Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Once a Day, TAK-375 (Ramelteon) Tablet for Sublingual Administration (TAK-375SL Tablet) 0.1 mg and 0.4 mg as an Adjunctive Therapy in the Treatment of Acute Depressive Episodes Associated With Bipolar 1 Disorder in Adult Subjects

Summary

EudraCT number	2012-001357-10
Trial protocol	GB DE CZ PL BG
Global end of trial date	03 September 2014

Results information

Result version number	v1 (current)
This version publication date	23 March 2016
First version publication date	23 March 2016

Trial information

Trial identification

Sponsor protocol code	TAK-375SL_301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01677182
WHO universal trial number (UTN)	U1111-1129-5184

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Clinical Study Manager, Takeda Global Research & Development Centre (Europe) Ltd (TGRD), +44 203116 8000, clinicaloperations@tgrd.com
Scientific contact	Clinical Study Manager, Takeda Global Research & Development Centre (Europe) Ltd (TGRD), +44 203116 8000, clinicaloperations@tgrd.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	14 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of TAK-375SL tablet 0.1 mg and 0.4 mg once daily at bedtime (QHS) compared with placebo as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) after 6 weeks of treatment in subjects with acute depressive episodes associated with Bipolar 1 Disorder.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Bulgaria: 88
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Romania: 24
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	Serbia: 67
Country: Number of subjects enrolled	Ukraine: 57
Country: Number of subjects enrolled	United States: 219
Worldwide total number of subjects	535
EEA total number of subjects	158

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)	520
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part at 98 sites in Bulgaria, the Czech Republic, Germany, Great Britain, Poland, Romania, Russia, Serbia, Ukraine, and the United States from 29 August 2012 to 03 September 2014.

Pre-assignment

Screening details:

Subjects with a historical diagnosis of bipolar 1 disorder were enrolled in 1 of 3 treatment groups as follows: placebo; TAK-375 0.1 milligram (mg); TAK-375 0.4 mg.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

TAK-375SL (ramelteon) placebo-matching tablet, sublingually, once daily for up to 6 weeks.

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

Dosage and administration details:

TAK-375SL (ramelteon) placebo-matching tablet, sublingually, once daily for up to 6 weeks.

Arm title	TAK-375SL 0.1 mg

Arm description:

TAK-375SL (ramelteon) 0.1 mg, tablet, sublingually, once daily for up to 6 weeks.

Arm type	Experimental
Investigational medicinal product name	TAK-375SL
Investigational medicinal product code	
Other name	Ramelteon
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

TAK-375SL (ramelteon) 0.1 mg, tablet, sublingually, once daily for up to 6 weeks.

Arm title	TAK-375SL 0.4 mg

Arm description:

TAK-375SL (ramelteon) 0.4 mg, tablet, sublingually, once daily for up to 6 weeks.

Arm type	Experimental

Investigational medicinal product name	TAK-375SL
Investigational medicinal product code	
Other name	Ramelteon
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

TAK-375SL (ramelteon) 0.4 mg, tablet, sublingually, once daily for up to 6 weeks.

Number of subjects in period 1	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg
Started	184	169	182
Completed	150	141	143
Not completed	34	28	39
Consent withdrawn by subject	7	12	10
Protocol violation	5	1	4
Study termination	12	9	11
Other	1	5	2
Adverse event	2	1	8
Lost to follow-up	4	-	3
Lack of efficacy	3	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
TAK-375SL (ramelteon) placebo-matching tablet, sublingually, once daily for up to 6 weeks.	
Reporting group title	TAK-375SL 0.1 mg
Reporting group description:	
TAK-375SL (ramelteon) 0.1 mg, tablet, sublingually, once daily for up to 6 weeks.	
Reporting group title	TAK-375SL 0.4 mg
Reporting group description:	
TAK-375SL (ramelteon) 0.4 mg, tablet, sublingually, once daily for up to 6 weeks.	

Reporting group values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg
Number of subjects	184	169	182
Age categorical Units: Subjects			
Less than or equal to (<=) 50 years	105	100	107
Greater than (>) 50 years	79	69	75
Age continuous Units: years			
arithmetic mean	46.67	45.44	44.87
standard deviation	± 11.332	± 11.49	± 11.608
Gender categorical Units: Subjects			
Female	119	98	108
Male	65	71	74
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	10	9
Not Hispanic or Latino	63	61	63
Unknown or Not Reported	109	98	110
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	0	1	2
Native Hawaiian or Other Pacific Islander	1	1	1
Black or African American	11	12	12
White	171	154	166
More than one race	0	0	1
Region of Enrollment Units: Subjects			
Bulgaria	31	27	30
Czech Republic	9	7	8
Germany	3	5	3
United Kingdom	1	0	0
Poland	2	4	4
Romania	8	7	9

Russian Federation	12	9	13
Serbia	22	20	25
Ukraine	20	19	18
United States	76	71	72
Smoking Classification Units: Subjects			
Had Never Smoked	84	75	79
Current Smoker	75	70	82
Ex-smoker	25	24	21
Subject Drinking Status Units: Subjects			
Had Never Drunk	97	92	109
Ex-Drinker	51	41	36
Current Drinker	36	36	37
Amount of Alcohol Consumed if Current Drinker			
Subjects evaluable for this measure included only those who were current drinkers (36, 36, and 37 for each group, respectively).			
Units: Subjects			
< 4 drinks per day	36	36	37
>= 4 drinks per day	0	0	0
Non consumer	148	133	145
Consumption of Caffeine Units: Subjects			
Consumer	140	128	144
Not a consumer	44	41	38
Psychiatric History for response to Lithium treatment for Bipolar 1 Disorder Units: Subjects			
Failed to Respond	7	7	7
Responded	101	92	100
Not Applicable	69	63	68
Unknown	7	7	7
Psychiatric History for response to Valproic Acid Treatment of Bipolar 1 Disorder Units: Subjects			
Failed to Respond	6	8	9
Responded	133	124	136
Not Applicable	35	29	27
Unknown	10	8	10
Female Reproductive Status Units: Subjects			
Postmenopausal	44	30	34
Surgically Sterile	20	14	12
Child-Bearing Potential	55	54	62
Not applicable (male subjects)	65	71	74
Height Units: centimeter (cm)			
arithmetic mean	168.86	170.66	169.8
standard deviation	± 9.227	± 8.423	± 8.87
Weight Units: kilogram (kg)			

arithmetic mean	80.82	83.21	82.38
standard deviation	± 23.503	± 18.638	± 19.202
Body Mass Index (BMI)			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	28.25	28.57	28.52
standard deviation	± 7.583	± 6.13	± 6.156

Reporting group values	Total		
Number of subjects	535		
Age categorical			
Units: Subjects			
Less than or equal to (<=) 50 years	312		
Greater than (>) 50 years	223		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	325		
Male	210		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	31		
Not Hispanic or Latino	187		
Unknown or Not Reported	317		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	3		
Native Hawaiian or Other Pacific Islander	3		
Black or African American	35		
White	491		
More than one race	1		
Region of Enrollment			
Units: Subjects			
Bulgaria	88		
Czech Republic	24		
Germany	11		
United Kingdom	1		
Poland	10		
Romania	24		
Russian Federation	34		
Serbia	67		
Ukraine	57		
United States	219		
Smoking Classification			
Units: Subjects			
Had Never Smoked	238		
Current Smoker	227		

Ex-smoker	70		
Subject Drinking Status Units: Subjects			
Had Never Drunk	298		
Ex-Drinker	128		
Current Drinker	109		
Amount of Alcohol Consumed if Current Drinker			
Subjects evaluable for this measure included only those who were current drinkers (36, 36, and 37 for each group, respectively).			
Units: Subjects			
< 4 drinks per day	109		
>= 4 drinks per day	0		
Non consumer	426		
Consumption of Caffeine Units: Subjects			
Consumer	412		
Not a consumer	123		
Psychiatric History for response to Lithium treatment for Bipolar 1 Disorder Units: Subjects			
Failed to Respond	21		
Responded	293		
Not Applicable	200		
Unknown	21		
Psychiatric History for response to Valproic Acid Treatment of Bipolar 1 Disorder Units: Subjects			
Failed to Respond	23		
Responded	393		
Not Applicable	91		
Unknown	28		
Female Reproductive Status Units: Subjects			
Postmenopausal	108		
Surgically Sterile	46		
Child-Bearing Potential	171		
Not applicable (male subjects)	210		
Height Units: centimeter (cm)			
arithmetic mean			
standard deviation	-		
Weight Units: kilogram (kg)			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI) Units: kilogram per square meter (kg/m^2)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
TAK-375SL (ramelteon) placebo-matching tablet, sublingually, once daily for up to 6 weeks.	
Reporting group title	TAK-375SL 0.1 mg
Reporting group description:	
TAK-375SL (ramelteon) 0.1 mg, tablet, sublingually, once daily for up to 6 weeks.	
Reporting group title	TAK-375SL 0.4 mg
Reporting group description:	
TAK-375SL (ramelteon) 0.4 mg, tablet, sublingually, once daily for up to 6 weeks.	

Primary: Change From Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at Week 6

End point title	Change From Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at Week 6
End point description:	
The MADRS is a clinician rated, validated and widely used scale to measure overall severity of depressive symptoms. It consists of 10-item rated from 0(normal) to 6(most abnormal) with a total score range from 0 to 60. Higher scores indicate greater severity of symptoms. Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy.	
End point type	Primary
End point timeframe:	
Baseline and Week 6	

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: units on scale				
least squares mean (standard error)				
Baseline (n= 179, 167, 176)	30.8 (± 0.28)	30.2 (± 0.29)	30.4 (± 0.29)	
Change at Week 6 (n= 149, 139, 143)	-14.7 (± 0.69)	-14 (± 0.71)	-15.1 (± 0.7)	

Statistical analyses

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.1 mg
Statistical analysis description:	
Mixed Model Repeated Measures (MMRM) model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.	
Comparison groups	Placebo v TAK-375SL 0.1 mg

Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.783
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Differences
Point estimate	0.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.4
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	0.98

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.4 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Differences
Point estimate	-0.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-2.6
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.97

Secondary: Change From Baseline in Young Mania Rating Scale (YMRS) Total Score at Week 6

End point title	Change From Baseline in Young Mania Rating Scale (YMRS) Total Score at Week 6

End point description:

The YMRS is a 11-item scale to assess manic symptoms. Four items are rated on a scale from 0 (symptom not present) to 8 (symptom extremely severe), and 7 items are rated on a scale from 0 to 4 with higher scores reflecting greater levels of mania. The YMRS total score is calculated as the sum of the 11 individual item scores and ranges from 0-60. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: units on a scale				
least squares mean (standard error)				
Baseline (n= 179, 167, 176)	4.4 (± 0.16)	4.3 (± 0.16)	4.4 (± 0.16)	
Change at Week 6 (n= 149, 139, 143)	-1.4 (± 0.19)	-0.9 (± 0.2)	-1.5 (± 0.2)	

Statistical analyses

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.1 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.1
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.27

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.4 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.642
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.7
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.27

Secondary: Clinical Global Impression Scale-Improvement (CGI-I) Score

End point title	Clinical Global Impression Scale-Improvement (CGI-I) Score

End point description:

The CGI-I assesses the clinician's impression of the subject's state of mental illness improvement and consists of 1 question for the investigator: "Compared to his condition at the start of the study, how much has this patient changed?" which is rated on a 7-point scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change relative to baseline; 5=minimally worse; 6= much worse; 7=very much worse). In all cases, the assessment was independent of whether the rater believed the improvement was drug-related or not. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	139	143	
Units: units on a scale				
least squares mean (standard error)	2.5 (± 0.08)	2.5 (± 0.09)	2.3 (± 0.09)	

Statistical analyses

Statistical analysis title	Placebo, TAK-375SL 0.1 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.792
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.2
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	Placebo, TAK-375SL 0.4 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.171
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: Change From Baseline in Clinical Global Impression Scale-Severity (CGI-S) to Week 6

End point title	Change From Baseline in Clinical Global Impression Scale-Severity (CGI-S) to Week 6

End point description:

The CGI-S assesses the clinician’s impression of the subject’s current state of mental illness and consists of 1 question for the investigator: “Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?” which is rated on a 7-point scale (1=normal, not ill at all; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill). FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: units on a scale				
least squares mean (standard error)				
Baseline (n= 179, 167, 176)	4.5 (± 0.04)	4.5 (± 0.04)	4.5 (± 0.04)	
Change at Week 6 (n= 149, 139, 143)	-1.4 (± 0.08)	-1.3 (± 0.09)	-1.4 (± 0.08)	

Statistical analyses

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.1 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.653
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.2
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.4 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.673
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.3
upper limit	0.2

Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: Change From Baseline in the Quick Inventory of Depressive Symptomatology - Self-Rated16 (QIDS-SR16) Total Score at Week 6

End point title	Change From Baseline in the Quick Inventory of Depressive Symptomatology - Self-Rated16 (QIDS-SR16) Total Score at Week 6

End point description:

The 16-item QIDS-SR16 version is a widely used validated scale designed to assess the severity of depressive symptoms. The subject was asked to rate the severity and frequency of specific symptoms present over the last 7 days. The QIDS-SR16 total scores range from 0 to 27, where higher scores indicate higher severity of symptoms. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: units on a scale				
least squares mean (standard error)				
Baseline (n= 178, 167, 176)	14.8 (± 0.26)	14.5 (± 0.27)	14.2 (± 0.26)	
Change at Week 6 (n= 148, 139, 143)	-7.2 (± 0.36)	-6.4 (± 0.38)	-7.3 (± 0.37)	

Statistical analyses

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.1 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.4
upper limit	2

Variability estimate	Standard error of the mean
Dispersion value	0.51

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.4 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.3
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.51

Secondary: Change From Baseline in Sheehan Disability Scale (SDS) Total Score at Week 6

End point title	Change From Baseline in Sheehan Disability Scale (SDS) Total Score at Week 6

End point description:

The SDS is a 3-item rating scale to assess functional impairment (panic, anxiety, phobic and depressive symptoms) over 3 inter-related domains (work/school, social life, and family life/home responsibilities) rated on an 11-point scale from 0 (not at all) to 10 (extremely) with a total score range from 0 to 30 where higher scores indicates greater severity of impairment. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: units on a scale				
least squares mean (standard error)				
Baseline (n= 174, 163, 172)	18.1 (± 0.43)	17.1 (± 0.44)	15.9 (± 0.43)	
Change at Week 6 (n= 148, 139, 143)	-6.8 (± 0.51)	-6.2 (± 0.52)	-6.4 (± 0.51)	

Statistical analyses

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.1 mg
Statistical analysis description:	
MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.	
Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1
upper limit	2.1
Variability estimate	Standard error of the mean
Dispersion value	0.7

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.4 mg
Statistical analysis description:	
MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.	
Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.655
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.3
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	0.7

Secondary: Change From Baseline in Quality of Life, Enjoyment, and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) Total Score at Week 6

End point title	Change From Baseline in Quality of Life, Enjoyment, and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) Total Score at Week 6

End point description:

Q-LES-Q-SF is a self-administered, widely used 16-item questionnaire to assess the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning, such as social relationships, living/housing, physical health, medication, and global satisfaction. The questionnaire consists of 16 items rated by the subjects on a 5-point scale. Of these, 14 items are summed to produce a total quality of life score with a maximum of 70 points. In addition, there are 2 global items that are scored individually. These items rate satisfaction with study medication and overall life satisfaction. The questionnaire is usually scored as a percent of the total possible score, with higher scores indicating better health status. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: percentage of total possible score				
least squares mean (standard error)				
Baseline (n= 174, 163, 172)	38.3 (± 0.93)	38.8 (± 0.95)	41 (± 0.93)	
Change at Week 6 (n= 148, 139, 143)	15.6 (± 1.19)	14.7 (± 1.22)	15.7 (± 1.21)	

Statistical analyses

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.1 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.696
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.8

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-4.5
upper limit	2.8
Variability estimate	Standard error of the mean
Dispersion value	1.64

Statistical analysis title	Week 6: Placebo, TAK-375SL 0.4 mg

Statistical analysis description:

MMRM model with baseline by week interaction, pooled center, week, treatment, baseline, and week by treatment interaction as factors was used for the analysis.

Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.472
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-3.6
upper limit	3.8
Variability estimate	Standard error of the mean
Dispersion value	1.63

Secondary: Percentage of Subjects With MADRS Response

End point title	Percentage of Subjects With MADRS Response

End point description:

MADRS response is defined as greater than or equal to (>=) 50 percent (%) decrease in the MADRS total score from baseline. The MADRS is a clinician rated, validated and widely used scale to measure overall severity of depressive symptoms. It consists of 10-item rated from 0 (normal) to 6 (most abnormal) with a total score range from 0 to 60, where higher scores indicate greater severity of symptoms. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy. Last observation carried forward (LOCF) method was used to impute missing data.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: percentage of subjects				
number (not applicable)	43.6	43.1	40.3	

Statistical analyses

Statistical analysis title	Placebo, TAK-375SL 0.1 mg
Statistical analysis description:	
Odds ratio, 95% confidence intervals and p-values are analyzed from logistic regression with explanatory variables for treatment and baseline MADRS total score.	
Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.994
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.651
upper limit	1.53

Statistical analysis title	Placebo, TAK-375SL 0.4 mg
Statistical analysis description:	
Odds ratio, 95% confidence intervals and p-values are analyzed from logistic regression with explanatory variables for treatment and baseline MADRS total score.	
Comparison groups	Placebo v TAK-375SL 0.4 mg
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.575
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.886
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.352

Secondary: Percentage of Subjects in MADRS Remission

End point title	Percentage of Subjects in MADRS Remission

End point description:

MADRS remission is defined as a MADRS total score less than or equal to (<=) 10. The MADRS is a clinician rated, validated and widely used scale to measure overall severity of depressive symptoms. It consists of 10-item rated from 0 (normal) to 6 (most abnormal) with a total score range from 0 to 60, where higher scores indicate greater severity of symptoms. FAS included all randomized subjects who received at least 1 dose of double-blind study medication and who had a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy. LOCF method was used to impute missing data.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	167	176	
Units: percentage of subjects				
number (not applicable)	26.8	26.9	24.4	

Statistical analyses

Statistical analysis title	Placebo, TAK-375SL 0.1 mg

Statistical analysis description:

Odds ratio, 95% confidence intervals and p-values are analyzed from logistic regression with explanatory variables for treatment and baseline MADRS total score.

Comparison groups	Placebo v TAK-375SL 0.1 mg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.927
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.978
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.606
upper limit	1.577

Statistical analysis title	Placebo, TAK-375SL 0.4 mg

Statistical analysis description:

Odds ratio, 95% confidence intervals and p-values are analyzed from logistic regression with explanatory variables for treatment and baseline MADRS total score.

Comparison groups	Placebo v TAK-375SL 0.4 mg

Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.553
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.865
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.536
upper limit	1.397

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug.

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the subject or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

TAK-375SL (ramelteon) placebo-matching tablet, sublingually, once daily for up to 6 weeks.

Reporting group title	TAK-375SL 0.1 mg

Reporting group description:

TAK-375SL (ramelteon) 0.1 mg, tablet, sublingually, once daily for up to 6 weeks.

Reporting group title	TAK-375SL 0.4 mg

Reporting group description:

TAK-375SL (ramelteon) 0.4 mg, tablet, sublingually, once daily for up to 6 weeks.

Serious adverse events	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 184 (0.54%)	0 / 169 (0.00%)	5 / 182 (2.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 184 (0.00%)	0 / 169 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			
subjects affected / exposed	0 / 184 (0.00%)	0 / 169 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			

subjects affected / exposed	0 / 184 (0.00%)	0 / 169 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric symptom			
subjects affected / exposed	1 / 184 (0.54%)	0 / 169 (0.00%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 169 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 169 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	TAK-375SL 0.1 mg	TAK-375SL 0.4 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 184 (9.78%)	14 / 169 (8.28%)	10 / 182 (5.49%)
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 184 (9.78%)	14 / 169 (8.28%)	10 / 182 (5.49%)
occurrences (all)	19	20	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2012	Addition of vitals and Columbia-Suicide Severity Rating Scale during the safety follow-up visit to assess general health and suicide ideation/behavior.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 July 2014	An independent Data Monitoring Committee (DMC) performed a planned interim analysis of efficacy and safety data from this study. Results of the interim analysis indicated a lack of efficacy after 6 weeks double-blind treatment and the DMC advised that the un blinded interim data met the predefined efficacy criteria for study termination for futility. Therefore, the sponsor terminated the study early.	-

Notes:

Limitations and caveats

None reported