Clinical trial results:
A Phase IIa, Multicenter, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-6096 for Treatment Augmentation in Patients with Major Depressive Disorder

Summary

EudraCT number	2011-005200-15
Trial protocol	DE FI SE NO
Global end of trial date	03 September 2013

Results information

Result version number	v3 (current)
This version publication date	14 December 2017
First version publication date	21 January 2015
Version creation reason	• New data added to full data set The record has been updated to present final data following trial completion.

Trial information

Trial identification

Sponsor protocol code	6096-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01554176
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	03 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 September 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of filorexant (MK-6096) versus placebo as adjunctive treatment for major depressive disorder (MDD), in participants who are partial responders to antidepressant monotherapy with one of identified selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or bupropion. The primary hypothesis of the study is that filorexant is superior to placebo as augmentation therapy with respect to change from baseline to Week 6 in the Montgomery Asberg Depression Rating Scale (MADRS) total score. Participants were randomized to receive filorexant or placebo for a 6-week treatment period. After completion of the treatment period, participants entered a 2-week run-out period. For the run-out period, participants receiving placebo in treatment period continued to receive placebo and participants receiving filorexant in treatment period were randomized to receive either filorexant or placebo.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Participants will continue to take their pretrial antidepressant medication as prescribed throughout the trial.

Evidence for comparator: -

Actual start date of recruitment	18 May 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	Norway: 3
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	129
EEA total number of subjects	77

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)	129
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One participant in the Filorexant 10 mg (Treatment Phase) arm did not receive study drug and was discontinued from the study; the reason given for discontinuation was "non-compliance with study drug".

Pre-assignment

Screening details:

During the 1-2 week screening period participants will be evaluated to determine if they meet study entry criteria. The screening period will serve as a wash-out period for participants taking prohibited medications.

Period 1

Period 1 title	Treatment Phase
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	Filorexant 10 mg (Treatment Phase)

Arm description:

Treatment Phase: Participants in this group were administered filorexant 10 mg once daily at bedtime for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	filorexant
Investigational medicinal product code	
Other name	MK-6096
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Filorexant, one 10 mg tablet, orally, once daily at bedtime

Arm title	Placebo (Treatment Phase)

Arm description:

Treatment Phase: Participants in this group were administered placebo once daily at bedtime for 6 weeks.

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:

Placebo, one tablet, orally, once daily at bedtime

Number of subjects in period 1	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)
Started	65	64
Treated	64	64
Completed	57	59
Not completed	8	5
Physician decision	1	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	1
Lost to follow-up	3	-
Not treated: Non-compliance with study drug	1	-
Protocol deviation	1	2
Lack of efficacy	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)

Arm description:

Run-out Phase: Following completion of the 6-week treatment phase, participants in this group were administered filorexant 10 mg once daily at bedtime for 2 weeks. Participants in this group had received filorexant 10 mg once daily during the treatment phase.

Arm type	Experimental
Investigational medicinal product name	filorexant
Investigational medicinal product code	
Other name	MK-6096
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Filorexant, one 10 mg tablet, orally, once daily at bedtime

Arm title	Filorexant 10 mg/Placebo (Run-out Phase)

Arm description:

Run-out Phase: Following completion of the 6-week treatment phase, participants in this group were administered placebo once daily at bedtime for 2 weeks. Participants in this group had received filorexant 10 mg once daily during the treatment phase.

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:

Placebo, one tablet, orally, once daily at bedtime

Arm title	Placebo/Placebo (Run-out Phase)

Arm description:

Run-out Phase: Following completion of the 6-week Treatment Phase, participants in this group were administered placebo once daily at bedtime for 2 weeks. Participants in this group had received placebo once daily during the Treatment Phase.

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:

Placebo, one tablet, orally, once daily at bedtime

Number of subjects in period 2	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)	Filorexant 10 mg/Placebo (Run-out Phase)	Placebo/Placebo (Run-out Phase)
Started	29	28	59
Completed	29	27	59
Not completed	0	1	0
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Filorexant 10 mg (Treatment Phase)
Reporting group description:	
Treatment Phase: Participants in this group were administered filorexant 10 mg once daily at bedtime for 6 weeks.	
Reporting group title	Placebo (Treatment Phase)
Reporting group description:	
Treatment Phase: Participants in this group were administered placebo once daily at bedtime for 6 weeks.	

Reporting group values	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)	Total
Number of subjects	65	64	129
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	65	64	129
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.8	50	
standard deviation	± 12.4	± 10.3	-
Gender categorical Units: Subjects			
Female	40	42	82
Male	25	22	47

End points

End points reporting groups

Reporting group title	Filorexant 10 mg (Treatment Phase)
Reporting group description:	
Treatment Phase: Participants in this group were administered filorexant 10 mg once daily at bedtime for 6 weeks.	
Reporting group title	Placebo (Treatment Phase)
Reporting group description:	
Treatment Phase: Participants in this group were administered placebo once daily at bedtime for 6 weeks.	
Reporting group title	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)
Reporting group description:	
Run-out Phase: Following completion of the 6-week treatment phase, participants in this group were administered filorexant 10 mg once daily at bedtime for 2 weeks. Participants in this group had received filorexant 10 mg once daily during the treatment phase.	
Reporting group title	Filorexant 10 mg/Placebo (Run-out Phase)
Reporting group description:	
Run-out Phase: Following completion of the 6-week treatment phase, participants in this group were administered placebo once daily at bedtime for 2 weeks. Participants in this group had received filorexant 10 mg once daily during the treatment phase.	
Reporting group title	Placebo/Placebo (Run-out Phase)
Reporting group description:	
Run-out Phase: Following completion of the 6-week Treatment Phase, participants in this group were administered placebo once daily at bedtime for 2 weeks. Participants in this group had received placebo once daily during the Treatment Phase.	

Primary: Change from Baseline to Week 6 in MADRS Total Score

End point title	Change from Baseline to Week 6 in MADRS Total Score
End point description:	
The MADRS is a 10-item clinician-rated instrument for evaluating severity of symptoms of depression. Each item is rated on a scale from 0 to 6, with total scores ranging from 0-60; higher scores correspond to greater symptom severity. The reported measure is the mean change from baseline to Week 6 of the Treatment Phase; improvement in symptoms is represented by negative values.	
End point type	Primary
End point timeframe:	
Baseline and Week 6	

End point values	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[1]	61[2]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	30.3 (± 4.6)	31 (± 4.3)		
Change at Week 6	-11 (± 9.5)	-10.3 (± 8.2)		

Notes:

[1] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

[2] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

Statistical analyses

Statistical analysis title	Change from Baseline in MADRS Total Score - Week 6

Statistical analysis description:

Number of participants included for calculation of mean ± SD baseline and mean ± SD change from baseline MADRS Total Score is 119. Constrained longitudinal data analysis (cLDA) model uses efficacy Full Analysis Set (FAS) population (number of participants: filorexant 10 mg – 64, placebo – 64; total number of participants in cLDA analysis – 128). FAS includes participants who took ≥1 dose of study drug and had ≥1 evaluable efficacy measurement, including those who had only a baseline measurement.

Comparison groups	Filorexant 10 mg (Treatment Phase) v Placebo (Treatment Phase)
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679 [3]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	2.5

Notes:

[3] - cLDA model included terms for treatment, time, the interaction of time by treatment, severity of disease (Hamilton Depression Rating Scale, 17-items [HAM-D17] ≤20, >20) and insomnia severity index (ISI ≤14, >14).

Primary: Number of Participants With an Adverse Event (AE) During Treatment Phase

End point title	Number of Participants With an Adverse Event (AE) During Treatment Phase

End point description:

An AE is any unfavorable and unintended change in the structure, function or chemistry of the body temporally associated with study drug administration, whether or not considered related to the study drug. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with study drug administration, is also an AE. Participants with one or more AEs during the treatment phase (up to study Week 6) are counted once in this summary.

End point type	Primary

End point timeframe:

Up to Week 6

End point values	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[4]	64[5]		
Units: Participants	27	17		

Notes:

[4] - Includes participants who took ≥1 dose of study drug

[5] - Includes participants who took ≥1 dose of study drug

Statistical analyses

Statistical analysis title	Participants with AEs During Treatment Phase

Statistical analysis description:

Estimated parameter is between-group difference in percentage of participants with an AE = percentage (filorexant 10 mg) − percentage (placebo)

Comparison groups	Filorexant 10 mg (Treatment Phase) v Placebo (Treatment Phase)
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other[6]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentage incidence
Point estimate	15.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	31.4

Notes:

[6] - Between-group comparison of AE incidence rate

Primary: Number of Participants Who Discontinued Study Drug Due to an AE During Treatment Phase

End point title	Number of Participants Who Discontinued Study Drug Due to an AE During Treatment Phase

End point description:

An AE is any unfavorable and unintended change in the structure, function or chemistry of the body temporally associated with study drug administration, whether or not considered related to the study drug. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with study drug administration, is also an AE. Participants who discontinued study drug treatment due to an AE during the treatment phase (up to study Week 6) are counted once in this summary.

End point type	Primary

End point timeframe:

Up to Week 6

End point values	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[7]	64[8]		
Units: participants	1	1		

Notes:

[7] - Includes participants who received ≥1 dose of study drug

[8] - Includes participants who received ≥1 dose of study drug

Statistical analyses

Statistical analysis title	Drug Discontinuation Due to AE (Treatment Phase)

Statistical analysis description:

Estimated parameter is between-group difference in percentage of participants discontinued from study drug due to an AE = percentage (filorexant 10 mg) − percentage (placebo)

Comparison groups	Filorexant 10 mg (Treatment Phase) v Placebo (Treatment Phase)
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other[9]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentage incidence
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	7

Notes:

[9] - Between-group comparison of incidence rate of drug discontinuation due to AE

Primary: Number of Participants With an AE During Run-out Phase

End point title	Number of Participants With an AE During Run-out Phase[10]

End point description:

An AE is any unfavorable and unintended change in the structure, function or chemistry of the body temporally associated with study drug administration, whether or not considered related to the study drug. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with study drug administration, is also an AE. Participants with one or more AEs during the 2-week run-out phase and/or during the 2-week follow up after the last dose of study drug, are counted once in this summary.

End point type	Primary

End point timeframe:

From first run-out dose (following Week 6 visit) up to 14 days after last dose of study drug (approximately 4 weeks)

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)	Filorexant 10 mg/Placebo (Run-out Phase)	Placebo/Placebo (Run-out Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[11]	28[12]	59[13]	
Units: participants	6	3	9	

Notes:

[11] - Includes participants who took ≥1 dose of study drug in run-out phase

[12] - Includes participants who took ≥1 dose of study drug in run-out phase

[13] - Includes participants who took ≥1 dose of study drug in run-out phase

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Study Drug Due to an AE During Run-out Phase

End point title	Number of Participants Who Discontinued Study Drug Due to an AE During Run-out Phase[14]

End point description:

An AE is any unfavorable and unintended change in the structure, function or chemistry of the body temporally associated with study drug administration, whether or not considered related to the study drug. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with study drug administration, is also an AE. Participants who discontinued study drug treatment due to an AE during the 2-week run-out phase are counted once in this summary.

End point type	Primary

End point timeframe:

From first run-out dose (following Week 6 visit) up to Week 8 (2 weeks)

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)	Filorexant 10 mg/Placebo (Run-out Phase)	Placebo/Placebo (Run-out Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[15]	28[16]	59[17]	
Units: participants	0	0	0	

Notes:

[15] - Includes participants who took ≥1 dose of study drug in run-out phase

[16] - Includes participants who took ≥1 dose of study drug in run-out phase

[17] - Includes participants who took ≥1 dose of study drug in run-out phase

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 6 in MADRS Total Score Excluding the Sleep Item

End point title	Change from Baseline to Week 6 in MADRS Total Score Excluding the Sleep Item

End point description:

The MADRS is a 10-item clinician-rated instrument for evaluating severity of symptoms of depression. Each item is rated on a scale from 0 to 6, with higher scores indicating greater symptom severity. The total score ranged from 0 to 54, with higher scores corresponding to greater symptom severity. This measure considered 9 of the 10 MADRS items: apparent sadness, reported sadness, inner tension, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. It excluded "reduced sleep." The reported measure is the mean change from baseline to Week 6 of the Treatment Phase; improvement in symptoms is represented by negative values.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[18]	61[19]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	26.5 (± 4.1)	27.2 (± 4.1)		
Change at Week 6	-9.5 (± 8.5)	-9.1 (± 7.4)		

Notes:

[18] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

[19] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

Statistical analyses

Statistical analysis title	Change at Week 6; MADRS Score minus Sleep Item

Statistical analysis description:

For the calculation of mean ± SD for baseline and change at 6 weeks in MADRS Score excluding the sleep item, the number of participants included is 119. The cLDA model uses efficacy Full Analysis Set (FAS) population (number of participants: filorexant 10 mg – 64, placebo – 64; total number of participants in cLDA analysis – 128). FAS includes participants who took ≥1 dose of study drug and had ≥1 evaluable efficacy measurement, including those who had only a baseline measurement.

Comparison groups	Filorexant 10 mg (Treatment Phase) v Placebo (Treatment Phase)
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.82 [21]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	2.5

Notes:

[20] - Pairwise Comparison: Filorexant 10 mg vs. Placebo

[21] - cLDA model included terms for treatment, time, the interaction of time by treatment, severity of disease (Hamilton Depression Rating Scale, 17-items [HAM-D17] ≤20, >20) and insomnia severity index (ISI ≤14, >14).

Secondary: Change from Baseline to Week 6 in the Hamilton Depression Rating Scale, 17-item Version (HAM-D17) Bech Subscale Score

End point title	Change from Baseline to Week 6 in the Hamilton Depression Rating Scale, 17-item Version (HAM-D17) Bech Subscale Score

End point description:

The HAM-D, an instrument for evaluating severity of symptoms of depression, was completed by the participant. The instrument used in this study was the 17-item version (HAM-D17). The Bech subscale of the HAM-D17 is composed of 6 identified items out of the 17 items rated. Each item is rated on either a 3-point scale (0 to 2) or a 5-point scale (0 to 4). Total score ranged from 0 to 22, with a higher score indicating greater symptom severity. The following symptoms were rated on a 5-point scale (0-4): depressed mood, low self-esteem (guilt), work and interests, psychomotor retardation, and anxiety (psychic). The following symptom was rated on a 3-point scale (0-2): somatic symptoms (general). The reported measure is the change from baseline to Week 6 of the Treatment Phase; improvement in symptoms is represented by negative values.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[22]	61[23]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	13.1 (± 2.4)	13.0 (± 2.1)		
Change at Week 6	-4.7 (± 4.8)	-4.2 (± 4.0)		

Notes:

[22] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

[23] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

Statistical analyses

Statistical analysis title	Change at Week 6; HAM-D17 Bech Subscale Score

Statistical analysis description:

For the calculation of mean ± SD for baseline and change at 6 weeks in HAM-D17 Bech Subscale Score, the number of participants included is 117. The cLDA model uses efficacy Full Analysis Set (FAS) population (number of participants: filorexant 10 mg – 64, placebo – 64; total number of participants in cLDA analysis – 128). FAS includes participants who took ≥1 dose of study drug and had ≥1 evaluable efficacy measurement, including those who had only a baseline measurement.

Comparison groups	Filorexant 10 mg (Treatment Phase) v Placebo (Treatment Phase)
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.701 [25]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.3

Notes:

[24] - Pairwise Comparison: Filorexant 10 mg vs. Placebo

[25] - cLDA model included terms for treatment, time, the interaction of time by treatment, severity of disease (Hamilton Depression Rating Scale, 17-items [HAM-D17] ≤20, >20) and insomnia severity index (ISI ≤14, >14).

Secondary: Percentage of Participants with HAM-D17 Remission (HAM-D17 Total Score ≤7) at Week 6

End point title	Percentage of Participants with HAM-D17 Remission (HAM-D17 Total Score ≤7) at Week 6

End point description:

The HAM-D, an instrument for evaluating severity of symptoms of depression, was completed by the participant. The instrument used in this study was the 17-item version (HAM-D17). Each item is rated on either a 3-point scale (0 to 2) or a 5-point scale (0 to 4), with higher scores indicating greater symptom severity. Total score ranged from 0 to 54. The following symptoms were rated on a 5-point scale (0-4): depressed mood, low self-esteem (guilt), suicidal thoughts, work and interests, psychomotor retardation, psychomotor agitation, anxiety (psychic), anxiety (somatic), and hypochondriasis (somatization). The following symptoms were rated on a 3-point scale (0-2): insomnia (initial), insomnia (middle), insomnia (late), gastrointestinal symptoms (appetite), somatic symptoms (general), sexual disturbances, insight, and weight loss. A participant with HAM-D17 total score ≤7 at Week 6 of the Treatment Phase was defined to have achieved HAM-D17 remission.

End point type	Secondary

End point timeframe:

Week 6

End point values	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[26]	61[27]		
Units: percentage of participants				
number (not applicable)	21.4	9.8		

Notes:

[26] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

[27] - Includes participants who took ≥1 dose of study drug and had baseline and Week 6 value

Statistical analyses

Statistical analysis title	Odds Ratio for HAM-D17 Remission at Week 6

Statistical analysis description:

The odds ratio for HAM-D17 Remission at Week 6 was calculated from a generalized linear mixed effects model utilizing the efficacy Full Analysis Set (FAS) population (number of participants: filorexant 10 mg – 64, placebo – 64; total number of participants in analysis – 128). FAS includes participants who took ≥1 dose of study drug and had ≥1 evaluable efficacy measurement, including those who had only a baseline measurement.

Comparison groups	Filorexant 10 mg (Treatment Phase) v Placebo (Treatment Phase)
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.0965 [29]
Method	Generalized Linear Mixed Effects Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	7.3

Notes:

[28] - Pairwise Comparison: Filorexant 10 mg vs. Placebo

[29] - Generalized linear mixed effects model included terms for treatment, time, and treatment-by-time interaction.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

[Treatment Phase]: Up to Week 6. [Run-out Phase]: From first run-out dose (following Week 6 visit) up to 14 days after last dose of study drug (approximately 4 weeks)

Adverse event reporting additional description:

All Participants as Treated (APaT): Population includes participants who took ≥1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Filorexant 10 mg (Treatment Phase)

Reporting group description:

Treatment Phase: Participants in this group were administered filorexant 10 mg once daily at bedtime for 6 weeks.

Reporting group title	Placebo (Treatment Phase)

Reporting group description:

Treatment Phase: Participants in this group were administered placebo once daily at bedtime for 6 weeks.

Reporting group title	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)

Reporting group description:

Run-out Phase: Following completion of the 6-week treatment phase, participants in this group were administered filorexant 10 mg once daily at bedtime for 2 weeks. Participants in this group had received filorexant 10 mg once daily during the treatment phase.

Reporting group title	Filorexant 10 mg/Placebo (Run-out Phase)

Reporting group description:

Run-out Phase: Following completion of the 6-week treatment phase, participants in this group were administered placebo once daily at bedtime for 2 weeks. Participants in this group had received filorexant 10 mg once daily during the treatment phase.

Reporting group title	Placebo/Placebo (Run-out Phase)

Reporting group description:

Run-out Phase: Following completion of the 6-week treatment phase, participants in this group were administered placebo once daily at bedtime for 2 weeks. Participants in this group had received placebo once daily during the treatment phase.

Serious adverse events	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	0 / 29 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Presyncope			

subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	0 / 29 (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

Serious adverse events	Filorexant 10 mg/Placebo (Run-out Phase)	Placebo/Placebo (Run-out Phase)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	1 / 59 (1.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 28 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Filorexant 10 mg (Treatment Phase)	Placebo (Treatment Phase)	Filorexant 10 mg/Filorexant 10 mg (Run-out Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 64 (20.31%)	7 / 64 (10.94%)	3 / 29 (10.34%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 64 (0.00%)	4 / 64 (6.25%)	0 / 29 (0.00%)
occurrences (all)	0	4	0
Headache			

subjects affected / exposed	4 / 64 (6.25%)	5 / 64 (7.81%)	0 / 29 (0.00%)
occurrences (all)	5	6	0
Somnolence			
subjects affected / exposed	5 / 64 (7.81%)	0 / 64 (0.00%)	0 / 29 (0.00%)
occurrences (all)	5	0	0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	5 / 64 (7.81%)	1 / 64 (1.56%)	3 / 29 (10.34%)
occurrences (all)	5	1	3

Non-serious adverse events	Filorexant 10 mg/Placebo (Run-out Phase)	Placebo/Placebo (Run-out Phase)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)	1 / 59 (1.69%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 28 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 28 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 28 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 28 (3.57%)	1 / 59 (1.69%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2012	Amendment 02: Primary reason for amendment was to incorporate revisions to eligibility criteria and timing of HAM-D assessment at screening.
14 December 2012	Amendment 03: Primary reason for amendment was to incorporate revisions to eligibility criteria, which were intended to address issue of slow rate of enrollment of participants in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 June 2013	Study recruitment was terminated early due to slow rate of participant enrollment; overall study enrollment planned in protocol was not achieved.	-

Notes:

Limitations and caveats

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

Study recruitment was terminated early due to slow rate of participant enrollment.

Notes: