



## Clinical trial results:

### The SPD489-344, Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Dose-optimization Study to Evaluate the Efficacy, Safety, and Tolerability of SPD489 in Adults Aged 18-55 Years with Moderate to Severe Binge Eating Disorder

#### Summary

EudraCT number	2012-003310-14
Trial protocol	ES IT
Global end of trial date	20 September 2013

#### Results information

Result version number	v1 (current)
This version publication date	19 September 2018
First version publication date	01 August 2015

#### Trial information

##### Trial identification

Sponsor protocol code	SPD489-344
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01718509
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Shire Development, LLC
Sponsor organisation address	725 Chesterbrook Boulevard, Wayne, United States, 19087
Public contact	Study Physician, Shire Development LLC, +1 8668425335,
Scientific contact	Study Physician, Shire Development LLC, +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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	20 September 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 September 2013
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To demonstrate the efficacy of SPD489 compared with placebo in adults (18-55 years of age inclusive) with moderate to severe binge eating disorder (BED) at Visit 8 (Weeks 11 and 12) as measured by the number of binge days (defined as days during which at least 1 binge episode occurs) per week as assessed by clinical interview based on subject diary.

Protection of trial subjects:

The subject's informed consent was a mandatory condition for taking part in the study. It was obtained in writing prior to the performance of any study-specific procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	United States: 370
Worldwide total number of subjects	390
EEA total number of subjects	20

Notes:

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**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)	390
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited to participate at 41 sites in the United States and 2 sites in Germany.

### Pre-assignment

Screening details:

A total of 390 subjects were randomized to treatment. Of these, 4 subjects in the placebo arm and 8 subjects in the SPD489 arm did not receive study drug. A total of 378 subjects started treatment.

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Both investigational products (SPD489 and placebo) were identical in appearance in order to protect the study blind.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	SPD489

Arm description:

Subjects received SPD489 for up to 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:

30, 50, or 70mg capsules administered once-daily. The starting dose was 30mg/day with subjects being individually titrated, based on efficacy and tolerability, to achieve an optimized dose (50 or 70mg/day) during the Dose-optimization Period. Following the Dose-optimization Period, subjects continued on their optimized dose for the duration of the 8-week Dose-maintenance Period.

<b>Arm title</b>	Placebo
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Arm description:

Subjects received placebo for up to 12 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule administered once-daily

<b>Number of subjects in period 1<sup>[1]</sup></b>	SPD489	Placebo
Started	181	185
Completed	147	145
Not completed	34	40
Protocol violation	1	4
Adverse event	7	5
Other reasons	4	7
Lost to follow-up	11	16
Withdrawal by subject	11	7
Lack of efficacy	-	1

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The numbers started represents the Safety Analysis Set, which included all randomized subjects who took at least 1 dose of investigational product and who had at least 1 follow-up safety assessment completed.

## Baseline characteristics

### Reporting groups

Reporting group title	SPD489
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Reporting group description:

Subjects received SPD489 for up to 12 weeks.

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo for up to 12 weeks

Reporting group values	SPD489	Placebo	Total
Number of subjects	181	185	366
Age categorical Units: Subjects			
< 40 years	108	90	198
> = 40 years	73	95	168
Age continuous Units: years			
arithmetic mean	37.1	38.7	
standard deviation	± 10	± 10.01	-
Gender categorical Units: Subjects			
Female	159	153	312
Male	22	32	54
Region of enrollment Units: Subjects			
Germany	11	9	20
United States	170	176	346

## End points

### End points reporting groups

Reporting group title	SPD489
Reporting group description: Subjects received SPD489 for up to 12 weeks.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo for up to 12 weeks	

### Primary: Change From Baseline in the Number of Binge Days Per Week at Visit 8 Which Spans Weeks 11/12

End point title	Change From Baseline in the Number of Binge Days Per Week at Visit 8 Which Spans Weeks 11/12
End point description: Binge days were defined as days during which at least 1 binge episode occurred. As assessed by clinical interview based on subject binge diary. The end point analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).	
End point type	Primary
End point timeframe: Baseline and Visit 8 Which Spans Weeks 11/12	

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: Binge days per week				
least squares mean (standard error)	-3.92 ( $\pm$ 0.135)	-2.26 ( $\pm$ 0.137)		

### Statistical analyses

Statistical analysis title	Analysis of the number of binge days
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	-1.28

### Secondary: Percent of Participants With Improvement on Clinical Global Impression-Improvement (CGI-I) Scores

End point title	Percent of Participants With Improvement on Clinical Global Impression-Improvement (CGI-I) Scores
End point description:	
Clinical Global Impression-Improvement (CGI-I) consists of a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved) or 2 (much improved) on the scale.	
This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).	
End point type	Secondary
End point timeframe:	
Up to 12 weeks	

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: percent of subjects				
number (confidence interval 95%)	86.2 (81.1 to 91.3)	42.9 (35.5 to 50.2)		

### Statistical analyses

Statistical analysis title	Analysis of CGI-I scores
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

### Secondary: Percent of Participants With a 4-Week Cessation From Binge Eating

End point title	Percent of Participants With a 4-Week Cessation From Binge Eating
End point description:	
Four-week cessation from binge eating is defined as no binge eating episodes for 28 consecutive days prior to the last study visit.	

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

End point type	Secondary
End point timeframe:	
Up to 12 weeks	

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: percent of subjects				
number (confidence interval 95%)	36.2 (29.1 to 43.3)	13.1 (8.1 to 18)		

### Statistical analyses

Statistical analysis title	Analysis of 4-Week cessation from binge eating
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

### Secondary: Percent Change From Baseline in Body Weight at Week 12

End point title	Percent Change From Baseline in Body Weight at Week 12
End point description:	
This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).	
End point type	Secondary
End point timeframe:	
Baseline and week 12	

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: percent change				
least squares mean (standard error)	-5.57 ( $\pm$ 0.35)	-0.15 ( $\pm$ 0.353)		



## Statistical analyses

<b>Statistical analysis title</b>	Analysis of body weight
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-5.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.39
upper limit	-4.44

## Secondary: Change From Baseline in Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) Total Score at Week 12

End point title	Change From Baseline in Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) Total Score at Week 12
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). Total scores range from 0 to 40. Reduction in total score indicates improvement. This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).	
End point type	Secondary
End point timeframe: Baseline and week 12	

<b>End point values</b>	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: units on a scale				
least squares mean (standard error)	-15.36 ( $\pm$ 0.563)	-7.42 ( $\pm$ 0.571)		

## Statistical analyses

<b>Statistical analysis title</b>	Analysis of Y-BOCS-BE total score
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.51
upper limit	-6.36

## Secondary: Change From Baseline in Fasting Triglyceride Levels at Up to 12 Weeks

End point title	Change From Baseline in Fasting Triglyceride Levels at Up to 12 Weeks
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End point description:

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
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End point timeframe:

Baseline and up to 12 weeks

<b>End point values</b>	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	153		
Units: mmol/L				
least squares mean (standard error)	-0.133 ( $\pm$ 0.0449)	0.062 ( $\pm$ 0.0453)		

## Statistical analyses

<b>Statistical analysis title</b>	Analysis of fasting triglyceride levels
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.321
upper limit	-0.07

## Secondary: Change From Baseline in Fasting Total Cholesterol Levels at Up to 12 Weeks

End point title	Change From Baseline in Fasting Total Cholesterol Levels at Up to 12 Weeks
End point description: This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week). Not all subjects had data for this outcome.	
End point type	Secondary
End point timeframe: Baseline and up to 12 weeks	

<b>End point values</b>	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	153		
Units: mmol/L				
least squares mean (standard error)	-0.204 (± 0.0456)	-0.126 (± 0.046)		

## Statistical analyses

<b>Statistical analysis title</b>	Analysis of fasting total cholesterol levels
Comparison groups	SPD489 v Placebo

Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.234
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.205
upper limit	0.05

## Secondary: Change From Baseline in Hemoglobin A1c Levels at Up to 12 Weeks

End point title	Change From Baseline in Hemoglobin A1c Levels at Up to 12 Weeks
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End point description:

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
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End point timeframe:

Baseline and up to 12 weeks

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	154		
Units: percent				
least squares mean (standard error)	0.01 ( $\pm$ 0.017)	-0.02 ( $\pm$ 0.017)		

## Statistical analyses

<b>Statistical analysis title</b>	Analysis of hemoglobin A1c levels
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.08

## Secondary: Binge Eating Response

End point title	Binge Eating Response
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End point description:

Response is based on the reduction in the number of binge eating episodes. Responses were categorized as follows:

- 1) 1-week Cessation = 100% reduction in binge episodes during the preceding 7 days
  - 2) Marked Reduction = 99% to 75% reduction during the time since the previous visit
  - 3) Moderate Reduction = 74% to 50% reduction during the time since the previous visit
  - 4) Negative to Minimal Reduction = <50% reduction during the time since the previous visit
- This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).  
Not all subjects had data for this outcome.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	142		
Units: percent of subjects				
number (not applicable)				
1-week cessation	55.9	23.9		
Marked reduction	22.8	13.4		
Moderate reduction	16.6	19.7		
Negative to minimal reduction	4.8	43		

## Statistical analyses

Statistical analysis title	Analysis of binge eating response
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[1]</sup>
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Multiplicity is not adjusted for this secondary efficacy end point in this study.

**Secondary: Change From Baseline in the Number of Binge Episodes Per Week at Visit 8 Which Spans Weeks 11/12**

End point title	Change From Baseline in the Number of Binge Episodes Per Week at Visit 8 Which Spans Weeks 11/12
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## End point description:

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

End point type	Secondary
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## End point timeframe:

Baseline and Visit 8 Which Spans Weeks 11/12

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: binge episodes per week				
least squares mean (standard error)	-5.54 ( $\pm$ 0.193)	-3.31 ( $\pm$ 0.194)		

**Statistical analyses**

<b>Statistical analysis title</b>	Analysis of binge episodes per week
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[2]</sup>
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.77
upper limit	-1.69

## Notes:

[2] - Multiplicity is not adjusted for this secondary efficacy end point in this study.

**Secondary: Change From Baseline in Eating Inventory Scores at Week 12**

End point title	Change From Baseline in Eating Inventory Scores at Week 12
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## End point description:

There are 36 true/false items, 14 items on a 4-point Likert scale (1=eat rarely to 4=always), and 1 item on a 6-point Likert scale (1=eat whatever you want to 6=constantly limiting food intake). Cognitive Restraint score ranges from 0-21. Hunger score ranges from 0-14. Disinhibition score ranges from 0-16. Higher scores denote higher levels of restrained eating, disinhibited eating and predisposition to hunger. This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

End point type	Secondary
End point timeframe:	
Baseline and week 12	

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: units on a scale				
least squares mean (standard error)				
Cognitive restraint of eating	3.71 ( $\pm$ 0.347)	2.44 ( $\pm$ 0.352)		
Disinhibition of eating	-5.61 ( $\pm$ 0.3)	-2.01 ( $\pm$ 0.305)		
Perceived hunger	-6.14 ( $\pm$ 0.313)	-1.93 ( $\pm$ 0.318)		

### Statistical analyses

<b>Statistical analysis title</b>	Analysis of cognitive restraint of eating
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 <sup>[3]</sup>
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	2.24

Notes:

[3] - Multiplicity is not adjusted for this secondary efficacy end point in this study.

<b>Statistical analysis title</b>	Analysis of disinhibition of eating
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[4]</sup>
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.44
upper limit	-2.76

Notes:

[4] - Multiplicity is not adjusted for this secondary efficacy end point in this study.

<b>Statistical analysis title</b>	Analysis of perceived hunger
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[5]</sup>
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.09
upper limit	-3.33

Notes:

[5] - Multiplicity is not adjusted for this secondary efficacy end point in this study.

## Secondary: Change From Baseline in Binge Eating Scale (BES) Score at Week 12

End point title	Change From Baseline in Binge Eating Scale (BES) Score at Week 12
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End point description:

The BES is a self-reported questionnaire containing 16 items designed to assess behavioral, affective, and attitudinal components of the subjective experience of binge eating. Each item is assessed based on 1 of 4 responses, with 1 denoting that a subject has greater control over eating behavior and 4 denoting that a subject had less control over eating behavior. A total score (sum of the 16 items) may range from 16-64. A lower score indicates greater control over eating behavior.

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

End point type	Secondary
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End point timeframe:

Baseline and week 12

<b>End point values</b>	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: units on a scale				
least squares mean (standard error)	-17.52 (± 0.771)	-8.24 (± 0.781)		



## Statistical analyses

<b>Statistical analysis title</b>	Analysis of BES score
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[6]</sup>
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-9.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.44
upper limit	-7.12

Notes:

[6] - Multiplicity is not adjusted for this secondary efficacy end point in this study.

## Secondary: Change From Baseline in Frontal Systems Behavior (FrSBe) Total Score at Up to 12 Weeks

End point title	Change From Baseline in Frontal Systems Behavior (FrSBe) Total Score at Up to 12 Weeks
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End point description:

The FrSBe is a 46-item self-rating scale designed to measure the neurobehavioral traits associated with the 3 primary regions of the prefrontal cortex. Subjects were asked to indicate the frequency with which they have engaged in certain behaviors using a rating scale from "1" (almost never) to "5" (almost always). Summary scores were calculated and converted to t-score. A decrease from baseline in FrSBe total score represents improvement.

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
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End point timeframe:

Baseline and up to 12 weeks

<b>End point values</b>	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	153		
Units: T-score				
least squares mean (standard error)	-4.05 (± 0.644)	-3.09 (± 0.655)		

## Statistical analyses

<b>Statistical analysis title</b>	Analysis of FrSBe Total Score
Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.298 <sup>[7]</sup>
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.77
upper limit	0.85

Notes:

[7] - Multiplicity is not adjusted for this secondary efficacy end point in this study.

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

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

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	168		
Units: percent of subjects				
number (not applicable)				
No problems in walking about	91.7	86.9		
Slight problems in walking about	7.1	8.9		
Moderate problems walking about	0.6	3		
Severe problems walking about	0.6	1.2		

Unable to walk about	0	0		
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## Statistical analyses

No statistical analyses for this end point

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

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

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	168		
Units: percent of subjects				
number (not applicable)				
No problems washing or dressing	97	97		
Slight problems washing or dressing	3	2.4		
Moderate problems washing or dressing	0	0.6		
Severe problems washing or dressing	0	0		
Unable to wash or dress	0	0		

## Statistical analyses

No statistical analyses for this end point

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

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

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
End point timeframe:	
Up to 12 weeks	

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	168		
Units: percent of subjects				
number (not applicable)				
No problems doing usual activities	89.9	82.1		
Slight problems doing usual activities	8.3	14.3		
Moderate problems doing usual activities	1.2	3		
Severe problems doing usual activities	0.6	0.6		
Unable to do usual activities	0	0		

## Statistical analyses

No statistical analyses for this end point

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

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

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
End point timeframe:	
Up to 12 weeks	

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	168		
Units: percent of subjects				
number (not applicable)				
No pain or discomfort	76.3	75.6		
Slight pain or discomfort	20.1	18.5		
Moderate pain or discomfort	3	3		
Severe pain or discomfort	0	3		
Extreme pain or discomfort	0.6	0		

## Statistical analyses

No statistical analyses for this end point

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

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

This end point analyzed the FAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (i.e., number of binge days per week calculated for at least 1 week).

Not all subjects had data for this outcome.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	168		
Units: percent of subjects				
number (not applicable)				
Not anxious or depressed	76.3	69.6		
Slightly anxious or depressed	20.7	23.2		
Moderately anxious or depressed	2.4	4.8		
Severely anxious or depressed	0	1.2		
Extremely anxious or depressed	0.6	1.2		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Columbia-Suicide Severity Rating Scale (C-SSRS)
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End point description:

C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behaviour occurred. The assessment is done by the nature of the responses, not by a numbered scale. This end point analyzed the Safety Analysis Set (SAS), defined as all randomized subjects who took at least 1 dose of investigational product and who had at least 1 post-baseline safety assessment completed. All subjects from Site 015 were excluded from the Safety Analysis Set.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

End point values	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	183		
Units: subjects				
Suicidal ideation	0	0		
Suicidal behavior	0	0		

### 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
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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. This end point analyzed the SAS, defined as all randomized subjects who took at least 1 dose of investigational product and who had at least 1 post-baseline safety assessment completed. All subjects from Site 015 were excluded from the Safety Analysis Set.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

<b>End point values</b>	SPD489	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	142		
Units: units on a scale				
arithmetic mean (standard deviation)	4.6 (± 5.83)	7 (± 7.69)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

13 weeks

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	SPD489
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Reporting group description:

Subjects received SPD489 for up to 12 weeks

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo for up to 12 weeks

<b>Serious adverse events</b>	SPD489	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 181 (0.55%)	2 / 185 (1.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 181 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 181 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			



subjects affected / exposed	0 / 181 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 181 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	SPD489	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 181 (55.25%)	43 / 185 (23.24%)	
Nervous system disorders			
Headache			
subjects affected / exposed	32 / 181 (17.68%)	16 / 185 (8.65%)	
occurrences (all)	37	19	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 181 (9.39%)	9 / 185 (4.86%)	
occurrences (all)	21	12	
Feeling jittery			
subjects affected / exposed	10 / 181 (5.52%)	0 / 185 (0.00%)	
occurrences (all)	10	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 181 (5.52%)	1 / 185 (0.54%)	
occurrences (all)	10	1	
Diarrhoea			
subjects affected / exposed	11 / 181 (6.08%)	3 / 185 (1.62%)	
occurrences (all)	12	3	
Dry mouth			
subjects affected / exposed	60 / 181 (33.15%)	11 / 185 (5.95%)	
occurrences (all)	60	11	
Nausea			

subjects affected / exposed occurrences (all)	16 / 181 (8.84%) 17	8 / 185 (4.32%) 9	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	19 / 181 (10.50%) 19	6 / 185 (3.24%) 6	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	11 / 181 (6.08%) 11	3 / 185 (1.62%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2012	<p>This amendment included the following important changes:</p> <ul style="list-style-type: none"><li>* Added an Overall Risk/Benefit Assessment to Section 1</li><li>* Changed comparison of the Y-BOCS-BE total score to a key secondary objective</li><li>* Added assessments of the EQ-5D-5L at Weeks 4, 6, 8, and 10 (Visits 4, 5, 6, and 7)</li><li>* Clarified inclusion criterion #7 to further describe indeterminate pregnancy test results</li><li>* Clarified exclusion criterion #1 to state a current diagnosis, rather than concurrent symptoms, of bulimia nervosa, or anorexia nervosa was exclusionary</li><li>* Added language regarding contraception requirements being reviewed at every study visit and document in source document</li><li>* Clarified language regarding use of psychoactive medications during the study and before study entry, and changed the language of the permitted window for psychotherapy</li><li>* Clarified that the MINI-Plus was to be used to exclude comorbid Axis I disorders rather than confirm diagnosis of BED</li><li>* Added further language addressing the management of positive responses on the C-SSRS</li><li>* Clarified that ACSA was to be collected at the Baseline Visit (Visit 0)</li><li>* Added a <math>\pm 2</math>-hour window to the 7:00 AM dosing instructions</li><li>* Added smoking status to items collected as part of medical history.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported