Clinical trial results:
A Phase 2a Randomized, Double-blind, Placebo-controlled, Parallel-group, Multi-center Study Investigating the Efficacy, Safety, and Tolerability of JNJ-42165279 in Subjects with Major Depressive Disorder and Anxious Distress

Summary

EudraCT number	2015-002007-29
Trial protocol	ES GB
Global end of trial date	04 February 2019

Results information

Result version number	v1 (current)
This version publication date	19 February 2020
First version publication date	19 February 2020

Trial information

Trial identification

Sponsor protocol code	42165279MDD2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02498392
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, South Raritan, United States,
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	04 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy in terms of reduction of symptoms of depression and anxiety, as assessed by the change from baseline on a 17-item Hamilton Depression Rating Scale (HDRS17), and overall safety and tolerability of treatment with adjunctive JNJ-42165279 compared to placebo in subjects with major depressive disorder (MDD) with anxiety symptoms who had inadequate response to treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonergic/noradrenergic reuptake inhibitor (SNRI).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Physical examination, neurological examination, vital signs, body weight, body temperature, clinical laboratory assessments, 12-lead electrocardiogram (ECG), urine drug screen, alcohol screening test, pregnancy testing, Columbia Suicide Severity Rating Scale (C-SSRS) assessments and evaluation of adverse events (AEs) and concomitant medications were performed during the study to monitor subject's safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2015
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: 6
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Moldova, Republic of: 18
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	160
EEA total number of subjects	41

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)	160
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 160 subjects were enrolled into the lead-in period, and 153 were randomized into the double-blind (DB) treatment period and received at least 1 dose of double-blind study agent. Of the 153 subjects, 137 completed study.

Period 1

Period 1 title	Double-blind (DB) Lead-in Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	Placebo

Arm description:

Lead-in Period: All subjects received matching placebo tablets orally once daily (qd). At the end of the lead-in period, response status of the subjects was assessed according to the double-blind response criteria based on reduction in Hamilton Depression Rating Scale (HDRS17) relative to lead-in baseline. Double-blind treatment period: Following initial placebo lead-in period, subjects self-administered adjunctive matching placebo tablets orally qd for 6 weeks. Withdrawal period: Subjects who completed the double-blind treatment period prior to Week 11 were treated with placebo for the remaining time of the treatment phase of the study, which varied depending on the duration of the placebo lead-in for the specific subject.

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

Dosage and administration details:

Matching placebo was administered orally.

Number of subjects in period 1	Placebo
Started	160
Completed	153
Not completed	7
Did not receive treatment	7

Period 2

Period 2 title	DB Treatment(6 week) + Withdrawal Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Lead-in Period: All subjects received matching placebo tablets orally once daily (qd). At the end of the lead-in period, response status of the subjects was assessed according to the double-blind response criteria based on reduction in HDRS17 relative to lead-in baseline. Double-blind treatment period: Following initial placebo lead-in period, subjects self-administered adjunctive matching placebo tablets orally qd for 6 weeks. Withdrawal period: Subjects who completed the double-blind treatment period prior to Week 11 were treated with placebo for the remaining time of the treatment phase of the study, which varied depending on the duration of the placebo lead-in for the specific subject.

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

Dosage and administration details:

Matching placebo was administered orally.

Arm title	JNJ-42165279 25 mg

Arm description:

Double-blind treatment period: Following the initial placebo lead-in period, the subjects self-administered JNJ-42165279 25 mg tablets orally once daily for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	JNJ-42165279
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

JNJ-42165279 was administered orally at a dose of 25 mg tablet once daily for 6 weeks.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline data was reported for safety analysis set for DB treatment period which was less than all enrolled analysis set.

Number of subjects in period 2[2]	Placebo	JNJ-42165279 25 mg
Started	76	77
Completed	70	67
Not completed	6	10
Adverse Event	3	-
Unspecified	1	3
Lost to follow-up	-	2
Withdrawal by subject	2	3

Lack of efficacy	-	2

Notes:

[2] - 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 baseline period shows the disposition of safety analysis set.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Lead-in Period: All subjects received matching placebo tablets orally once daily (qd). At the end of the lead-in period, response status of the subjects was assessed according to the double-blind response criteria based on reduction in HDRS17 relative to lead-in baseline. Double-blind treatment period: Following initial placebo lead-in period, subjects self-administered adjunctive matching placebo tablets orally qd for 6 weeks. Withdrawal period: Subjects who completed the double-blind treatment period prior to Week 11 were treated with placebo for the remaining time of the treatment phase of the study, which varied depending on the duration of the placebo lead-in for the specific subject.	
Reporting group title	JNJ-42165279 25 mg
Reporting group description:	
Double-blind treatment period: Following the initial placebo lead-in period, the subjects self-administered JNJ-42165279 25 mg tablets orally once daily for 6 weeks.	

Reporting group values	Placebo	JNJ-42165279 25 mg	Total
Number of subjects	76	77	153
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	76	77	153
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	44.4	42.1	
standard deviation	± 11.92	± 11.96	-
Title for Gender Units: subjects			
Female	59	53	112
Male	17	24	41

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Lead-in Period: All subjects received matching placebo tablets orally once daily (qd). At the end of the lead-in period, response status of the subjects was assessed according to the double-blind response criteria based on reduction in Hamilton Depression Rating Scale (HDRS17) relative to lead-in baseline. Double-blind treatment period: Following initial placebo lead-in period, subjects self-administered adjunctive matching placebo tablets orally qd for 6 weeks. Withdrawal period: Subjects who completed the double-blind treatment period prior to Week 11 were treated with placebo for the remaining time of the treatment phase of the study, which varied depending on the duration of the placebo lead-in for the specific subject.

Reporting group title	Placebo

Reporting group description:

Lead-in Period: All subjects received matching placebo tablets orally once daily (qd). At the end of the lead-in period, response status of the subjects was assessed according to the double-blind response criteria based on reduction in HDRS17 relative to lead-in baseline. Double-blind treatment period: Following initial placebo lead-in period, subjects self-administered adjunctive matching placebo tablets orally qd for 6 weeks. Withdrawal period: Subjects who completed the double-blind treatment period prior to Week 11 were treated with placebo for the remaining time of the treatment phase of the study, which varied depending on the duration of the placebo lead-in for the specific subject.

Reporting group title	JNJ-42165279 25 mg

Reporting group description:

Double-blind treatment period: Following the initial placebo lead-in period, the subjects self-administered JNJ-42165279 25 mg tablets orally once daily for 6 weeks.

Primary: Double-blind Treatment Period: Change from Baseline in Hamilton Depression Rating Scale (HDRS17) Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Change from Baseline in Hamilton Depression Rating Scale (HDRS17) Total Score at Week 6 (eITT Population)

End point description:

HDRS-17 is clinician-administered rating scale designed to assess severity of symptoms in subjects diagnosed with depression. Each of 17 items is rated by clinician on either 3-point (0-2) or 5-point (0-4) scale with rating of 0:absent, 1:doubtful to mild, 2:mild to moderate, 3:moderate to severe, and 4:very severe. A total score (0 to 52) was calculated by adding scores of all 17 items. For each item as well as total score, higher score represents more severe condition. The enriched intention-to-treat (eITT) analysis set included all enrolled subjects who were randomized into double-blind treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard deviation)	-6.1 (± 5.90)	-6.5 (± 4.01)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Here 'MMRM' refers to Mixed-effects Model Using Repeated Measures.	
Comparison groups	Placebo v JNJ-42165279 25 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.416
Method	MMRM
Parameter estimate	Difference of Least Square (LS) Means
Point estimate	-0.2
Confidence interval	
level	Other: 60 %
sides	2-sided
lower limit	-1.1
upper limit	0.66
Variability estimate	Standard error of the mean
Dispersion value	1.04

Primary: Double-blind Treatment Period: Change from Baseline in Hamilton Depression Rating Scale (HDRS17) Total Score at Week 6 (fITT Population)

End point title	Double-blind Treatment Period: Change from Baseline in Hamilton Depression Rating Scale (HDRS17) Total Score at Week 6 (fITT Population)

End point description:

HDRS17 is a clinician-administered rating scale designed to assess severity of symptoms in subjects diagnosed with depression. Each of the 17 items is rated by clinician on either a 3-point (0 to 2) or a 5-point (0 to 4) scale which used a rating of 0:absent, 1:doubtful to mild, 2:mild to moderate, 3:moderate to severe, and 4:very severe. HDRS17 total score is calculated as sum of 17 item scores and ranges from 0 to 52. For each item as well as the total score, higher scores indicate greater severity of depression. The full intent-to-treat (fITT) analysis set included both placebo responders and placebo non-responders. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	69		
Units: Units on a scale				
arithmetic mean (standard deviation)	-5.0 (± 6.34)	-5.2 (± 4.68)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Here 'MMRM' refers to Mixed-effects Model Using Repeated Measures.	
Comparison groups	Placebo v JNJ-42165279 25 mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647 [1]
Method	MMRM
Parameter estimate	Difference of Least Square (LS) Means
Point estimate	0.3
Confidence interval	
level	Other: 60 %
sides	2-sided
lower limit	-0.41
upper limit	1.07
Variability estimate	Standard error of the mean
Dispersion value	0.88

Notes:

[1] - 1-sided

Secondary: Double-blind Treatment Period: Change from Baseline in Hamilton Anxiety Rating Subscale (HAM-A6) Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Change from Baseline in Hamilton Anxiety Rating Subscale (HAM-A6) Score at Week 6 (eITT Population)

End point description:

The HAM-A6 is a 6-item subscale derived from the original Hamilton Anxiety scale (HAM-A) which consists of 5 psychic anxiety symptoms (anxious mood, psychic tension, fears, intellectual disturbances, and anxious behavior observed at the interview), as well as one somatic item (muscular tension). The HAM-A6 score ranges from 0 to 24; higher scores indicate greater severity of symptoms. The HAM-A6 score is calculated by summing the 6 item scores. The eITT analysis set included all enrolled subjects who were randomized into double-blind treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in the double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard deviation)	-2.4 (± 3.15)	-2.9 (± 2.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Change from Baseline in Hamilton Depression Rating Subscale (HAM-D6) Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Change from Baseline in Hamilton Depression Rating Subscale (HAM-D6) Score at Week 6 (eITT Population)

End point description:

HAM-D6 is a 6-item subscale derived from HDRS17 and consists of depressed mood, guilt feelings, work and interests, psychomotor retardation, psychic anxiety, and somatics symptoms (tiredness and pains), rated on a 5-point scale, where 0 = not present, and 1-4 represent increasingly severe symptoms. One item (that is, somatic symptoms) is rated on only a 3-point scale, ranging from 0-2. The HAM-D6 is calculated from summing the 6 items and the score ranges from 0 (normal) to 22 (severe), with higher scores indicating greater severity of core symptoms. The eITT analysis set included all enrolled subjects who were randomized into double-blind treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard deviation)	-3.1 (± 3.20)	-3.6 (± 2.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Change from Baseline in Structured Interview Guide of the Hamilton Anxiety Scale (SIGH-A) Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Change from Baseline in Structured Interview Guide of the Hamilton Anxiety Scale (SIGH-A) Total Score at Week 6 (eITT Population)

End point description:

The SIGH-A scale consists of 14 items with a score of 0 to 4, where 0=absent, 1=mild, 2=moderate, 3=severe, 4=incapacitating. The SIGH-A total score is calculated by summing the 14 item scores, and ranges from 0 to 56. For each individual item score and total score, higher scores indicate greater severity. The eITT analysis set included all enrolled subjects who were randomized into double-blind treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in the double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard deviation)	-5.7 (± 7.11)	-6.8 (± 5.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Change from Baseline in the HDRS17 Anxiety/Somatization Factor Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Change from Baseline in the HDRS17 Anxiety/Somatization Factor Total Score at Week 6 (eITT Population)

End point description:

HDRS17 anxiety/somatization factor is derived from HDRS including 6 items: psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight. Each of 6 items is rated by clinician on either a 3-point (0 to 2) or a 5-point (0 to 4) scale with rating of 0:absent, 1:doubtful to mild, 2:mild to moderate, 3:moderate to severe, and 4:very severe and is calculated as sum of 6 item scores ranging from 0 to 18, with higher scores indicating greater severity of symptoms for each item as well as total score. The eITT analysis set included all enrolled subjects who were randomized into DB treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard deviation)	-2.1 (± 2.35)	-2.3 (± 1.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Percentage of Subjects With Greater than or Equal to (>=) 30 Percent (%) Improvement on the HDRS-17 Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Percentage of Subjects With Greater than or Equal to (>=) 30 Percent (%) Improvement on the HDRS-17 Total Score at Week 6 (eITT Population)

End point description:

Percentage of subjects who had >=30% improvement on HDRS17 total score at Week 6 was reported. HDRS-17 is clinician-administered rating scale designed to assess severity of symptoms in subjects diagnosed with depression. Each of 17 items is rated by clinician on either 3-point (0-2) or 5-point (0-4) scale with rating of 0:absent, 1:doubtful to mild, 2:mild to moderate, 3:moderate to severe, and 4:very severe. A total score (0 to 52) was calculated by adding scores of all 17 items. For each item as well as total score, higher score represents more severe condition. eITT analysis set included all enrolled subjects who were randomized into DB treatment period,who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Percentage of subjects				
number (not applicable)	51.1	55.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Percentage of Subjects With >= 50% Improvement on the HDRS-17 Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Percentage of Subjects With >= 50% Improvement on the HDRS-17 Total Score at Week 6 (eITT Population)

End point description:

Percentage of subjects who had >=50% improvement on HDRS17 total score at Week 6 was reported. HDRS-17 is clinician-administered rating scale designed to assess severity of symptoms in subjects diagnosed with depression. Each of 17 items is rated by clinician on either 3-point (0-2) or 5-point (0-4) scale with rating of 0:absent, 1:doubtful to mild, 2:mild to moderate, 3:moderate to severe, and 4:very severe. A total score (0 to 52) was calculated by adding scores of all 17 items. For each item as well as total score, higher score represents more severe condition. eITT analysis set included all enrolled subjects who were randomized into DB treatment period,who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS-17 assessment in DB treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Percentage of subjects				
number (not applicable)	27.7	21.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Percentage of Subjects With Remission as Assessed by HDRS-17 Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Percentage of Subjects With Remission as Assessed by HDRS-17 Total Score at Week 6 (eITT Population)

End point description:

Percentage of subjects with HDRS-17 total score less than or equal to 7 were considered as remitters. HDRS-17 is clinician-administered rating scale designed to assess severity of symptoms in subjects with depression. Each of 17 items is rated by clinician on either 3-point(0-2) or 5-point(0-4) scale with rating of 0:absent,1:doubtful to mild,2:mild to moderate,3:moderate to severe, and 4:very severe. A total score (0 to 52) was calculated by adding scores of all 17 items. For each item as well as total score, higher score represents more severe condition. eITT analysis set included all enrolled subjects who were randomized into double-blind treatment period,who were lead-in placebo non-responder,who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Percentage of subjects				
number (not applicable)	14.9	8.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Percentage of Subjects With >= 30% Improvement on SIGH-A Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Percentage of Subjects With >= 30% Improvement on SIGH-A Total Score at Week 6 (eITT Population)

End point description:

The percentage of subjects who had >= 30% improvement on SIGH-A total score at Week 6 was reported. The SIGH-A scale consists of 14 items with a score of 0 to 4, where 0=absent, 1=mild, 2=moderate, 3=severe, 4=incapacitating. The SIGH-A total score is calculated by summing the 14 item scores, and ranges from 0 to 56. For each individual item score and total score, higher scores indicate greater severity. The eITT analysis set included all enrolled subjects who were randomized into double-blind treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in the double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Percentage of subjects				
number (not applicable)	48.9	51.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Percentage of Subjects With >= 50% Improvement on SIGH-A Total Score at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Percentage of Subjects With >= 50% Improvement on SIGH-A Total Score at Week 6 (eITT Population)

End point description:

The percentage of subjects who had >= 50% improvement on SIGH-A total score at Week 6 was

reported. The SIGH-A scale consists of 14 items with a score of 0 to 4, where 0=absent, 1=mild, 2=moderate, 3=severe, 4=incapacitating. The SIGH-A total score is calculated by summing the 14 item scores, and ranges from 0 to 56. For each individual item score and total score, higher scores indicate greater severity. The eITT analysis set included all enrolled subjects who were randomized into double-blind treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in the double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Percentage of subjects				
number (not applicable)	29.8	21.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Period: Percentage of Subjects With a Clinical Global Impression Improvement (CGI-I) Score of Very Much Improved or Much Improved at Week 6 (eITT Population)

End point title	Double-blind Treatment Period: Percentage of Subjects With a Clinical Global Impression Improvement (CGI-I) Score of Very Much Improved or Much Improved at Week 6 (eITT Population)

End point description:

The percentage of subjects with a CGI-I score of very much improved or much improved at Week 6 was reported. CGI-I is a 7-point scale that required the clinician to assess how much the subject’s illness had improved or worsened relative to a baseline state at the beginning of the intervention. The CGI-I is rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse. For each individual item score and total score, higher scores indicate greater severity. The eITT analysis set included all enrolled subjects who were randomized into double-blind treatment period, who were lead-in placebo non-responder, who received at least one dose of double-blind study medication (either placebo or JNJ-42165279) and had at least one post-baseline HDRS17 assessment in the double-blind treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	JNJ-42165279 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Percentage of subjects				
number (not applicable)	57.4	55.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6 weeks

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Lead-in Period: All subjects received matching placebo tablets orally once daily (qd). At the end of the lead-in period, response status of the subjects was assessed according to the double-blind response criteria based on reduction in HDRS17 relative to lead-in baseline. Double-blind treatment period: Following initial placebo lead-in period, subjects self-administered adjunctive matching placebo tablets orally qd for 6 weeks. Withdrawal period: Subjects who completed the double-blind treatment period prior to Week 11 were treated with placebo for the remaining time of the treatment phase of the study, which varied depending on the duration of the placebo lead-in for the specific subject.

Reporting group title	JNJ-42165279 25mg

Reporting group description:

Double-blind treatment period: Following the Lead-in Period, the subjects self-administered JNJ-42165279 25 milligrams (mg) tablets orally once daily for 6 weeks.

Serious adverse events	Placebo	JNJ-42165279 25mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (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	JNJ-42165279 25mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 76 (5.26%)	3 / 77 (3.90%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 76 (5.26%)	3 / 77 (3.90%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2015	The overall reason for Amendment INT-1 was to clarify the updated procedure performed by an independent central rater and to address the US Food and Drug Administration (FDA) comments.
03 July 2017	The overall reason for Amendment INT-2 was to update the information on toxicology, to increase the number of subjects participating in the study from 140 to 143, to replace 3 subjects who had to stop early when the study was put on hold, to add neurological examinations to confirm the safety of participation in the study and treatment with JNJ 42165279, to make change in allowed medication and control of drug intake.
25 August 2017	The overall reason for Amendment INT-4 was based on a regulatory decision, to allow women of childbearing potential to participate in this study under conditions of pregnancy testing and the use of high-quality contraception, and additionally, to add the optional use of a diary or electronic device to document the intake of study medication.
24 October 2017	The overall reason for Amendment INT-5 was based on regulator's request to exclude subjects with abnormal high liver function analytes from the study, to add an exclusion criterion for breast feeding women; on request of investigators: to add Venlafaxine (immediate release) to the list of allowed antidepressant drugs, on request of investigators: to add instructions on the use of PRN (as needed) non-benzodiazepine sleep aids, and additionally, to add specific instructions of the calculation of corrected QT (QTc) interval to determine stopping or exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The relationship of plasma anandamide and trough drug concentrations observed suggest that few subjects had substantial recovery of fatty acid amide hydrolase activity between doses. Higher doses or exposures could have resulted in greater effects.

Notes: