / 76 (7.89%)
occurrences (all)	1	5	6
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 78 (1.28%)	4 / 77 (5.19%)	0 / 76 (0.00%)
occurrences (all)	1	4	0
Psychiatric disorders			
Bruxism			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	2 / 78 (2.56%)	7 / 77 (9.09%)	2 / 76 (2.63%)
occurrences (all)	2	9	2
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 78 (2.56%)	1 / 77 (1.30%)	4 / 76 (5.26%)
occurrences (all)	3	1	4
Nasopharyngitis			
subjects affected / exposed	0 / 78 (0.00%)	5 / 77 (6.49%)	4 / 76 (5.26%)
occurrences (all)	0	5	5
Upper respiratory tract infection			
subjects affected / exposed	0 / 78 (0.00%)	3 / 77 (3.90%)	3 / 76 (3.95%)
occurrences (all)	0	3	3
Urinary tract infection			
subjects affected / exposed	5 / 78 (6.41%)	1 / 77 (1.30%)	2 / 76 (2.63%)
occurrences (all)	5	1	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 78 (1.28%)	4 / 77 (5.19%)	5 / 76 (6.58%)
occurrences (all)	1	4	6

Non-serious adverse events	Antidepressant + Double-blind SPD489 50mg	Antidepressant + Double-blind SPD489 70mg	
Total subjects affected by non-serious			

adverse events subjects affected / exposed	36 / 78 (46.15%)	44 / 80 (55.00%)	
Investigations Blood pressure increased subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 3	4 / 80 (5.00%) 4	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	5 / 78 (6.41%) 5 3 / 78 (3.85%) 5	1 / 80 (1.25%) 1 8 / 80 (10.00%) 9	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	4 / 80 (5.00%) 4	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 2 10 / 78 (12.82%) 10 1 / 78 (1.28%) 1	5 / 80 (6.25%) 5 10 / 80 (12.50%) 10 6 / 80 (7.50%) 7	
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	3 / 80 (3.75%) 3	
Psychiatric disorders Bruxism subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 4 8 / 78 (10.26%) 10	6 / 80 (7.50%) 7 9 / 80 (11.25%) 11	

Infections and infestations			
Influenza			
subjects affected / exposed	4 / 78 (5.13%)	1 / 80 (1.25%)	
occurrences (all)	5	1	
Nasopharyngitis			
subjects affected / exposed	2 / 78 (2.56%)	7 / 80 (8.75%)	
occurrences (all)	2	8	
Upper respiratory tract infection			
subjects affected / exposed	4 / 78 (5.13%)	3 / 80 (3.75%)	
occurrences (all)	4	3	
Urinary tract infection			
subjects affected / exposed	1 / 78 (1.28%)	2 / 80 (2.50%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 78 (6.41%)	4 / 80 (5.00%)	
occurrences (all)	5	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2011	• Updated emergency contact information • Removed the Probabilistic Reward Task • Specified that the 2 antidepressants were "as provided by the sponsor" • Revised exclusion criteria • Clarified that subjects with no improvement in or a worsening of depressive symptoms at Visit 8 were to be discontinued and that average readings were to be used when referring to the management of blood pressure and pulse • Reduced the requirement for post-study contraception • Updated withdrawal criteria with respect to additional vital signs collected at Visits 8, 10, 12, and 14 • Added commercial lisdexamfetamine dimesylate as being excluded • Clarified that medications not affecting blood pressure, heart rate, or the CNS, and necessary for the subject's welfare were not restricted • Specified assessments to be conducted if background product was tapered • Defined target dose of background product and re-dispensing procedures for background products and investigational product • Clarified assessments to be carried out if down-titration of investigational product occurred and that for subjects who discontinued early, the Visit 14 procedures would be performed and dosing • Qualified that subjects "whose depressive symptoms have improved based on MADRS total score, but" who did not meet randomization criteria at Visit 8 were allowed to continue receiving placebo • Specified that Visit 8 is the beginning of the Forced-dose Titration Period • Increased duration of Forced-dose Titration Period • Added a collection of additional vital signs measurements at specified visits • Revised language to include necessary tapering of background product for subjects who terminated early or who completed but did not enter the long-term safety study • Clarified pharmacokinetic sample collection and processing procedures • Updated criteria on the C-SSRS for evaluating suitability to remain in the study • Updated the MADRS version and date and language on product storage

01 October 2012	• Increased the number of screened subjects • Increased the number of planned sites • Clarified the use of background product containers • Specified that any down titration of antidepressant should be managed by the investigator • Changed the level of significance for "other" efficacy assessments from a 0.05 to a 0.10 level and 95% CI coverage to 90%. • Added 2 exploratory objectives to summarize efficacy of SPD489 • Revised exclusion criteria • Added the CGI-I and CGI-S as efficacy assessments • Clarified that clinical laboratory tests and ECGs were to be repeated prior to Visit 2 and the results verified before enrollment. • Removed the suggestion for the investigator to contact the CRO medical monitor prior to subject withdrawal • Specified that, in determining whether a subject should be discontinued from study, the investigator was to consult with the CRO medical monitor. • Added that contraceptive requirements were to be reviewed with subjects at all visits • Added that a subject who required a change to their MDD treatment that was prohibited by the protocol must be discontinued from the study • The following reasons for discontinuation were added under the category of Other: _ Change in background product for MDD treatment required _ Treatment for MDD by a prohibited medication required _ Other reasons for discontinuation (must be specified) • Specified that the investigator was to contact the CRO medical monitor as soon as possible after becoming unblinded • Removed the requirement to report in the IV/WRS any investigational or background product that had been damaged after a temperature excursion and the requirement to discard these products • Added the formula to calculate medication compliance • Clarified that the discontinuation of prohibited medications that were used prior to Visit 2 was at the discretion of the investigator and that subjects who discontinued these were to have a negative urine drug screen prior to Visit 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported