Clinical trial results:
A Phase 3, Open-label, Multicenter, 12-month Extension Safety and Tolerability Study of SPD489 in Combination With an Antidepressant in the Treatment of Adults With Major Depressive Disorder With Residual Symptoms or Inadequate Response Following Treatment With an Antidepressant

Summary

EudraCT number	2011-003019-47
Trial protocol	DE HU PL CZ ES BE EE FI SE GB
Global end of trial date	27 March 2014

Results information

Result version number	v1 (current)
This version publication date	27 September 2018
First version publication date	21 February 2015

Trial information

Trial identification

Sponsor protocol code	SPD489-329

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01436175
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard Wayne, Pennsylvania, United States, 19087
Public contact	Medical Communications, Shire 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	27 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the long-term safety and tolerability of SPD489 administered as a daily morning dose (20, 30, 50, and 70 milligram per day [mg/day]) as adjunctive therapy to an antidepressant for the treatment of major depressive disorder (MDD) in adults (18-65 years of age inclusive at the time of consent for the respective short-term antecedent SPD489 MDD study). Long-term safety was described using:
• Occurrence of treatment-emergent adverse events (TEAEs),
• Responses to the Columbia Suicide Severity Rating Scale (C-SSRS), and
• Specific evaluation of blood pressure and pulse rate, clinical laboratory evaluations, and electrocardiogram (ECG) results.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Czech Republic: 83
Country: Number of subjects enrolled	Estonia: 24
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 69
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	United States: 1190
Country: Number of subjects enrolled	Mexico: 27
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Chile: 33

Country: Number of subjects enrolled	Argentina: 27
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Croatia: 5
Worldwide total number of subjects	1559
EEA total number of subjects	228

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)	1559
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study enrolled eligible adults with MDD who had completed treatment in a short-term antecedent SPD489 (lisdexamfetamine dimesylate) MDD study (SPD489-209 [2011-003615-28], SPD489-322 [2011-003018-17], and SPD489-323 [2011-003006-25]).

Pre-assignment

Screening details:

A total of 1570 subjects were enrolled. Of these, 11 subjects excluded from the Safety Analysis Set (reasons for discontinuation were 3 subjects lost to follow up, 3 subject withdrew and 5 subjects were without a post-Visit 0 safety assessment). A total of 1559 subjects were included in Safety Analysis Set.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SPD489 + Antidepressant

Arm description:

SPD489 20, 30, 50 or 70 mg once daily orally for 52 weeks along with the assigned background product that subject had received during the antecedent study (antidepressant: either escitalopram oxalate, sertraline hydrochloride [HCl], venlafaxine HCl extended-release, or duloxetine HCl) at a dose consistent with applicable local labeling guidelines.

Arm type	Experimental
Investigational medicinal product name	lisdexamfetamine dimesylate (LDX)
Investigational medicinal product code	SPD489
Other name	Vyvanse, Venvanse, Elvanse, Tyvense
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SPD489 20, 30, 50 or 70 mg once daily orally for 52 weeks along with the assigned background product that subject had received during the antecedent study.

Number of subjects in period 1	SPD489 + Antidepressant
Started	1559
Completed	300
Not completed	1259
Consent withdrawn by subject	105
Adverse Event	111
Protocol Violation	44
Lost to follow-up	86
'Unspecified '	826
Met blood pressure or pulse withdrawal	63
Lack of efficacy	24

Baseline characteristics

Reporting groups	
Reporting group title	SPD489 + Antidepressant

Reporting group description:

SPD489 20, 30, 50 or 70 mg once daily orally for 52 weeks along with the assigned background product that subject had received during the antecedent study (antidepressant: either escitalopram oxalate, sertraline hydrochloride [HCl], venlafaxine HCl extended-release, or duloxetine HCl) at a dose consistent with applicable local labeling guidelines.

Reporting group values	SPD489 + Antidepressant	Total	
Number of subjects	1559	1559	
Age categorical			
Safety Analysis Set consisted of all subjects who took at least 1 dose of investigational product and had at least 1 post-Visit 0 safety assessment.			
Units: Subjects			
18-55 Years	1333	1333	
56-65 Years	226	226	
Age continuous			
Safety Analysis Set.			
Units: years			
arithmetic mean	41.9		
standard deviation	± 11.89	-	
Gender categorical			
Safety Analysis Set.			
Units: Subjects			
Female	1056	1056	
Male	503	503	

End points

End points reporting groups

Reporting group title	SPD489 + Antidepressant

Reporting group description:

SPD489 20, 30, 50 or 70 mg once daily orally for 52 weeks along with the assigned background product that subject had received during the antecedent study (antidepressant: either escitalopram oxalate, sertraline hydrochloride [HCl], venlafaxine HCl extended-release, or duloxetine HCl) at a dose consistent with applicable local labeling guidelines.

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

End point title	Columbia-Suicide Severity Rating Scale (C-SSRS)[1]

End point description:

C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviour 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 behaviour occurred. The assessment is done by the nature of the responses, not by a numbered scale.

Safety analysis set included all subjects who took at least 1 dose of investigational product and had at least 1 post-Visit 0 (Week 0) safety assessment in this study.

End point type	Primary

End point timeframe:

Week 5 up to Week 52/Early Termination(ET)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since this is a single arm study, no statistical analysis was planned.

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1559			
Units: subjects				
Positive Suicidal Ideation	68			
Suicidal Attempt	4			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Systolic Blood Pressure at Week 52

End point title	Change From Baseline in Systolic Blood Pressure at Week 52[2]

End point description:

Baseline was defined as the Augmentation Baseline Visit of the antecedent study (SPD489-209 [2011-003615-28], SPD489-322 [2011-003018-17], and SPD489-323 [2011-003006-25]).

Safety Analysis Set. Here n = subjects evaluable at specified time-points.

End point type	Primary

End point timeframe:

Baseline, Week 52/ET

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since this is a single arm study, no statistical analysis was planned.

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1559			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n = 1559)	117.6 (± 11.13)			
Change at Week 52/ET (n = 1558)	2.4 (± 10.37)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Diastolic Blood Pressure at Week 52

End point title	Change From Baseline in Diastolic Blood Pressure at Week 52[3]

End point description:

Baseline was defined as the Augmentation Baseline Visit of the antecedent study (SPD489-209 [2011-003615-28], SPD489-322 [2011-003018-17], and SPD489-323 [2011-003006-25]).

Safety Analysis Set. Here n = subjects evaluable at specified time-points.

End point type	Primary

End point timeframe:

Baseline, Week 52/ET

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since this is a single arm study, no statistical analysis was planned.

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1559			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n = 1559)	75.4 (± 8.15)			
Change at Week 52/ET (n = 1558)	1.2 (± 7.94)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Pulse Rate at Week 52

End point title	Change From Baseline in Pulse Rate at Week 52[4]

End point description:

Baseline was defined as the Augmentation Baseline Visit of the antecedent study (SPD489-209 [2011-003615-28], SPD489-322 [2011-003018-17], and SPD489-323 [2011-003006-25]).

Safety Analysis Set. Here n = subjects evaluable at specified time-points.

End point type	Primary

End point timeframe:

Baseline, Week 52/ET

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since this is a single arm study, no statistical analysis was planned.

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1559			
Units: beats per minute(bpm)				
arithmetic mean (standard deviation)				
Baseline (n = 1559)	72.7 (± 9.9)			
Change at Week 52/ET (n = 1558)	5.2 (± 10.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sheehan Disability Scale (SDS) Total Score at Week 52/ET

End point title	Change From Baseline in Sheehan Disability Scale (SDS) Total Score at Week 52/ET

End point description:

Designed to evaluate the extent to which illness symptoms impact a subject's life in 3 areas: work, 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.
Baseline was defined as the Augmentation Baseline Visit of the antecedent study (SPD489-209 [2011-003615-28], SPD489-322 [2011-003018-17], and SPD489-323 [2011-003006-25]).

Full Analysis Set (FAS) included all subjects in the Safety Analysis Set who had at least 1 clinical experience outcome assessment in the study. Here n = subjects evaluable at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1556			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=1548)	12.7 (± 7.06)			

Change at Week 52/ET (n = 1530)	-4.3 (± 7.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Improvement on Clinical Global Impressions - Global Improvement (CGI-I)

End point title	Number of Subjects With Improvement on Clinical Global Impressions - Global Improvement (CGI-I)

End point description:

Subjects who did not have Clinical Global Impressions - Severity of Illness (CGI-S) assessed at Week 8 in the antecedent study should not have had CGI-I assessed in this study and were excluded from the summary of CGI-I. CGI-I consists of a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Improvement includes a score of 1 (very much improved) or 2 (much improved) on the scale.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1345			
Units: subjects				
Number of Subjects With Improvement on CGI-I	1021			

Statistical analyses

No statistical analyses for this end point

Secondary: Short Form-12 Health Survey Version 2 (SF-12V2)

End point title	Short Form-12 Health Survey Version 2 (SF-12V2)

End point description:

SF-12V2 is a multi-purpose, 7-item survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It is expressed by two summary measures (Aggregate Physical and Aggregate Mental) for which values can range from 0 to 100. A higher score is indicative of a better health state.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:
Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1531			
Units: units on a scale				
arithmetic mean (standard deviation)				
Aggregate Physical	49.1 (± 9.67)			
Aggregate Mental	42.7 (± 11.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Mobility

End point title	EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Mobility

End point description:

Quality of life was assessed using the EQ-5D-5L, which is one of the most widely used generic index measures of health-related quality of life. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:
Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1537			
Units: subjects				
No problems in walking about	1193			
Slight problems in walking about	237			
Moderate problems in walking about	82			
Severe problems in walking about	24			
Unable to walk about	1			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Self-Care

End point title	EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Self-Care

End point description:

Quality of life was assessed using the EQ-5D-5L, which is one of the most widely used generic index measures of health-related quality of life. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1537			
Units: subjects				
No problems washing or dressing myself	1304			
Slight problems washing or dressing myself	174			
Moderate problems washing or dressing myself	49			
Severe problems washing or dressing myself	9			
Unable to wash or dress myself	1			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Usual Activities

End point title	EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Usual Activities

End point description:

Quality of life was assessed using the EQ-5D-5L, which is one of the most widely used generic index measures of health-related quality of life. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1537			
Units: subjects				
No problems doing my usual activities	800			
Slight problems doing my usual activities	475			
Moderate problems doing my usual activities	197			
Severe problems doing my usual activities	55			
Unable to do my usual activities	10			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Pain/Discomfort

End point title	EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Pain/Discomfort

End point description:

Quality of life was assessed using the EQ-5D-5L, which is one of the most widely used generic index measures of health-related quality of life. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1537			
Units: subjects				
No pain or discomfort	715			
Slight pain or discomfort	536			
Moderate pain or discomfort	208			
Severe pain or discomfort	68			
Extreme pain or discomfort	10			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Anxiety/Depression

End point title	EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Anxiety/Depression

End point description:

Quality of life was assessed using the EQ-5D-5L, which is one of the most widely used generic index measures of health-related quality of life. It consists of a 5-item descriptive system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1537			
Units: subjects				
Not anxious or depressed	461			
Slightly anxious or depressed	687			
Moderately anxious or depressed	289			
Severely anxious or depressed	73			
Extremely anxious or depressed	27			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Visual Analog Scale

End point title	EuroQoL Group 5-Dimension 5-Level Self Report Questionnaire (EQ-5D-5L): Visual Analog Scale

End point description:

EQ-5D-5L is one of the most widely used generic index measures of health-related quality of life. EQ-5D-5L Visual Analog Scale score is numbered from 0 to 100, where a score of 100 is the best health a subject can imagine.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1537			
Units: units on a scale				
arithmetic mean (standard deviation)	75.7 (± 18.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR)

End point title	Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR)

End point description:

QIDS-SR is a validated, self-reported rating scale that contains 16 items scored on a scale from 0-3 with total scores ranging from 0 (no depression) to 27 (very severe depression). Lower scores indicate less depression. The QIDS-SR was only assessed in the SPD489-322 antecedent study. The QIDS-SR total score is calculated as the sum of the highest score on any 1 of Items 1-4, Item 5, the highest score on any 1 of Items 6-9, Items 10-14, the highest score on either Item 15 or 16.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: units on a scale				
arithmetic mean (standard deviation)				
QIDS-SR	6.9 (± 4.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Enjoyment Satisfaction Questionnaire Short Form (Q-LES-

Q-SF)

End point title	Quality of Life Enjoyment Satisfaction Questionnaire Short Form (Q-LES-Q-SF)

End point description:

The Q-LES-Q-SF is a 16-item self-report questionnaire which evaluates general subject satisfaction with health, mood, relationships, functioning in daily life, and their treatment. Each item is rated on a 5-point scale from 1 (very poor) to 5 (very good). The total raw score (summary scale score) was calculated by summing item scores 1 to 14 (total raw score range: 14 to 70). Item 15 (satisfaction with medication, raw score range: 1 to 5) and Item 16 (overall satisfaction and contentment; raw score range: 1 to 5) were stand-alone items. For reporting, summary scale, Item 15 and Item 16 raw scores were transformed into percentage maximum possible score which ranged from 0 to 100, where higher scores are indicative of greater enjoyment or satisfaction.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint, n = subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: units on a scale				
arithmetic mean (standard deviation)				
Summary Scale (n = 506)	61.5 (± 17.22)			
Satisfaction with Medication (n = 478)	68.6 (± 19.66)			
Overall Satisfaction and Contentment (n = 506)	63.2 (± 21.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sexual Functioning Questionnaire - 14 Item Scale (CSFQ-14) Total Score at Week 52/ET

End point title	Change From Baseline in Sexual Functioning Questionnaire - 14 Item Scale (CSFQ-14) Total Score at Week 52/ET

End point description:

CSFQ-14 is a 14 item self-report tool that evaluates sexual functioning. Each item is scored on a 5-point Likert scale ranging from 1 (never) to 5 (always) with total scores ranging from 14 to 70. Higher scores reflect better sexual functioning. Baseline was defined as the Augmentation Baseline Visit of the antecedent study (SPD489-209 [2011-003615-28], SPD489-322 [2011-003018-17], and SPD489-323 [2011-003006-25]).

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint, n = subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	508			
Units: units on a scale				
arithmetic mean (standard deviation)				
Male: Baseline (n=167)	46.6 (± 9.17)			
Male: Change at Week 52/ET (n=164)	1.7 (± 7.16)			
Female: Baseline (n=341)	37.2 (± 9.65)			
Female: Change at Week 52/ET (n=330)	2.8 (± 8.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Amphetamine Cessation Symptom Assessment (ACSA) Total Score

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

End point description:

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.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 53

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	1349			
Units: units on a scale				
arithmetic mean (standard deviation)				
ACSA Total Score	14.3 (± 10.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Resource Utilization Questionnaire - Major Depressive Disorder (PRUQ-MDD)

End point title	Patient Resource Utilization Questionnaire - Major Depressive Disorder (PRUQ-MDD)

End point description:

The PRUQ-MDD assessed the long term economic outcomes. It collects utilization of healthcare resources reported by the study subjects. Subjects answered the following questions:
1. Were you hospitalized in the past month, 2. Do you work for pay, 3. If you missed time at work last week, please note all the reasons why, 4. Would you say that the past week was typical, like the rest of the 3 weeks this month, in terms of your working hours, 5. Do you do volunteer work (VW), and 6. If you do not receive money for your work and do not participate in volunteer work, the reason is.
Number of subjects with response is reported.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	482			
Units: subjects				
Hospitalized in Past Month	4			
Work for Pay	337			
Reason Missing Work Time: Had a Day Off	24			
Reason Missing Work Time: Physically Ill	10			
Reason Missing Work Time: Upset/Depressed/Nervous	15			
Reason Missing Work Time: Other	36			
Past Week Was Typical: Yes	249			
Past Week Was Typical: No, Worked More Hours	43			
Past Week Was Typical: No, Worked Less Hours	45			
Volunteer Work	86			
Reason no Money/VW: Physically Ill	6			
Reason no Money/VW: Upset/Depressed/Nervous	30			
Reason no Money/VW: Cannot Find Work	39			
Reason no Money/VW: Other	48			
Reason no Money/VW: Not Applicable	348			

Statistical analyses

No statistical analyses for this end point

Secondary: PRUQ-MDD – Number of Days of Resource Utilization

End point title	PRUQ-MDD – Number of Days of Resource Utilization

End point description:

The PRUQ-MDD assessed the long term economic outcomes. It collects utilization of healthcare

resources reported by the study subjects. Number of nights in medical/surgical ward, number of nights in ICU, and number of days a subject received home care in the past month are reported.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint, n = subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	482			
Units: days				
arithmetic mean (standard deviation)				
Number of nights in medical/surgical ward (n=4)	1.3 (± 0.5)			
Number of nights in ICU (n=4)	0 (± 0)			
Number of days received home care in past month	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: PRUQ-MDD – Number of Events (Visit to Health Care Provider/Visit to Hospital Facilities/Number of Times a Test Was Performed)

End point title	PRUQ-MDD – Number of Events (Visit to Health Care Provider/Visit to Hospital Facilities/Number of Times a Test Was Performed)

End point description:

The PRUQ-MDD assessed the long term economic outcomes. It collects utilization of healthcare resources reported by the study subjects. Subjects answered following questions - 1. How many times did you visit the following healthcare providers in the past month: Family doctor/primary care, Non-physician healthcare practitioner (NPHP), Psychiatrist/Psychologist/Counselor (PPC); 2. How many times did you take one of the tests, mentioned below, during the past month: Blood test, CT Scan, X Ray, Renal function, Thyroid function; and 3. How many times did you visit the hospital emergency room (ER), urgent care facility (UCF) or an after-hours clinic (AHC) in the past month. Number of events (visit to health care provider, visit to hospital facilities, number of times a test was performed) are reported. FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint, n = subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	482			
Units: events				
arithmetic mean (standard deviation)				
Visit to Family doctor/primary care (n=481)	0.2 (± 0.58)			
Visit to NPHP(n=480)	0.1 (± 0.43)			
Visit to PPC(n=481)	0.1 (± 0.86)			
Test performed: Blood Test (n=480)	0.2 (± 2.3)			
Test performed: CT Scan (n=480)	0 (± 0.08)			
Test performed: X Ray (n=480)	0 (± 0.2)			
Test performed: Renal function (n=480)	0 (± 0)			
Test performed: Thyroid function (n=480)	0 (± 0.09)			
Test performed: Other test (n=479)	0.1 (± 0.49)			
Visit to Hospital ER, UCF or AHC (n=482)	0 (± 0.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: PRUQ-MDD – Number of Hours

End point title	PRUQ-MDD – Number of Hours

End point description:

The PRUQ-MDD assessed the long term economic outcomes. It collects utilization of healthcare resources reported by the study subjects. Subjects answered following questions - 1. How many hours do you usually work or would you usually be expected to work (hrs/week); 2. How many hours did you actually work last week; 3. On average, how many hours do you volunteer per week. Number of hours are reported.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint, n = subjects evaluable for specified categories.

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	482			
Units: hours				
arithmetic mean (standard deviation)				
Work or usually expect to work (n=337)	34 (± 11.85)			
Actual work (n=337)	31.2 (± 15.13)			
Average volunteer per week (n=86)	8.6 (± 8.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: PRUQ-MDD – Effect of Depressive Symptoms

End point title	PRUQ-MDD – Effect of Depressive Symptoms

End point description:

The PRUQ-MDD assessed the long term economic outcomes. It collects utilization of healthcare resources reported by the study subjects. Subjects answered following questions on a 0 to 10 point scale - 1. During past week, how much did depressive symptoms affect work productivity; 2. During past week, how much did depressive symptoms affect regular non-work daily activities. Higher scores indicates more effect of depressive symptoms on work productivity and non-work daily activities.

FAS. Here, Number of Subjects Analyzed = subjects who were evaluable for this endpoint, n = subjects evaluable for specified categories

End point type	Secondary

End point timeframe:

Week 52/ET

End point values	SPD489 + Antidepressant			
Subject group type	Reporting group			
Number of subjects analysed	482			
Units: units on scale				
arithmetic mean (standard deviation)				
Affected work productivity (n= 335)	2.1 (± 2.37)			
Affected regular non work daily activities (n=482)	2.5 (± 2.43)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 53

Adverse event reporting additional description:

TEAEs were defined as Adverse Events (AEs) that started or deteriorated on or after the date of the first dose of investigational product and no later than 3 days after the last dose of investigational product.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	SPD489 + Antidepressant

Reporting group description:

SPD489 20, 30, 50 or 70 mg once daily orally for 52 weeks along with the assigned background product that subject had received during the antecedent study (antidepressant: either escitalopram oxalate, sertraline hydrochloride [HCl], venlafaxine HCl extended-release, or duloxetine HCl) at a dose consistent with applicable local labeling guidelines.

Serious adverse events	SPD489 + Antidepressant		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 1559 (2.12%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyolipoma			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian fibroma			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 1559 (0.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions				
Chest pain				
subjects affected / exposed	1 / 1559 (0.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-Cardiac chest pain				
subjects affected / exposed	2 / 1559 (0.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Epistaxis				
subjects affected / exposed	1 / 1559 (0.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 1559 (0.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	1 / 1559 (0.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 1559 (0.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumomediastinum				
subjects affected / exposed	1 / 1559 (0.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 1559 (0.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 1559 (0.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Depressive symptom			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination, auditory			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	3 / 1559 (0.19%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	3 / 1559 (0.19%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gun shot wound			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal strangulation			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal mass			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cyst			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Costochondritis			

subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 1559 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SPD489 + Antidepressant		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	921 / 1559 (59.08%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	91 / 1559 (5.84%)		
occurrences (all)	102		

Headache			
subjects affected / exposed	241 / 1559 (15.46%)		
occurrences (all)	347		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	80 / 1559 (5.13%)		
occurrences (all)	82		
Feeling jittery			
subjects affected / exposed	82 / 1559 (5.26%)		
occurrences (all)	89		
Irritability			
subjects affected / exposed	79 / 1559 (5.07%)		
occurrences (all)	87		
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	212 / 1559 (13.60%)		
occurrences (all)	233		
Nausea			
subjects affected / exposed	116 / 1559 (7.44%)		
occurrences (all)	132		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	83 / 1559 (5.32%)		
occurrences (all)	94		
Bruxism			
subjects affected / exposed	89 / 1559 (5.71%)		
occurrences (all)	97		
Insomnia			
subjects affected / exposed	204 / 1559 (13.09%)		
occurrences (all)	235		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	137 / 1559 (8.79%)		
occurrences (all)	156		
Upper respiratory tract infection			

subjects affected / exposed	100 / 1559 (6.41%)		
occurrences (all)	117		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	189 / 1559 (12.12%)		
occurrences (all)	210		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2011	Specified that the 4 antidepressants (background product) were to be provided by the sponsor. Clarified psychiatric disorders that were exclusionary to study participation. Specified that the systolic and diastolic blood pressure readings were based on an average of 3 readings. Included medications having Central Nervous System (CNS) effects as being exclusionary to study participation. Clarified prior use of investigational product, participation in a previous clinical study, and use of commercial LDX as being exclusionary to study participation. Reduced the duration after the study that a subject was to take contraception from 30 days after the last dose of investigational product to 7 (+2) days. 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. Updated excluded treatments to describe excluded investigational compounds and to add LDX as being an excluded treatment. Expanded permitted concomitant medications during the study to include any medication (not just over the counter medications or antibiotics) not affecting blood pressure, heart rate, or the CNS and that were considered necessary for the subject's welfare. Specified that background product was to be taken in conjunction with investigational product. Noted which study assessments were to be performed when background product was tapered or investigational product was down-titrated. Noted that investigational product was to be stored based on the temperature range specified on the label. Added that eligible subjects who declined participation were not permitted to enroll in the study at a later date. Updated specific items of interest on the C-SSRS for the investigator to use when evaluating a subject's suitability to remain in the study. Updated Q-LES-Q-SF version and date.

15 November 2012	Female subjects must "not have a positive beta-human chorionic gonadotropin (β-hCG)" rather than "must have a negative β-hCG." Specified that a female subject's pregnancy was to be reported within 24 hours. Updated to include requirements regarding malignancy and skin cancer history exclusion. Specified that an average QT interval calculated using Fridericia's formula (QTcF) or QT interval calculated using Bazett's formula (QTcB) interval greater than (>) 450 millisecond (msec) (males) or >470msec (females) was exclusionary to study participation. Limited use of prohibited medications to "current use" rather than "current use or prior use (during the antecedent study)." Removed the requirement that the investigator contact the contract research organization (CRO) medical monitor prior to withdrawal of the subject from investigational product. Added that, in the opinion of the investigator, changes in physical examination, clinical laboratory, or ECG results precluding treatment with SPD489 would require the subject to discontinue from the study. Specified that subjects requiring a change in MDD treatment prohibited by the protocol were discontinued from the study. Specified intervals for QTcF and QTcB for which a subject would be excluded. The following reasons for discontinuation were added under the category of "other": – Change in background product for MDD treatment required, Treatment for MDD, or any other condition, by a prohibited medication, Other reasons for discontinuation (must be specified) Added that occasional non-chronic use of sedatives and anxiolytics was permitted. Updated window for Visit 0 (Dose Optimization) study assessments for subjects not entering this study directly from the pre-defined antecedent study. Also specified that these subjects must have signed informed consent prior to these assessments being done.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 February 2014	The study was terminated as SPD489 failed to demonstrate a benefit as adjunctive treatment to antidepressants in two Phase 3 studies (SPD489-322 [2011-003018-17] and SPD489-323 [2011-003006-25]) . Termination was not related to any new safety findings.	-

Notes:

Limitations and caveats

None reported