



Clinical trial results:

A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized-withdrawal Study to Evaluate the Maintenance of Efficacy of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder **Summary**

EudraCT number	2012-004457-88
Trial protocol	SE DE ES
Global end of trial date	08 April 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2016
First version publication date	09 April 2016

Trial information

Trial identification

Sponsor protocol code	SPD489-346
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02009163
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC and International Affiliates
Sponsor organisation address	1200 Morris Drive, Wayne, United States, 19087
Public contact	Study Physician, Shire Development LLC and International Affiliates , +1 8668425335,
Scientific contact	Study Physician, Shire Development LLC and International Affiliates , +1 8668425335,

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	08 April 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate maintenance of efficacy based on time to relapse between SPD489 (50 or 70mg) and placebo, as measured by the number of binge days (defined as days during which at least 1 binge episode occurred) per week as assessed by clinical interview based on subject diary and Clinical Global Impression – Severity (CGI-S) scores for subjects who responded to SPD489 by the end of the Open-label Treatment Phase.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, 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 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Sweden: 24
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 337
Worldwide total number of subjects	418
EEA total number of subjects	76

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	418
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited to participate at 49 sites in the US (38 sites), Germany (6 sites), Sweden (2 sites), Spain (2 sites), and Canada (1 site).

Pre-assignment

Screening details:

Subjects were screened for eligibility over a period of 4 weeks

Period 1

Period 1 title	Open-label Period (Non-randomized)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	SPD489 (Open-label Period)
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Arm description:

SPD489 treatment was taken orally once daily at approximately 7:00 AM. All participants began treatment with SPD489 at the lowest dose level (30mg) during the 4- week open-label dose-optimization period. After 1 week of treatment at 30mg, all participants were titrated to the next dose level (50mg). After 1 week of treatment at 50mg, all participants were titrated to the highest dose level (70mg), as tolerated and as clinically indicated. After 1 week of treatment at the highest dose, the participant could have been down-titrated to 50mg; no further dose adjustments were permitted. The optimal daily dose of 50 or 70mg achieved during dose- optimization was maintained throughout the 8-week dose- maintenance period. The total time of the open-label period was 12 weeks.

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

Dosage and administration details:

Participants were administered one 30, 50, or 70mg capsule once daily.

Number of subjects in period 1	SPD489 (Open-label Period)
Started	418
Completed	275
Not completed	143
Adverse Event	22
Failure to Meet Randomization Criteria	48
Not specified	13
Pregnancy	1
Withdrawal by Subject	29
Protocol Violation	10
Lost to follow-up	20

Period 2

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

Blinding implementation details:

SPD489 and placebo were identical in appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Randomized-withdrawal Period)

Arm description:

During the 26--week double--blind randomized--withdrawal phase, participants randomized to placebo received matching placebo capsules daily. After the 26--week double--blind randomized--withdrawal phase, participants were followed for 1 week

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:

Participants were administered a placebo capsule once daily.

Arm title	SPD489 (Randomized-withdrawal Period)
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Arm description:

For participants randomized to SPD489, the optimal daily dose of 50 or 70mg was continued throughout the 26--week double--blind randomized--withdrawal phase. After the 26--week double--blind randomized--withdrawal phase, participants were followed for 1 week.

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

Dosage and administration details:

Participants were administered one 50 or 70mg capsule once daily.

Number of subjects in period 2	Placebo (Randomized- withdrawal Period)	SPD489 (Randomized- withdrawal Period)
Started	138	137
Completed	50	102
Not completed	88	35
Adverse Event	-	6
Not specified	9	5
Pregnancy	-	2
Relapse Criteria Met	40	5
Withdrawal by Subject	25	9
Protocol Violation	1	2
Lost to follow-up	13	6

Baseline characteristics

Reporting groups

Reporting group title	Open-label Period (Non-randomized)
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Reporting group description:

All participants enrolled in the open-label population.

Reporting group values	Open-label Period (Non-randomized)	Total	
Number of subjects	418	418	
Age categorical Units: Subjects			
< 40 years of age	223	223	
>/= 40 years of age	195	195	
Age continuous Units: years			
arithmetic mean	38.2		
standard deviation	± 10.41	-	
Gender categorical Units: Subjects			
Female	363	363	
Male	55	55	

End points

End points reporting groups

Reporting group title	SPD489 (Open-label Period)
Reporting group description: SPD489 treatment was taken orally once daily at approximately 7:00 AM. All participants began treatment with SPD489 at the lowest dose level (30mg) during the 4- week open-label dose-optimization period. After 1 week of treatment at 30mg, all participants were titrated to the next dose level (50mg). After 1 week of treatment at 50mg, all participants were titrated to the highest dose level (70mg), as tolerated and as clinically indicated. After 1 week of treatment at the highest dose, the participant could have been down-titrated to 50mg; no further dose adjustments were permitted. The optimal daily dose of 50 or 70mg achieved during dose- optimization was maintained throughout the 8-week dose- maintenance period. The total time of the open-label period was 12 weeks.	
Reporting group title	Placebo (Randomized-withdrawal Period)
Reporting group description: During the 26--week double--blind randomized--withdrawal phase, participants randomized to placebo received matching placebo capsules daily. After the 26--week double--blind randomized--withdrawal phase, participants were followed for 1 week	
Reporting group title	SPD489 (Randomized-withdrawal Period)
Reporting group description: For participants randomized to SPD489, the optimal daily dose of 50 or 70mg was continued throughout the 26--week double--blind randomized--withdrawal phase. After the 26--week double--blind randomized--withdrawal phase, participants were followed for 1 week.	

Primary: Time to Relapse From Date of Randomization to Endpoint of The Randomized--withdrawal Period

End point title	Time to Relapse From Date of Randomization to Endpoint of The Randomized--withdrawal Period
End point description: Relapse status was assessed during the double-blind treatment phase and was defined as having 2 or more binge days per week for 2 consecutive weeks (14 consecutive days) prior to any visit and having an increase in Clinical Global Impressions-Severity (CGI-S) score of 2 or more points compared to the randomized-withdrawal baseline (date of relapse - date of randomization). Binge eating information was captured via a self-report paper diary. The binge diary captured the number of binges per day, total hours per day spent bingeing, type of binge (at mealtime or at another time other than mealtime), and a description of the binge (amounts and types of foods). Binge frequency was reviewed by the clinician with the participant to confirm reported binge episodes per day. The CGI-S was performed to rate the severity of a participant's condition using a 7--point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). This endpoint assessed the Full Analysis Set (FAS)	
End point type	Primary
End point timeframe: Visit 21 (26 weeks after randomization [Week 38] or Early Termination). Visit 21 could include participants who discontinued but completed a final safety and efficacy assessment.	

End point values	Placebo (Randomized- withdrawal Period)	SPD489 (Randomized- withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131 ^[1]	136 ^[2]		
Units: days				
median (inter-quartile range (Q1-Q3))	99999 (55 to	99999 (99999		

Notes:

[1] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

[2] - For both arms, 9999 is used to indicate that the median time to relapse or range was not calculable.

Statistical analyses

Statistical analysis title	Analysis of Relapse
Comparison groups	Placebo (Randomized-withdrawal Period) v SPD489 (Randomized-withdrawal Period)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	Logrank

Notes:

[3] - P-value based on a log-rank test, stratified by 4-week cessation status (Yes, No). 4-week cessation was defined as a subject having no binge days during the 4 weeks prior to randomization.

Secondary: Change From Randomized-withdrawal Baseline in The Number of Binge-Eating Days Per Week During The Randomized--withdrawal Period

End point title	Change From Randomized-withdrawal Baseline in The Number of Binge-Eating Days Per Week During The Randomized--withdrawal Period
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End point description:

A binge day was defined as days during which at least 1 binge episode occurred. As assessed by clinical interview based on participant binge diary. Binge eating information was captured via a self-report paper diary. The binge diary captured the number of binges per day, total hours per day spent bingeing, type of binge (at mealtime or at another time other than mealtime), and a description of the binge (amounts and types of foods). Binge frequency was reviewed by the clinician with the participant to confirm reported binge episodes per day. A negative change from Baseline indicates that binge--related behavior decreased. The randomized-withdrawal baseline was defined as the weekly average number of binge days for the 14 days prior to the Randomization Visit (Visit 8).

This endpoint assessed the FAS. Not all participants in the FAS had data collected for this outcome. Visit 21 included only participants who completed randomized treatment (placebo: n=50; SPD489: n=102).

End point type	Secondary
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End point timeframe:

Randomized--withdrawal baseline (Visit 8; 12 weeks after start of open-label treatment [Week 12]), Visit 21 (26 weeks after randomization [Week 38])

End point values	Placebo (Randomized-withdrawal Period)	SPD489 (Randomized-withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131 ^[4]	136		
Units: days				
least squares mean (standard error)	0.63 (± 0.076)	0.02 (± 0.061)		

Notes:

[4] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

Statistical analyses

Statistical analysis title	Analysis of Binge Eating Days
Comparison groups	Placebo (Randomized-withdrawal Period) v SPD489 (Randomized-withdrawal Period)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[5]
Method	mixed-effects model for repeated measure
Parameter estimate	difference in LS mean
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.42

Notes:

[5] - Nominal P--value not adjusted for multiplicity. MMRM over all post-randomization visits during the randomized-withdrawal phase. Value for change from baseline = outcome variable.

Secondary: Percent of Participants Within Each Category of The Clinical Global Impression-Severity of Illness (CGI--S) Scale at Endpoint of The Randomized-withdrawal Period

End point title	Percent of Participants Within Each Category of The Clinical Global Impression-Severity of Illness (CGI--S) Scale at Endpoint of The Randomized-withdrawal Period
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End point description:

The CGI--S permits a global evaluation of a participant's condition and severity of symptoms. The CGI--S was performed to rate the severity of a participant's condition based on a 7--point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). This endpoint assessed the FAS, defined as participants in the Randomized Safety Analysis Set (RSAS) with at least 1 post--randomization CGI--S assessment.

End point type	Secondary
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End point timeframe:

Visit 21 (26 weeks after randomization [Week 38] or Early Termination). Visit 21 could include participants who discontinued but completed a final safety and efficacy assessment.

End point values	Placebo (Randomized-withdrawal Period)	SPD489 (Randomized-withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131 ^[6]	136		
Units: percentage of subjects				
number (not applicable)				
Normal, Not at All Ill	45	81.6		
Borderline Mentally Ill	10.7	11.8		
Mildly Ill	14.5	2.2		
Moderately Ill	22.1	2.2		
Markedly Ill	6.9	2.2		
Severely Ill	0	0		
Among the Most Extremely Ill	0.8	0		

Notes:

[6] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

Statistical analyses

Statistical analysis title	Analysis of CGI-S
Comparison groups	Placebo (Randomized-withdrawal Period) v SPD489 (Randomized-withdrawal Period)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Cochran-Mantel-Haenszel

Notes:

[7] - Unadjusted P-value for the difference in distribution between treatment groups in CGI-S. Cochran-Mantel-Haenszel test with a modified ridit score, adjusting for Visit 8 (Week 12) CGI-S as the covariate.

Secondary: Change From Randomized-withdrawal Baseline in The Total Score of The Yale--Brown Obsessive Compulsive Scale Modified for Binge Eating (Y--BOCS--BE) During The Randomized--withdrawal Period

End point title	Change From Randomized-withdrawal Baseline in The Total Score of The Yale--Brown Obsessive Compulsive Scale Modified for Binge Eating (Y--BOCS--BE) During The Randomized--withdrawal Period
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End point description:

The Y--BOCS--BE measures the obsession of binge eating thoughts and compulsiveness of binge eating behaviors. The scale is a clinician rated, 10--item scale, each item rated from 0 (no symptoms) to 4 (extreme symptoms). The scale includes questions regarding the amount of time spent on obsessions, impairment or distress experienced, and resistance and control over these thoughts. The same types of questions were asked about compulsions (ie, time spent, interference, etc.). Total scores range from 0 to 40. A total score of 0--7 is sub-clinical, 8--15 is mild, 16--23 is moderate, 24--31 is severe, and 32--40 is extreme. A decrease from baseline in Y--BOCS--BE Total Score represents an improvement in obsession with binge-eating thoughts or compulsiveness of binge-eating behaviors.

The endpoint assessed the FAS. Not all participants in the FAS had data collected for this outcome. Visit 21 included only participants who completed randomized treatment (placebo: n=54; SPD489: n=107).

End point type	Secondary
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End point timeframe:

Randomized-withdrawal baseline (Visit 8; 12 weeks after start of open-label treatment [Week 12]), Visit 21 (26 weeks after randomization [Week 38])

End point values	Placebo (Randomized- withdrawal Period)	SPD489 (Randomized- withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131 ^[8]	136		
Units: units on a scale				
least squares mean (standard error)	5.5 (± 0.66)	0 (± 0.52)		

Notes:

[8] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

Statistical analyses

Statistical analysis title	Analysis of Y-BOCS-BE
Comparison groups	Placebo (Randomized-withdrawal Period) v SPD489 (Randomized-withdrawal Period)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[9]
Method	mixed-effects model for repeated measure
Parameter estimate	difference in LS mean
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	-3.9

Notes:

[9] - Nominal P--value not adjusted for multiplicity. MMRM over all post-randomization visits during the randomized-withdrawal phase. Value for change from baseline = outcome variable.

Secondary: Percent of Participants Within Each Category of The Euro-QoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Mobility at Endpoint of the Open-label Period

End point title	Percent of Participants Within Each Category of The Euro-QoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Mobility at Endpoint of the Open-label Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the Open-label Safety Population (OSP), defined as participants who had taken at least 1 dose of SPD489 in the open-label period and who had a post-baseline safety assessment. Not all participants had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 8 (12 weeks after start of open-label treatment [Week 12] or Early Termination). Visit 8 could include participants who discontinued but completed a safety and efficacy assessment.

End point values	SPD489 (Open-label Period)			
Subject group type	Reporting group			
Number of subjects analysed	397			
Units: percentage of subjects				
number (not applicable)				
I have no problems in walking about	87.9			
I have slight problems in walking about	9.8			
Moderate problems in walking about	1.5			
I have severe problems in walking about	0.8			
I am unable to walk about	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The EuroQol Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Mobility at Endpoint of the Randomized-withdrawal Period

End point title	Percent of Participants Within Each Category of The EuroQol Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Mobility at Endpoint of the Randomized-withdrawal Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the FAS. Not all participants in the FAS had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 21 (26 weeks after randomization [Week 38] or Early Termination). Visit 21 could include participants who discontinued but completed a final safety and efficacy assessment.

End point values	Placebo (Randomized-withdrawal Period)	SPD489 (Randomized-withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[10]	127		
Units: percentage of subjects				
number (not applicable)				
I have no problems in walking about	83.6	91.3		
I have slight problems in walking about	14.7	6.3		
Moderate problems in walking about	1.7	1.6		
I have severe problems in walking about	0	0.8		
I am unable to walk about	0	0		

Notes:

[10] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The Euro-QoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L) For Self Care at Endpoint of the Open-label Period

End point title	Percent of Participants Within Each Category of The Euro-QoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L) For Self Care at Endpoint of the Open-label Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the Open-label Safety Population (OSP), defined as participants who had taken at least 1 dose of SPD489 in the open-label period and who had a post-baseline safety assessment. Not all participants had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 8 (12 weeks after start of open-label treatment [Week 12] or Early Termination). Visit 8 could include participants who discontinued but completed a safety and efficacy assessment.

End point values	SPD489 (Open-label Period)			
Subject group type	Reporting group			
Number of subjects analysed	397			
Units: percentage of subjects				
number (not applicable)				
I have no problems washing or dressing myself	98.7			
I have slight problems washing or dressing myself	0.8			
Moderate problems washing or dressing myself	0.3			
I have severe problems washing or dressing myself	0.3			
I am unable to wash or dress myself	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The EuroQol Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Self Care at Endpoint of the Randomized-withdrawal Period

End point title	Percent of Participants Within Each Category of The EuroQol Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Self Care at Endpoint of the Randomized-withdrawal Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the FAS. Not all participants in the FAS had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 21 (26 weeks after randomization [Week 38] or Early Termination). Visit 21 could include participants who discontinued but completed a final safety and efficacy assessment.

End point values	Placebo (Randomized- withdrawal Period)	SPD489 (Randomized- withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[11]	127		
Units: percentage of subjects				
number (not applicable)				
I have no problems washing or dressing myself	98.3	98.4		
I have slight problems washing or dressing myself	0.9	0.8		
Moderate problems washing or dressing myself	0.9	0.8		
I have severe problems washing or dressing myself	0	0		
I am unable to wash or dress myself	0	0		

Notes:

[11] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The Euro-Qol Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Usual Activities at Endpoint of the Open-label Period

End point title	Percent of Participants Within Each Category of The Euro-Qol Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Usual Activities at Endpoint of the Open-label Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the Open-label Safety Population (OSP), defined as participants who had taken at least 1 dose of SPD489 in the open-label period and who had a post-baseline safety assessment. Not all participants had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 8 (12 weeks after start of open-label treatment [Week 12] or Early Termination). Visit 8 could include participants who discontinued but completed a safety and efficacy assessment.

End point values	SPD489 (Open-label Period)			
Subject group type	Reporting group			
Number of subjects analysed	397			
Units: percentage of subjects				
number (not applicable)				
I have no problems doing my usual activities	88.9			
I have slight problems doing my usual activities	8.1			
Moderate problems doing my usual activities	2.3			
I have severe problems doing my usual activities	0.8			
I am unable to do my usual activities	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The EuroQoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Usual Activities at Endpoint of the Randomized-withdrawal Period

End point title	Percent of Participants Within Each Category of The EuroQoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Usual Activities at Endpoint of the Randomized-withdrawal Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the FAS. Not all participants in the FAS had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 21 (26 weeks after randomization [Week 38] or Early Termination). Visit 21 could include participants who discontinued but completed a final safety and efficacy assessment.

End point values	Placebo (Randomized- withdrawal Period)	SPD489 (Randomized- withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[12]	127		
Units: percentage of subjects				
number (not applicable)				
I have no problems doing my usual activities	79.3	86.6		
I have slight problems doing my usual activities	16.4	11		
Moderate problems doing my usual activities	2.6	0.8		
I have severe problems doing my usual activities	0	1.6		
I am unable to do my usual activities	1.7	0		

Notes:

[12] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The Euro-QoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Pain And Discomfort at Endpoint of the Open-label Period

End point title	Percent of Participants Within Each Category of The Euro-QoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Pain And Discomfort at Endpoint of the Open-label Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the Open-label Safety Population (OSP), defined as participants who had taken at least 1 dose of SPD489 in the open-label period and who had a post-baseline safety assessment. Not all participants had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 8 (12 weeks after start of open-label treatment [Week 12] or Early Termination). Visit 8 could include participants who discontinued but completed a safety and efficacy assessment.

End point values	SPD489 (Open-label Period)			
Subject group type	Reporting group			
Number of subjects analysed	397			
Units: percentage of subjects				
number (not applicable)				
I have no pain or discomfort	72.3			
I have slight pain or discomfort	20.9			
Moderate pain or discomfort	5.3			
I have severe pain or discomfort	1.3			
I have extreme pain or discomfort	0.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The EuroQoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Pain And Discomfort at Endpoint of the Randomized-withdrawal Period

End point title	Percent of Participants Within Each Category of The EuroQoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Pain And Discomfort at Endpoint of the Randomized-withdrawal Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the FAS. Not all participants in the FAS had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 21 (26 weeks after randomization [Week 38] or Early Termination). Visit 21 could include participants who discontinued but completed a final safety and efficacy assessment.

End point values	Placebo (Randomized-withdrawal Period)	SPD489 (Randomized-withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[13]	127		
Units: percentage of subjects				
number (not applicable)				
I have no pain or discomfort	75	71.7		
I have slight pain or discomfort	16.4	18.1		
Moderate pain or discomfort	8.6	8.7		
I have severe pain or discomfort	0	0		
I have extreme pain or discomfort	0	1.6		

Notes:

[13] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The Euro-QoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Anxiety And Depression at Endpoint of the Open-label Period

End point title	Percent of Participants Within Each Category of The Euro-QoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Anxiety And Depression at Endpoint of the Open-label Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the Open-label Safety Population (OSP), defined as participants who had taken at least 1 dose of SPD489 in the open-label period and who had a post-baseline safety assessment. Not all participants had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 8 (12 weeks after start of open-label treatment [Week 12] or Early Termination). Visit 8 could include participants who discontinued but completed a safety and efficacy assessment.

End point values	SPD489 (Open-label Period)			
Subject group type	Reporting group			
Number of subjects analysed	397			
Units: percentage of subjects				
number (not applicable)				
I am not anxious or depressed	80.9			
I am slightly anxious or depressed	15.6			
Moderately anxious or depressed	2.3			
I am severely anxious or depressed	1			
I am extremely anxious or depressed	0.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants Within Each Category of The EuroQoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Anxiety And

Depression at Endpoint of the Randomized-withdrawal Period

End point title	Percent of Participants Within Each Category of The EuroQoL Group 5--Dimension 5--Level Self--Report Questionnaire (EQ--5D--5L) For Anxiety And Depression at Endpoint of the Randomized-withdrawal Period
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End point description:

The EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ--5D--5L) is a health-related quality of life (QoL) measure that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as current overall health. 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, from poor health to good health.

This endpoint assessed the FAS. Not all participants in the FAS had data collected for this outcome.

End point type	Secondary
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End point timeframe:

Visit 21 (26 weeks after randomization [Week 38] or Early Termination). Visit 21 could include participants who discontinued but completed a final safety and efficacy assessment.

End point values	Placebo (Randomized- withdrawal Period)	SPD489 (Randomized- withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[14]	127		
Units: percentage of subjects				
number (not applicable)				
I am not anxious or depressed	66.4	79.5		
I am slightly anxious or depressed	26.7	15.7		
Moderately anxious or depressed	4.3	3.1		
I am severely anxious or depressed	2.6	0.8		
I am extremely anxious or depressed	0	0.8		

Notes:

[14] - Three subjects in the placebo group were randomized and included in the RSAS but not the FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Positive Response on The Columbia Suicide Severity Rating Scale (C--SSRS) at Endpoint of The Open--label Period

End point title	Number of Participants With a Positive Response on The Columbia Suicide Severity Rating Scale (C--SSRS) at Endpoint of The Open--label Period
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End point description:

The C--SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide--related thoughts and behaviors. It includes definitions and suggested questions to solicit the type of information needed to determine if a suicide--related thought or behavior occurred. The interview was initiated with 5 (yes/no) questions, presented in ascending order of severity, about suicidal ideation. The most severe type of ideation was rated for frequency, duration, controllability, deterrents, and reason. "Yes" answers to the first 2 ideation questions led the clinician to ask questions 3--5. Active suicidal ideation included any "yes" answer to questions 2--5. If the answers to ideation questions 1 and 2 were "No," then the clinician proceeded to 5 (yes/no) questions that addressed suicidal behavior, which was categorized as actual attempt, interrupted attempt, aborted attempt, preparatory acts or behaviors, and completed suicide.

This endpoint assessed the OSP.

End point type	Secondary
End point timeframe:	
Visit 8 (12 weeks after start of open-label treatment [Week 12]). Visit 8 included only participants who completed open-label treatment.	

End point values	SPD489 (Open-label Period)			
Subject group type	Reporting group			
Number of subjects analysed	408 ^[15]			
Units: subjects				
Suicidal Behavior	0			
Active Suicidal Ideation	0			
Non--Suicidal Self--Injurious Behavior	2			

Notes:

[15] - Three participants in the OSP did not have data collected for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Positive Response on The Columbia Suicide Severity Rating Scale (C--SSRS) at Endpoint of The Randomized--withdrawal Period

End point title	Number of Participants With a Positive Response on The Columbia Suicide Severity Rating Scale (C--SSRS) at Endpoint of The Randomized--withdrawal Period
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End point description:

The C--SSRS is a semistructured interview that captures the occurrence, severity, and frequency of suicide--related thoughts and behaviors. It includes definitions and suggested questions to solicit the type of information needed to determine if a suicide--related thought or behavior occurred. The interview was initiated with 5 (yes/no) questions, presented in ascending order of severity, about suicidal ideation. The most severe type of ideation was rated for frequency, duration, controllability, deterrents, and reason. "Yes" answers to the first 2 ideation questions led the clinician to ask questions 3--5. Active suicidal ideation included any "yes" answer to questions 2--5. If the answers to ideation questions 1 and 2 were "No," then the clinician proceeded to 5 (yes/no) questions that addressed suicidal behavior, which was categorized as actual attempt, interrupted attempt, aborted attempt, preparatory acts or behaviors, and completed suicide.

This endpoint assessed the RSAS.

End point type	Secondary
End point timeframe:	
Visit 21 (26 weeks after randomization [Week 38] or Early Termination).	

End point values	Placebo (Randomized-withdrawal Period)	SPD489 (Randomized-withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131 ^[16]	136 ^[17]		
Units: subjects				
Suicidal Behavior	0	0		
Active Suicidal Ideation	0	0		

Non--Suicidal Self--Injurious Behavior	0	1		
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Notes:

[16] - Four subjects were randomized but not treated and thus not included in the RSAS.

[17] - One subject was randomized but not treated and thus not included in the RSAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Scores For The Amphetamine Cessation Symptom Assessment (ACSA) Scale During Follow-up

End point title	Total Scores For The Amphetamine Cessation Symptom Assessment (ACSA) Scale During Follow-up
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End point description:

The ACSA was used in this study to assess potential withdrawal symptoms associated with chronic use of SPD489. The ACSA is a self-completed scale used to assess withdrawal symptoms. The scale has 16 symptom items rated on a 5-point scale ranging from 0 (not at all) to 4 (extremely). The ACSA total score ranges from 0-64, where a higher score indicates greater withdrawal symptom severity.

The endpoint assessed the Randomized Safety Analysis Set (RSAS), defined as participants in the SAS who were randomized and took at least 1 dose of investigational product in the randomized-withdrawal period. Not all participants had data for this or the previous outcome.

End point type	Secondary
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End point timeframe:

Visit 21 (26 weeks after randomization [Week 38] or Early Termination) and Visit 22 (7 days post last dose). Visits 21 and 22 could include participants who discontinued but completed a final safety and efficacy assessment.

End point values	Placebo (Randomized- withdrawal Period)	SPD489 (Randomized- withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134 ^[18]	136 ^[19]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Visit 21, n=88, 94	7.6 (± 8.33)	4.9 (± 7.81)		
Visit 22, n=75, 78	4.6 (± 5.84)	5.3 (± 7.98)		

Notes:

[18] - Four subjects were randomized but not treated and thus not included in the RSAS.

[19] - One subject was randomized but not treated and thus not included in the RSAS.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

39 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	SPD489 (Open-label Period)
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Reporting group description:

SPD489 treatment was taken orally once daily at approximately 7:00 AM. All participants began treatment with SPD489 at the lowest dose level (30mg) during the 4- week open-label dose-optimization period. After 1 week of treatment at 30mg, all participants were titrated to the next dose level (50mg). After 1 week of treatment at 50mg, all participants were titrated to the highest dose level (70mg), as tolerated and as clinically indicated. After 1 week of treatment at the highest dose, the participant could have been down-titrated to 50mg; no further dose adjustments were permitted. The optimal daily dose of 50 or 70mg achieved during dose- optimization was maintained throughout the 8-week dose- maintenance period. The total time of the open- label period was 12 weeks.

Reporting group title	Placebo (Randomized-withdrawal Period)
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Reporting group description:

During the 26--week double--blind randomized--withdrawal phase, participants randomized to placebo received matching placebo capsules daily. After the 26--week double--blind randomized--withdrawal phase, participants were followed for 1 week .

Reporting group title	SPD489 (Randomized-withdrawal Period)
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Reporting group description:

For participants randomized to SPD489, the optimal daily dose of 50 or 70mg was continued throughout the 26--week double--blind randomized--withdrawal phase. After the 26--week double--blind randomized--withdrawal phase, participants were followed for 1 week.

Serious adverse events	SPD489 (Open-label Period)	Placebo (Randomized-withdrawal Period)	SPD489 (Randomized-withdrawal Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 411 (0.73%)	0 / 134 (0.00%)	2 / 136 (1.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 411 (0.00%)	0 / 134 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital Anomaly in Offspring			

subjects affected / exposed	1 / 411 (0.24%)	0 / 134 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 411 (0.24%)	0 / 134 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve root compression			
subjects affected / exposed	0 / 411 (0.00%)	0 / 134 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 411 (0.24%)	0 / 134 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	SPD489 (Open-label Period)	Placebo (Randomized-withdrawal Period)	SPD489 (Randomized-withdrawal Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	303 / 411 (73.72%)	45 / 134 (33.58%)	59 / 136 (43.38%)
Investigations			
Blood pressure increased			
subjects affected / exposed	15 / 411 (3.65%)	0 / 134 (0.00%)	1 / 136 (0.74%)
occurrences (all)	17	0	1
Heart rate increased			
subjects affected / exposed	14 / 411 (3.41%)	0 / 134 (0.00%)	1 / 136 (0.74%)
occurrences (all)	16	0	1
Weight decreased			
subjects affected / exposed	14 / 411 (3.41%)	1 / 134 (0.75%)	1 / 136 (0.74%)
occurrences (all)	14	1	1
Weight increased			

subjects affected / exposed occurrences (all)	0 / 411 (0.00%) 0	1 / 134 (0.75%) 1	3 / 136 (2.21%) 3
Cardiac disorders			
Palpitations			
subjects affected / exposed	13 / 411 (3.16%)	0 / 134 (0.00%)	1 / 136 (0.74%)
occurrences (all)	13	0	1
Tachycardia			
subjects affected / exposed	17 / 411 (4.14%)	0 / 134 (0.00%)	2 / 136 (1.47%)
occurrences (all)	20	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 411 (2.43%)	0 / 134 (0.00%)	1 / 136 (0.74%)
occurrences (all)	11	0	4
Headache			
subjects affected / exposed	66 / 411 (16.06%)	9 / 134 (6.72%)	12 / 136 (8.82%)
occurrences (all)	84	9	14
Somnolence			
subjects affected / exposed	1 / 411 (0.24%)	3 / 134 (2.24%)	5 / 136 (3.68%)
occurrences (all)	1	3	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 411 (4.38%)	7 / 134 (5.22%)	4 / 136 (2.94%)
occurrences (all)	19	7	4
Feeling jittery			
subjects affected / exposed	21 / 411 (5.11%)	0 / 134 (0.00%)	0 / 136 (0.00%)
occurrences (all)	26	0	0
Irritability			
subjects affected / exposed	19 / 411 (4.62%)	4 / 134 (2.99%)	4 / 136 (2.94%)
occurrences (all)	22	5	4
Thirst			
subjects affected / exposed	9 / 411 (2.19%)	0 / 134 (0.00%)	0 / 136 (0.00%)
occurrences (all)	11	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	9 / 411 (2.19%)	1 / 134 (0.75%)	2 / 136 (1.47%)
occurrences (all)	10	1	2

Constipation subjects affected / exposed occurrences (all)	28 / 411 (6.81%) 29	1 / 134 (0.75%) 1	4 / 136 (2.94%) 4
Diarrhoea subjects affected / exposed occurrences (all)	21 / 411 (5.11%) 24	3 / 134 (2.24%) 3	2 / 136 (1.47%) 2
Dry mouth subjects affected / exposed occurrences (all)	139 / 411 (33.82%) 145	2 / 134 (1.49%) 2	7 / 136 (5.15%) 7
Dyspepsia subjects affected / exposed occurrences (all)	3 / 411 (0.73%) 3	1 / 134 (0.75%) 1	3 / 136 (2.21%) 3
Nausea subjects affected / exposed occurrences (all)	35 / 411 (8.52%) 37	3 / 134 (2.24%) 3	6 / 136 (4.41%) 6
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 411 (1.22%) 6	2 / 134 (1.49%) 2	3 / 136 (2.21%) 3
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	23 / 411 (5.60%) 24	0 / 134 (0.00%) 0	3 / 136 (2.21%) 3
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	29 / 411 (7.06%) 32	2 / 134 (1.49%) 2	2 / 136 (1.47%) 2
Initial insomnia subjects affected / exposed occurrences (all)	6 / 411 (1.46%) 7	2 / 134 (1.49%) 3	4 / 136 (2.94%) 4
Insomnia subjects affected / exposed occurrences (all)	46 / 411 (11.19%) 46	2 / 134 (1.49%) 2	1 / 136 (0.74%) 1
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed occurrences (all)	7 / 411 (1.70%) 8	1 / 134 (0.75%) 1	3 / 136 (2.21%) 3
Back pain subjects affected / exposed occurrences (all)	2 / 411 (0.49%) 2	0 / 134 (0.00%) 0	3 / 136 (2.21%) 3
Musculoskeletal pain subjects affected / exposed occurrences (all)	4 / 411 (0.97%) 5	0 / 134 (0.00%) 0	4 / 136 (2.94%) 4
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	5 / 411 (1.22%) 5	0 / 134 (0.00%) 0	3 / 136 (2.21%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 411 (4.87%) 20	9 / 134 (6.72%) 9	13 / 136 (9.56%) 15
Rhinitis subjects affected / exposed occurrences (all)	0 / 411 (0.00%) 0	0 / 134 (0.00%) 0	3 / 136 (2.21%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 411 (2.68%) 11	5 / 134 (3.73%) 7	11 / 136 (8.09%) 12
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 411 (1.70%) 7	4 / 134 (2.99%) 4	4 / 136 (2.94%) 4
Gastroenteritis subjects affected / exposed occurrences (all)	5 / 411 (1.22%) 5	3 / 134 (2.24%) 3	2 / 136 (1.47%) 2
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	38 / 411 (9.25%) 44	0 / 134 (0.00%) 0	0 / 136 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2013	<p>This amendment included the following important changes:</p> <ul style="list-style-type: none">* Updated the number of participating sites and countries* Added region (North America, non-North America) as a stratification factor for Randomization* Added SDS and PRUQ-BED as exploratory efficacy endpoints* Clarified collection times for pharmacogenomic samples* Updated duration between study visits* Increased the number of Y-BOCS-BE assessments during the double-blind randomized withdrawal phase* Added the SDS as a health-related quality of life assessment* Added change from randomized baseline in SDS total score as an exploratory objective* Clarified that the date of relapse should be captured in the source documents and on the case report form* Added clarification for the review and documentation of contraceptive requirements for FOCPs* Added "failure to meet randomization criteria" as a reason for discontinuation* Added "met relapse criteria" as a reason for discontinuation* Added details for data input regarding stratum assignment during randomization and relapse assessment using IWRS* Clarified process for assessing abnormal ECG results* Clarified the purpose of the MINI-plus* Clarified binge frequency to be reviewed by clinician and subject to confirm reported binge episodes per day

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported