



Clinical trial results:

The SPD489-343, 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	2012-003309-91
Trial protocol	SE DE ES
Global end of trial date	25 September 2013

Results information

Result version number	v2 (current)
This version publication date	24 February 2016
First version publication date	13 March 2015
Version creation reason	- Correction of full data set - Updating the result in the full data set.

Trial information

Trial identification

Sponsor protocol code	SPD489-343
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01718483
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire Development, LLC
Sponsor organisation address	725 Chesterbrook Boulevard Wayne, Pennsylvania, United States, 19087
Public contact	Medical Communications, Shire Pharmaceuticals Ltd, +44 8000556614, medinfo@shire.com
Scientific contact	Medical Communications, Shire Pharmaceuticals Ltd, +44 8000556614, medinfo@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2013
Was the trial ended prematurely?	No

Notes:

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 11-12) 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:

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	12 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 29
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 341
Worldwide total number of subjects	383
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	383
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited between 12-Nov-2012 and 19-June-2013 and locations included medical clinics & research centers.

Pre-assignment

Screening details:

A total of 383 subjects were randomized to treatment. Of these, 4 subjects from the placebo arm discontinued the study prior to study drug administration (reasons for discontinuation for 4 'randomized but not treated' subjects were: 2 subjects lost to follow-up and 2 withdrew due to protocol violation). A total of 379 subjects started treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matching SPD489 capsule administered orally, once-daily 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 matching SPD489 capsule administered orally, once-daily for up to 12 weeks.

Arm title	SPD489
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Arm description:

SPD489 capsule 30 (titration purpose only), 50 or 70 milligram (mg) administered orally, once-daily for up to 12 weeks once the optimal dose is reached.

Arm type	Experimental
Investigational medicinal product name	Lisdexamfetamine dimesylate
Investigational medicinal product code	SPD489
Other name	LDX, Vyvanse®, Elvanse, Tyvense, Elvanse Adult, Elvanse Vuxen, Aduvanz
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SPD489 capsule 30 (titration purpose only), 50 or 70 milligram (mg) administered orally, once-daily for up to 12 weeks once the optimal dose is reached.

Number of subjects in period 1^[1]	Placebo	SPD489
Started	187	192
Completed	157	158
Not completed	30	34
Consent withdrawn by subject	14	12
Protocol violation	2	2
Not specified	1	4
Pregnancy	1	1
Adverse event	5	12
Lost to follow-up	6	3
Lack of efficacy	1	-

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: All enrolled subjects were not treated with study drug. Since baseline included treated subjects only, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo matching SPD489 capsule administered orally, once-daily for up to 12 weeks.

Reporting group title	SPD489
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Reporting group description:

SPD489 capsule 30 (titration purpose only), 50 or 70 milligram (mg) administered orally, once-daily for up to 12 weeks once the optimal dose is reached.

Reporting group values	Placebo	SPD489	Total
Number of subjects	187	192	379
Age categorical			
Units: Subjects			
<40 years	102	98	200
>=40 years	85	94	179
Age continuous			
Units: years			
arithmetic mean	37.6	38.5	
standard deviation	± 10.21	± 10.4	-
Gender categorical			
Units: Subjects			
Female	163	165	328
Male	24	27	51

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matching SPD489 capsule administered orally, once-daily for up to 12 weeks.	
Reporting group title	SPD489
Reporting group description: SPD489 capsule 30 (titration purpose only), 50 or 70 milligram (mg) administered orally, once-daily for up to 12 weeks once the optimal dose is reached.	

Primary: Change From Baseline in the Number of Binge Days Per Week at Visit 8 (Weeks 11-12)

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

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: Binge days per week				
least squares mean (standard error)				
Change From Baseline in the Number of Binge Days	-2.51 ($\pm$ 0.125)	-3.87 ($\pm$ 0.124)		

Statistical analyses

Statistical analysis title	Number of Binge Days Per Week at Visit 8
Statistical analysis description: Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.001
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least squares mean difference
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-1.01

Notes:

[1] - Placebo controlled

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

End point title	Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Scores
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End point description:

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.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (number of binge days per week calculated for at least 1 week).

End point type	Secondary
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End point timeframe:

Up to 12 weeks

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: percentage of subjects				
number (confidence interval 95%)				
Improvement on CGI-I Score	47.3 (40.1 to 54.5)	82.1 (76.7 to 87.6)		

Statistical analyses

Statistical analysis title	Improvement on CGI-I Score
Statistical analysis description:	
Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	< 0.001 ^[3]
Method	Chi-squared

Notes:

[2] - Placebo controlled

[3] - Placebo controlled

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

End point title	Percent of Subjects With a 4-Week Cessation From Binge Eating
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End point description:

4-week cessation from binge eating is defined as no binge eating episodes for 28 consecutive days prior to the last study visit.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (number of binge days per week calculated for at least 1 week).

End point type	Secondary
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End point timeframe:

Up to 12 weeks

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: percentage of subjects				
number (confidence interval 95%)				
4-Week Cessation From Binge Eating	14.1 (9.1 to 19.2)	40 (33 to 47)		

Statistical analyses

Statistical analysis title	Four-Week Cessation From Binge Eating
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Statistical analysis description:

Analysis was SPD489 vs Placebo

Comparison groups	Placebo v SPD489
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	< 0.001
Method	Chi-squared

Notes:

[4] - Placebo controlled

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

End point title	Percent Change From Baseline in Body Weight at Week 12
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End point description:

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: Percent change				
least squares mean (standard error)				
Percent Change in Body Weight	0.11 ($\pm$ 0.295)	-6.25 ($\pm$ 0.292)		

Statistical analyses

Statistical analysis title	Percent Change in Body weight
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Statistical analysis description:

Analysis was SPD489 vs Placebo

Comparison groups	SPD489 v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	< 0.001
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least squares mean difference
Point estimate	-6.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.17
upper limit	-5.54

Notes:

[5] - Placebo controlled

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
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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). Total scores range from 0 to 40. Reduction in total score indicates improvement.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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 week 12	

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	188		
Units: units on a scale				
least squares mean (standard error)				
Y-BOCS-BE Total Score at Week 12	-8.28 ($\pm$ 0.55)	-15.68 ($\pm$ 0.546)		

Statistical analyses

Statistical analysis title	Y-BOCS-BE Total Score at Week 12
Statistical analysis description:	
Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	< 0.001
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least squares mean difference
Point estimate	-7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.93
upper limit	-5.88

Notes:

[6] - Placebo controlled

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
End point description:	
The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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 Week 12/Early termination (ET)	

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	190		
Units: millimole per litre (mmol/L)				
least squares mean (standard error)				
Fasting Triglyceride Levels at Up to 12 Weeks	0.122 ($\pm$ 0.0405)	-0.077 ($\pm$ 0.0393)		

Statistical analyses

Statistical analysis title	Fasting Triglyceride Levels at Up to 12 Weeks
Statistical analysis description: Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	other ^[7]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.199
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.088

Notes:

[7] - Placebo controlled

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: The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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 Week 12/ET	

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	190		
Units: mmol/L				
least squares mean (standard error)				
Fasting Total Cholesterol Levels at Up to 12 Weeks	-0.094 ($\pm$ 0.0435)	-0.305 ($\pm$ 0.0422)		

Statistical analyses

Statistical analysis title	Fasting Total Cholesterol Levels at Up to 12 Weeks
Statistical analysis description: Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	-0.092

Notes:

[8] - Placebo controlled

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
End point description: The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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 Week 12/ET	

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	189		
Units: percent hemoglobin				
least squares mean (standard error)				
Hemoglobin A1c Levels at Up to 12 Weeks	0.01 ($\pm$ 0.016)	-0.02 ($\pm$ 0.015)		

Statistical analyses

Statistical analysis title	Hemoglobin A1c Levels at Up to 12 Weeks
Statistical analysis description: Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	= 0.308
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Notes:

[9] - Placebo controlled

Secondary: Binge Eating Response

End point title	Binge Eating Response
End point description: Response is based on the reduction in the number of binge eating episodes. Percentage of subjects with response was reported. Responses were categorized as follows: 1-week Cessation = 100% reduction in binge episodes during the preceding 7 days. Marked Reduction = 99% to 75% reduction during the time since the previous visit. Moderate Reduction = 74% to 50% reduction during the time since the previous visit. Negative to Minimal Reduction = <50% reduction during the time since the previous visit. The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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: Week 12/ET	

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	187		
Units: percentage of subjects				
number (not applicable)				
1-week cessation	26.6	47.1		
Marked Reduction	15.2	31.6		

Moderate Reduction	17.9	11.8		
Negative to Minimal Reduction	40.2	9.6		

Statistical analyses

Statistical analysis title	Binge Eating Response
Statistical analysis description: Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	other ^[10]
P-value	< 0.001 ^[11]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - Placebo controlled

[11] - Multiplicity is not adjusted for this secondary efficacy endpoint in this study.

Secondary: Change From Baseline in the Number of Binge Episodes Per Week at Visit 8 (Weeks 11-12)

End point title	Change From Baseline in the Number of Binge Episodes Per Week at Visit 8 (Weeks 11-12)
End point description: The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (number of binge days per week calculated for at least 1 week).	
End point type	Secondary
End point timeframe: Baseline and Visit 8 (Weeks 11-12)	

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: Binge episodes per week				
least squares mean (standard error)				
Number of Binge Episodes Per Week at Visit 8	-3.49 (± 0.17)	-5.27 (± 0.168)		

Statistical analyses

Statistical analysis title	Number of Binge Episodes Per Week at Visit 8
Statistical analysis description: Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	other ^[12]
P-value	< 0.001 ^[13]
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least squares mean difference
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	-1.3

Notes:

[12] - Placebo controlled

[13] - Multiplicity is not adjusted for this secondary efficacy endpoint 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:

The Eating Inventory also known as the Three-Factor Eating Questionnaire is a 51-item self-reported questionnaire intended to assess 3 dimensions of eating behavior. 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.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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 week 12

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	188		
Units: units on a scale				
least squares mean (standard error)				
Cognitive Restraint of Eating	1.63 (± 0.331)	3.27 (± 0.329)		
Disinhibition of Eating	-2.12 (± 0.286)	-6.31 (± 0.285)		
Perceived Hunger	-1.9 (± 0.286)	-6.6 (± 0.285)		

Statistical analyses

Statistical analysis title	Cognitive Restraint of Eating
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Statistical analysis description:

Analysis was SPD489 vs Placebo

Comparison groups	Placebo v SPD489
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Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other ^[14]
P-value	< 0.001 ^[15]
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least squares mean difference
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.57

Notes:

[14] - Placebo controlled

[15] - Multiplicity is not adjusted for this secondary efficacy endpoint in this study.

Statistical analysis title	Disinhibition of Eating
Statistical analysis description:	
Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other ^[16]
P-value	< 0.001 ^[17]
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least squares mean difference
Point estimate	-4.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.98
upper limit	-3.39

Notes:

[16] - Placebo controlled

[17] - Multiplicity is not adjusted for this secondary efficacy endpoint in this study.

Statistical analysis title	Perceived Hunger
Statistical analysis description:	
Analysis was SPD489 vs Placebo	
Comparison groups	Placebo v SPD489
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	< 0.001 ^[19]
Method	Mixed Models Repeated Measures Analysis
Parameter estimate	Least squares mean difference
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.49
upper limit	-3.91

Notes:

[18] - Placebo controlled

[19] - Multiplicity is not adjusted for this secondary efficacy endpoint 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.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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 week 12

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	189		
Units: units on a scale				
least squares mean (standard error)				
BES Score at Week 12	-8.55 ($\pm$ 0.763)	-18.87 ($\pm$ 0.755)		

Statistical analyses

Statistical analysis title	BES Score at Week 12
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Statistical analysis description:

Analysis was SPD489 vs Placebo

Comparison groups	Placebo v SPD489
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Number of subjects included in analysis	373
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Analysis specification	Pre-specified
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Analysis type	other ^[20]
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P-value	< 0.001
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Method	Mixed Models Repeated Measures Analysis
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Parameter estimate	Least squares mean difference
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Point estimate	-10.32
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-12.43
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upper limit	-8.21
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Notes:

[20] - Placebo controlled

Secondary: Change From Baseline in Frontal Systems Behavior (FrSBe) Total Score at Week 12

End point title	Change From Baseline in Frontal Systems Behavior (FrSBe) Total Score at Week 12
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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.

The Full Analysis Set was 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 week 12

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	187		
Units: t-scores				
least squares mean (standard error)				
FrSBe Total Score at Week 12	-3.09 ($\pm$ 0.592)	-3.4 ($\pm$ 0.572)		

Statistical analyses

Statistical analysis title	FrSBe Total Score at Week 12
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Statistical analysis description:

Analysis was SPD489 vs Placebo

Comparison groups	Placebo v SPD489
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Number of subjects included in analysis	369
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Analysis specification	Pre-specified
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Analysis type	other ^[21]
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P-value	= 0.706
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Method	ANCOVA
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Parameter estimate	Least squares mean difference
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Point estimate	-0.31
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-1.93
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upper limit	1.31
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Notes:

[21] - Placebo controlled

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. Percentage of subjects with various mobility conditions were reported.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	187		
Units: percentage of subjects				
number (not applicable)				
No problems walking about	82.6	87.2		
Slight problems walking about	14	10.7		
Moderate problems walking about	2.8	2.1		
Severe problems walking about	0.6	0		
Unable to walk about	0	0		

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. Percentage of subjects with various self-care conditions were reported.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	187		
Units: percentage of subjects				
number (not applicable)				
No problems washing or dressing	89.3	95.7		
Slight problems washing or dressing	6.7	3.2		
Moderate problems washing or dressing	3.9	1.1		
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. Percentage of subjects with various usual activities conditions were reported.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	186		
Units: percentage of subjects				
number (not applicable)				
No problems doing usual activities	78	87.1		
Slight problems doing usual activities	14.7	9.7		
Moderate problems doing usual activities	6.2	3.2		
Severe problems doing usual activities	1.1	0		
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. Percentage of subjects with various pain/discomfort conditions were reported.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	187		
Units: percentage of subjects				
number (not applicable)				
No pain or discomfort	64.6	71.1		
Slight pain or discomfort	27.5	20.9		
Moderate pain or discomfort	7.3	7.5		
Severe pain or discomfort	0.6	0.5		
Extreme pain or discomfort	0	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. Percentage of subjects with various anxiety/depression conditions were reported.

The Full Analysis Set was defined as all randomized subjects who took at least 1 dose of investigational product and who had 1 post-baseline primary efficacy assessment (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	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	187		
Units: percentage of subjects				
number (not applicable)				
Not anxious or depressed	70.2	72.2		
Slightly anxious or depressed	19.7	16.6		
Moderately anxious or depressed	7.9	9.1		
Severely anxious or depressed	2.2	1.6		
Extremely anxious or depressed	0	0.5		

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. Number of participants with suicidal ideation and suicidal behavior were reported.

The Safety Analysis Set was 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. Not all subjects had data for this outcome.

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

End point values	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	191		
Units: Subjects				
number (not applicable)				
Suicidal Ideation	3	2		
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.

The Safety Analysis Set was 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. 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	Placebo	SPD489		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	155		
Units: units on a scale				
arithmetic mean (standard deviation)	7.3 (± 7.74)	5.7 (± 7.37)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 3 days after the last dose at up to 12 weeks

Assessment type	Non-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	PLACEBO
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Reporting group description:

Placebo matching SPD489 capsule administered orally, once-daily for up to 12 weeks.

Reporting group title	SPD489
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Reporting group description:

SPD489 capsule 30 (titration purpose only), 50 or 70 mg administered orally, once-daily for up to 12 weeks once the optimal dose is reached.

Serious adverse events	PLACEBO	SPD489	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 187 (1.07%)	3 / 192 (1.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 187 (0.00%)	2 / 192 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 187 (0.53%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Conversion disorder			
subjects affected / exposed	1 / 187 (0.53%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	PLACEBO	SPD489	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 187 (35.83%)	125 / 192 (65.10%)	
Investigations			
Heart rate increased			
subjects affected / exposed	5 / 187 (2.67%)	14 / 192 (7.29%)	
occurrences (all)	5	14	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 187 (9.09%)	26 / 192 (13.54%)	
occurrences (all)	19	32	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 187 (5.35%)	7 / 192 (3.65%)	
occurrences (all)	11	7	
Feeling jittery			
subjects affected / exposed	2 / 187 (1.07%)	11 / 192 (5.73%)	
occurrences (all)	3	13	
Irritability			
subjects affected / exposed	13 / 187 (6.95%)	16 / 192 (8.33%)	
occurrences (all)	13	18	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 187 (2.14%)	11 / 192 (5.73%)	
occurrences (all)	4	11	
Dry mouth			
subjects affected / exposed	16 / 187 (8.56%)	76 / 192 (39.58%)	
occurrences (all)	19	86	
Nausea			

subjects affected / exposed occurrences (all)	14 / 187 (7.49%) 15	16 / 192 (8.33%) 19	
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 187 (0.53%) 1	10 / 192 (5.21%) 10	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	2 / 187 (1.07%) 2 14 / 187 (7.49%) 15	13 / 192 (6.77%) 13 34 / 192 (17.71%) 44	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 187 (5.88%) 12	8 / 192 (4.17%) 10	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 187 (3.21%) 6	17 / 192 (8.85%) 17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2012	• Added an Overall Risk/Benefit Assessment • Changed comparison of the Y-BOCS-BE total score to a key secondary objective • Added assessments of the EQ-5D-5L at Weeks 4, 6, 8, and 10 (Visits 4, 5, 6, and 7) • Clarified inclusion criterion to further describe indeterminate pregnancy test results • Clarified exclusion criterion to state a current diagnosis, rather than concurrent symptoms, of bulimia nervosa or anorexia nervosa was exclusionary • Added language regarding contraception requirements being reviewed at every study visit and document in source document • Clarified language regarding use of psychoactive medications during the study and before study entry, and changed the language of the permitted window for psychotherapy • Clarified that the Mini International Neuropsychiatric Interview (MINI-Plus) was to be used to exclude comorbid Axis I disorders rather than confirm diagnosis of BED • Added further language addressing the management of positive responses on the C-SSRS • Clarified that the ACSA was to be collected at the Baseline Visit (Visit 0) • Added a ± 2-hour window to the 7:00 AM dosing instructions • Added smoking status to items collected as part of medical history

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported