A Long-Term Safety Study of Org 50081 (Esmirtazapine) in Elderly Outpatients With Chronic Primary Insomnia (176005/P05697/MK-8265-001) (Jade)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier:
NCT00561574

First received: November 19, 2007
Last updated: May 18, 2015
Last verified: May 2015
History of Changes

Purpose

The current study is a 52-week safety study in elderly outpatients with chronic primary insomnia randomized to treatment with 1.5 mg or 3.0 mg of esmirtazapine (Org 50081, SCH 900265, MK-8265) to investigate the safety and tolerability of long-term treatment with esmirtazapine in elderly patients.

Condition	Intervention	Phase
Sleep Initiation and Maintenance Disorder; Elderly Mental Disorder Dyssomnias Sleep Disorders Sleep Disorder, Intrinsic	Drug: Esmirtazapine	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

Official Title: A Randomized Long-Term Safety Study of Org 50081 in Elderly Outpatients With Chronic Primary Insomnia Examining the Effects of 1.5 mg or 3.0 mg of Org 50081

Further study details as provided by Merck Sharp & Dohme Corp.:

Primary Outcome Measures:

- Number of Participants Who Experience at Least One Adverse Event (AE) [Time Frame: Up to 53 weeks] [Designated as safety issue: Yes]

  An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug.

- Number of Participants Who Discontinue Study Drug Due to an AE [Time Frame: Up to 52 weeks] [Designated as safety issue: Yes]

  An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug.

- Change From Baseline in Alertness at Awakening [Time Frame: Baseline and Week 52] [Designated as safety issue: Yes]

  Alertness at awakening was assessed by participants using a 0-100 mm visual analog scale (VAS) in response to Weekly Sleep Diary question 6 "How did you feel upon awakening over the past 7 days?". Scores could range from 0=Tired to 100=Alert. Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an observed cases (OC) approach.

- Change From Baseline in Feeling Full of Energy [Time Frame: Baseline and Week 52] [Designated as safety issue: Yes]

  Feeling full of energy was assessed by participants using a 0-100 mm visual analog scale (VAS) in response to Weekly Sleep Diary question 7 "How full of energy have you felt over the past 7 days?". Scores could range from 0=Terribly tired to 100=Full of energy. Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an OC approach.

- Change From Baseline in Ability to Work/Function [Time Frame: Baseline and Week 52] [Designated as safety issue: Yes]

  Ability to work/function was assessed by participants using a 0-100 mm visual analog scale (VAS) in response to Weekly Sleep Diary question 8 "How were you able to work or function over the past 7 days?". Scores could range from 0=Not at all to 100=Very well. Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an OC approach.

- Change From Baseline in Total Nap Time [Time Frame: Baseline and Week 52] [Designated as safety issue: Yes]

  Total nap time was assessed by participants in response to Weekly Sleep Diary question 9a "How much time per day did you nap, on average?". Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an OC approach.

Secondary Outcome Measures:

- Change From Baseline in Total Sleep Time (TST) [Time Frame: Baseline and Week 52] [Designated as safety issue: No]

  TST was defined as the time recorded by participants in response to Weekly Sleep Diary question 4 "During the past 7 nights, how much time did you actually spend sleeping, on average?". Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a last observation carried forward (LOCF) approach.

- Change From Baseline in Wake Time After Sleep Onset (WASO) [Time Frame: Baseline and Week 52] [Designated as safety issue: No]

  WASO was defined as the time recorded by participants in response to Weekly Sleep Diary question 4 "During the past 7 nights, how much time were you awake, on average, after falling asleep initially?" Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a LOCF approach.

- Change From Baseline in Sleep Latency (SL) [Time Frame: Baseline and Week 52] [Designated as safety issue: No]

  SL was defined as the time recorded by participants in response to Weekly Sleep Diary question 4 "During the past 7 nights, how long did it take you to fall asleep, on average?" Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a LOCF approach.

- Change From Baseline in Number of Awakenings (NAW) [Time Frame: Baseline and Week 52] [Designated as safety issue: No]

  NAW was defined as the time recorded by participants in response to Weekly Sleep Diary question 2a "During the past 7 nights, how many times did you wake up, on average?" Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a LOCF approach.

Enrollment:	259
Study Start Date:	January 2008
Study Completion Date:	February 2010
Primary Completion Date:	February 2010 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Esmirtazapine 1.5 mg	Drug: Esmirtazapine

Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks	One tablet daily
Experimental: Esmirtazapine 3.0 mg Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks	Drug: Esmirtazapine One tablet daily

Detailed Description:

Insomnia is a common complaint or disorder throughout the world. About one third of the population in the industrial countries reports difficulty initiating or maintaining sleep, resulting in a non-refreshing or non-restorative sleep. The majority of the insomniacs suffer chronically from their complaints.

The maleic acid salt of Org 4420, code name Org 50081 (esmirtazapine), was selected for development in the treatment of insomnia. The first clinical trial with esmirtazapine was a proof-of-concept trial with a four-way cross-over design. All 3 esmirtazapine dose groups showed a statistically significant positive effect on Total Sleep Time (TST) (objective and subjective) and Wake Time After Sleep Onset (WASO), as compared to placebo.

The current study is a 52-week safety study in elderly outpatients with chronic primary insomnia randomized to treatment with 1.5 mg or 3.0 mg of esmirtazapine to investigate the safety and tolerability of long-term treatment with esmirtazapine in elderly patients.

Eligibility

Ages Eligible for Study: 65 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- are at least 65 years of age at screening;
- sign written informed consent after the scope and nature of the investigation have been explained to them, before screening evaluations;
- are able to speak, read and understand the language of the investigator, study staff (including raters) and the informed consent form, and possess the ability to respond to questions, follow instructions and complete questionnaires;
- have demonstrated capability to independently complete the LogPad questionnaires in the week preceding randomization;
- normal bedtime should be within the 21:00 - 01:00 hour range, with no more variation than 2 hours for 5 nights out of 7;
- have a documented diagnosis of chronic primary insomnia, defined as fulfillment of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria for primary insomnia [DSM-IV-TR 307.42]) with a duration of >= 1 month;
- fulfill the following criteria based on medical or sleep history. Each of these criteria should be present for at least 3 nights per week for at least one month;
  - TST <= 6.5 hours
  - WASO >= 60 minutes
  - Sleep Latency (SL) >= 30 minutes

Exclusion Criteria:

- have other sleep disorders (DSM-IV-TR) e.g. rapid eye movement (REM) behavioral disorders, sleep related breathing disorders, periodic leg movement disorder, restless leg syndrome, narcolepsy, circadian sleep wake rhythm disorders, or any parasomnia;
- have any significant medical or DSM-IV-TR psychiatric illness causing the sleep disturbances;
- currently meet diagnostic criteria for DSM-IV-TR depression (Major Depressive Disorder [MDD]) or have been diagnosed and treated for MDD within the last 2 years;
- have signs of dementia or other serious cognitive impairment, defined by a score of less than 26 on the Mini-Mental State Examination (MMSE);
- have a history of bipolar disorder, a history of suicide attempt or a family history of suicide; A family history of suicide is defined as any history of suicide in the first and second degree family (parents, siblings, grandparents, or offspring), or a pattern of completed suicides (more than one) in the third degree family (aunts, uncles, nieces, and nephews);
- are night workers or rotating shift workers;
- are traveling, or have plans to travel, through more than three time zones during the trial, from the screening visit onwards;
- have a significant, unstable medical illness e.g. acute or chronic pain, hepatic, renal, metabolic or cardiac disease;
- have clinically relevant electrocardiogram (ECG) abnormalities at screening, as judged by the investigator;
- have clinically relevant abnormal hematology or biochemistry values at screening, as judged by the investigator;
- have DSM-IV-TR substance abuse or DSM-IV-TR addiction within the last year;
- drink more than 2 alcoholic drinks in a day. One drink is approximately equal to: 12 oz or 360 mL of beer (regular or light), or 4 oz or 120 mL of red or white wine, or 2 oz or 60 mL of desert wine (e.g. port, sherry), or 12 oz or 360 mL of wine cooler (regular or light), or 1 oz or 30 mL or

spirits (80 to 100 proof, e.g. whiskey, vodka);

- had serious head injury or stroke within the past year, or a history of (non-febrile) seizures;
- use psychotropic drugs affecting sleep within 2 weeks prior to randomization (fluoxetine: 5 weeks);
- use concomitant medication affecting sleep (see Protocol Section 3.4, Concomitant medication);
- smoke > 15 cigarettes per day and/or can not abstain from smoking during the night;
- drink excessive amounts of caffeinated beverages (more than 500 mg caffeine per day);
- have a positive urine drug screen at screening;
- are routinely sleeping during daytime (napping) for more than 60 minutes per day, 3 times/ week;
- have a body mass index (BMI) >= 36;
- have a known hypersensitivity to mirtazapine or to any of the excipients;
- participated in another clinical trial within the last 30 days prior to screening;
- participated in another clinical trial using esmirtazapine (Org 50081) at any time.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT00561574

Sponsors and Collaborators

Merck Sharp & Dohme Corp.

Investigators

Study Director: Medical Director Merck Sharp & Dohme Corp.

More Information

Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00561574 History of Changes
Other Study ID Numbers:	P05697 176005 2007-003636-35
Study First Received:	November 19, 2007
Results First Received:	June 5, 2014
Last Updated:	May 18, 2015
Health Authority:	United States: Food and Drug Administration

Keywords provided by Merck Sharp & Dohme Corp.:
elderly
randomized
double blind

Additional relevant MeSH terms:

Disease	Dyssomnias
Mental Disorders	Nervous System Diseases
Parasomnias	Neurologic Manifestations
Psychotic Disorders	Pathologic Processes
Sleep Disorders	Schizophrenia and Disorders with Psychotic Features
Sleep Disorders, Intrinsic	Signs and Symptoms
Sleep Initiation and Maintenance Disorders	

ClinicalTrials.gov processed this record on May 08, 2016

TO TOP

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First received: November 19, 2007
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History of Changes

Results First Received: June 5, 2014

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
Conditions:	Sleep Initiation and Maintenance Disorder; Elderly Mental Disorder Dyssomnias Sleep Disorders Sleep Disorder, Intrinsic
Intervention:	Drug: Esmirtazapine

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Participant Flow: Overall Study

	Esmirtazapine 1.5 mg	Esmirtazapine 3.0 mg
STARTED	**128**	**131**
COMPLETED	**80**	**73**
NOT COMPLETED	**48**	**58**
Adverse Event	**21**	**24**
Lack of Efficacy	**11**	**21**
Withdrawal by Subject	**4**	**4**
Reason Unrelated to Trial	**6**	**2**
Lost to Follow-up	**1**	**0**
Unspecified	**5**	**7**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks
Total	Total of all reporting groups

Baseline Measures

	Esmirtazapine 1.5 mg	Esmirtazapine 3.0 mg	Total
Number of Participants [units: participants]	**128**	**131**	**259**
Age [units: Years]	**70.7 (5.2)**	**71.1 (5.1)**	**70.9 (5.2)**

Mean (Standard Deviation)			
Gender [units: Participants]			
Female	**83**	**79**	**162**
Male	**45**	**52**	**97**

Outcome Measures

Hide All Outcome Measures

1. Primary: Number of Participants Who Experience at Least One Adverse Event (AE) [Time Frame: Up to 53 weeks]

Measure Type	Primary
Measure Title	Number of Participants Who Experience at Least One Adverse Event (AE)
Measure Description	An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug.
Time Frame	Up to 53 weeks
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The All-Subjects-Treated (AST) population consisted of all participants who received at least one dose of study drug.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Number of Participants Analyzed [units: participants]	**128**	**131**
Number of Participants Who Experience at Least One Adverse Event (AE) [units: Participants]	**115**	**116**

No statistical analysis provided for Number of Participants Who Experience at Least One Adverse Event (AE)

2. Primary: Number of Participants Who Discontinue Study Drug Due to an AE [Time Frame: Up to 52 weeks]

Measure Type	Primary

Measure Title	Number of Participants Who Discontinue Study Drug Due to an AE
Measure Description	An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug.
Time Frame	Up to 52 weeks
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The AST population consisted of all participants who received at least one dose of study drug.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Number of Participants Analyzed [units: participants]	**128**	**131**
Number of Participants Who Discontinue Study Drug Due to an AE [units: Participants]	**21**	**24**

No statistical analysis provided for Number of Participants Who Discontinue Study Drug Due to an AE

3. Primary: Change From Baseline in Alertness at Awakening [Time Frame: Baseline and Week 52]

Measure Type	Primary
Measure Title	Change From Baseline in Alertness at Awakening
Measure Description	Alertness at awakening was assessed by participants using a 0-100 mm visual analog scale (VAS) in response to Weekly Sleep Diary question 6 "How did you feel upon awakening over the past 7 days?". Scores could range from 0=Tired to 100=Alert. Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an observed cases (OC) approach.
Time Frame	Baseline and Week 52
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The AST population consisted of all participants who received at least one dose of study drug.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	Esmirtazapine 3.0 mg
Number of Participants Analyzed [units: participants]	**128**	**131**
Change From Baseline in Alertness at Awakening [units: Score on a Scale] Mean (Standard Deviation)		
Baseline (BL) (n=121, 123)	**38.3 (17.2)**	**38.3 (18.3)**
Change from BL at Week 52 (n=61, 53)	**25.6 (29.1)**	**21.7 (25.1)**

Statistical Analysis 1 for Change From Baseline in Alertness at Awakening

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Alertness at Awakening

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

	Two-sided significance level of 0.05

4. Primary: Change From Baseline in Feeling Full of Energy [Time Frame: Baseline and Week 52]

Measure Type	Primary
Measure Title	Change From Baseline in Feeling Full of Energy
Measure Description	Feeling full of energy was assessed by participants using a 0-100 mm visual analog scale (VAS) in response to Weekly Sleep Diary question 7 "How full of energy have you felt over the past 7 days?". Scores could range from 0=Terribly tired to 100=Full of energy. Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an OC approach.
Time Frame	Baseline and Week 52
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The AST population consisted of all participants who received at least one dose of study drug.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Number of Participants Analyzed [units: participants]	**128**	**131**
Change From Baseline in Feeling Full of Energy **[units: Score on a Scale]** **Mean (Standard Deviation)**		
BL (n=121, 123)	**42.6 (16.8)**	**43.3 (18.2)**
Change from BL at Week 52 (n=61, 53)	**20.1 (29.3)**	**20.8 (22.6)**

Statistical Analysis 1 for Change From Baseline in Feeling Full of Energy

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:

	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Feeling Full of Energy

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

5. Primary: Change From Baseline in Ability to Work/Function [Time Frame: Baseline and Week 52]

Measure Type	Primary
Measure Title	Change From Baseline in Ability to Work/Function
Measure Description	Ability to work/function was assessed by participants using a 0-100 mm visual analog scale (VAS) in response to Weekly Sleep Diary question 8 "How were you able to work or function over the past 7 days?". Scores could range from 0=Not at all to 100=Very well. Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an OC approach.
Time Frame	Baseline and Week 52
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The AST population consisted of all participants who received at least one dose of study drug.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	Esmirtazapine 3.0 mg
Number of Participants Analyzed [units: participants]	128	131
Change From Baseline in Ability to Work/Function [units: Score on a Scale] Mean (Standard Deviation)		
BL (n=121, 123)	46.9 (16.8)	45.9 (18.7)
Change from BL at Week 52 (n=61, 53)	19.7 (27.3)	21.7 (21.5)

Statistical Analysis 1 for Change From Baseline in Ability to Work/Function

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Ability to Work/Function

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

6. Primary: Change From Baseline in Total Nap Time [Time Frame: Baseline and Week 52]

Measure Type	Primary

Measure Title	Change From Baseline in Total Nap Time
Measure Description	Total nap time was assessed by participants in response to Weekly Sleep Diary question 9a "How much time per day did you nap, on average?". Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using an OC approach.
Time Frame	Baseline and Week 52
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The AST population consisted of all participants who received at least one dose of study drug.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Number of Participants Analyzed [units: participants]	**128**	**131**
Change From Baseline in Total Nap Time **[units: Minutes]** **Mean (Standard Deviation)**		
BL (n=48, 45)	**23.3 (16.0)**	**30.5 (31.6)**
Change from BL at Week 52 (n=18, 14)	**10.7 (65.2)**	**2.9 (16.3)**

Statistical Analysis 1 for Change From Baseline in Total Nap Time

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	0.3129

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Total Nap Time

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided
P Value [3]	0.3154

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

7. Secondary: Change From Baseline in Total Sleep Time (TST) [Time Frame: Baseline and Week 52]

Measure Type	Secondary
Measure Title	Change From Baseline in Total Sleep Time (TST)
Measure Description	TST was defined as the time recorded by participants in response to Weekly Sleep Diary question 4 "During the past 7 nights, how much time did you actually spend sleeping, on average?". Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a last observation carried forward (LOCF) approach.
Time Frame	Baseline and Week 52
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The Intent-To-Treat (ITT) population consisted of all participants who received at least one dose of study drug and had at least one postbaseline TST assessment.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Number of Participants Analyzed [units: participants]	**128**	**129**
Change From Baseline in Total Sleep Time (TST)		

[units: Minutes] Mean (Standard Deviation)		
BL (n=121,121)	294.3 (71.0)	292.3 (67.4)
Change from BL at Week 52 (n=123,128)	88.3 (89.5)	86.3 (96.3)

Statistical Analysis 1 for Change From Baseline in Total Sleep Time (TST)

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Total Sleep Time (TST)

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

8. Secondary: Change From Baseline in Wake Time After Sleep Onset (WASO) [Time Frame: Baseline and Week 52]

Measure Type	Secondary
Measure Title	Change From Baseline in Wake Time After Sleep Onset (WASO)
Measure Description	WASO was defined as the time recorded by participants in response to Weekly Sleep Diary question 4 "During the past 7 nights, how much time were you awake, on average, after falling asleep initially?" Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a LOCF approach.
Time Frame	Baseline and Week 52

Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The ITT population consisted of all participants who received at least one dose of study drug and had at least one postbaseline WASO assessment.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Number of Participants Analyzed [units: participants]	**128**	**129**
Change From Baseline in Wake Time After Sleep Onset (WASO) [units: Minutes] Mean (Standard Deviation)		
BL (n=121,121)	**110.2 (88.0)**	**102.4 (72.2)**
Change from BL at Week 52 (n=122,128)	**-62.7 (81.2)**	**-47.2 (84.9)**

Statistical Analysis 1 for Change From Baseline in Wake Time After Sleep Onset (WASO)

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Wake Time After Sleep Onset (WASO)

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided

P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

9. Secondary: Change From Baseline in Sleep Latency (SL) [Time Frame: Baseline and Week 52]

Measure Type	Secondary
Measure Title	Change From Baseline in Sleep Latency (SL)
Measure Description	SL was defined as the time recorded by participants in response to Weekly Sleep Diary question 4 "During the past 7 nights, how long did it take you to fall asleep, on average?" Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a LOCF approach.
Time Frame	Baseline and Week 52
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The ITT population consisted of all participants who received at least one dose of study drug and had at least one postbaseline SL assessment.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Number of Participants Analyzed [units: participants]	**128**	**129**
Change From Baseline in Sleep Latency (SL) **[units: Minutes]** **Mean (Standard Deviation)**		
BL (n=121,121)	**89.8 (73.6)**	**92.5 (79.1)**
Change from BL at Week 52 (n=123,128)	**-26.1 (99.2)**	**-22.2 (101.3)**

Statistical Analysis 1 for Change From Baseline in Sleep Latency (SL)

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	<0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Sleep Latency (SL)

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided
P Value [3]	0.0001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

10. Secondary: Change From Baseline in Number of Awakenings (NAW) [Time Frame: Baseline and Week 52]

Measure Type	Secondary
Measure Title	Change From Baseline in Number of Awakenings (NAW)
Measure Description	NAW was defined as the time recorded by participants in response to Weekly Sleep Diary question 2a "During the past 7 nights, how many times did you wake up, on average?" Baseline was defined as the Day 1 assessment of Days -7 to 1 before any study drug was taken. Change from Baseline was calculated using a LOCF approach.
Time Frame	Baseline and Week 52
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The ITT population consisted of all participants who received at least one dose of study drug and had at least one postbaseline NAW assessment.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Measured Values

	Esmirtazapine 1.5 mg	Esmirtazapine 3.0 mg
Number of Participants Analyzed [units: participants]	**128**	**129**
Change From Baseline in Number of Awakenings (NAW) [units: Number of Awakenings] Mean (Standard Deviation)		
BL (n=118,114)	**2.5 (1.4)**	**2.6 (1.3)**
Change from BL at Week 52 (n=114, 109)	**-0.3 (1.3)**	**-0.4 (1.2)**

Statistical Analysis 1 for Change From Baseline in Number of Awakenings (NAW)

Groups [1]	Esmirtazapine 1.5 mg
Method [2]	t-test, 2 sided
P Value [3]	0.0116

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Statistical Analysis 2 for Change From Baseline in Number of Awakenings (NAW)

Groups [1]	Esmirtazapine 3.0 mg
Method [2]	t-test, 2 sided
P Value [3]	0.0004

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.

[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Two-sided significance level of 0.05

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Up to 30 days after last dose of study drug for serious AEs. Up to 7 days after last dose of study drug for non-serious AEs
Additional Description	No text entered.

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Serious Adverse Events

	Esmirtazapine 1.5 mg	Esmirtazapine 3.0 mg
Total, serious adverse events		
# participants affected / at risk	**9/128 (7.03%)**	**6/131 (4.58%)**
Cardiac disorders		
Atrial fibrillation † 1		
# participants affected / at risk	**0/128 (0.00%)**	**1/131 (0.76%)**
# events	**0**	**1**
Cardiac failure † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Coronary artery occlusion † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Hypertensive heart disease † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Mitral valve incompetence † 1		
# participants affected / at risk	**0/128 (0.00%)**	**1/131 (0.76%)**
# events	**0**	**1**
Gastrointestinal disorders		
Haemorrhoidal haemorrhage † 1		
# participants affected / at risk	**2/128 (1.56%)**	**0/131 (0.00%)**
# events	**2**	**0**

General disorders		
Chest pain † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Hernia † 1		
# participants affected / at risk	**0/128 (0.00%)**	**1/131 (0.76%)**
# events	**0**	**1**
Infections and infestations		
Diverticulitis † 1		
# participants affected / at risk	**0/128 (0.00%)**	**1/131 (0.76%)**
# events	**0**	**1**
Pneumonia † 1		
# participants affected / at risk	**1/128 (0.78%)**	**1/131 (0.76%)**
# events	**1**	**1**
Injury, poisoning and procedural complications		
Contusion † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Fall † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Narcotic intoxication † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Musculoskeletal and connective tissue disorders		
Intervertebral disc protrusion † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Glioma † 1		
# participants affected / at risk	**0/128 (0.00%)**	**1/131 (0.76%)**
# events	**0**	**1**
Nervous system disorders		
Dizziness † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**
Surgical and medical procedures		
Angioplasty † 1		
# participants affected / at risk	**0/128 (0.00%)**	**1/131 (0.76%)**
# events	**0**	**1**
Knee arthroplasty † 1		
# participants affected / at risk	**1/128 (0.78%)**	**0/131 (0.00%)**
# events	**1**	**0**

Vascular disorders		
Temporal arteritis † 1		
# participants affected / at risk	**0/128 (0.00%)**	**1/131 (0.76%)**
# events	**0**	**1**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA 12.1

Other Adverse Events

Hide Other Adverse Events

Time Frame	Up to 30 days after last dose of study drug for serious AEs. Up to 7 days after last dose of study drug for non-serious AEs
Additional Description	No text entered.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Esmirtazapine 1.5 mg	Participants receive esmirtazapine 1.5 mg tablets, one tablet administered orally once daily for up to 52 weeks
Esmirtazapine 3.0 mg	Participants receive esmirtazapine 3.0 mg tablets, one tablet administered orally once daily for up to 52 weeks

Other Adverse Events

	Esmirtazapine 1.5 mg	**Esmirtazapine 3.0 mg**
Total, other (not including serious) adverse events		
# participants affected / at risk	**83/128 (64.84%)**	**102/131 (77.86%)**
Gastrointestinal disorders		
Diarrhoea † 1		
# participants affected / at risk	**7/128 (5.47%)**	**9/131 (6.87%)**
# events	**7**	**9**
Dry mouth † 1		
# participants affected / at risk	**10/128 (7.81%)**	**14/131 (10.69%)**
# events	**13**	**15**
General disorders		
Fatigue † 1		
# participants affected / at risk	**17/128 (13.28%)**	**15/131 (11.45%)**
# events	**18**	**18**
Infections and infestations		
Nasopharyngitis † 1		

# participants affected / at risk	21/128 (16.41%)	17/131 (12.98%)
# events	26	21
Urinary tract infection † 1		
# participants affected / at risk	2/128 (1.56%)	10/131 (7.63%)
# events	3	10
Investigations		
Weight increased † 1		
# participants affected / at risk	11/128 (8.59%)	20/131 (15.27%)
# events	13	20
Metabolism and nutrition disorders		
Increased appetite † 1		
# participants affected / at risk	5/128 (3.91%)	12/131 (9.16%)
# events	7	15
Musculoskeletal and connective tissue disorders		
Arthralgia † 1		
# participants affected / at risk	6/128 (4.69%)	9/131 (6.87%)
# events	6	11
Back pain † 1		
# participants affected / at risk	8/128 (6.25%)	8/131 (6.11%)
# events	9	11
Nervous system disorders		
Dizziness † 1		
# participants affected / at risk	12/128 (9.38%)	19/131 (14.50%)
# events	13	21
Headache † 1		
# participants affected / at risk	13/128 (10.16%)	12/131 (9.16%)
# events	14	13
Restless legs syndrome † 1		
# participants affected / at risk	3/128 (2.34%)	8/131 (6.11%)
# events	3	8
Respiratory, thoracic and mediastinal disorders		
Cough † 1		
# participants affected / at risk	8/128 (6.25%)	3/131 (2.29%)
# events	9	3
Vascular disorders		
Hypertension † 1		
# participants affected / at risk	3/128 (2.34%)	11/131 (8.40%)
# events	3	12

† Events were collected by systematic assessment

1 Term from vocabulary, MedDRA 12.1

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data

No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

- [x] The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.
- [ ] The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.
- [ ] Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Title: Senior Vice President, Global Clinical Development
Organization: Merck Sharp & Dohme Corp.
phone: 1-800-672-6372
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Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00561574 History of Changes
Other Study ID Numbers:	P05697 176005 (Other Identifier: Organon Protocol Number) 2007-003636-35 (EudraCT Number)
Study First Received:	November 19, 2007
Results First Received:	June 5, 2014
Last Updated:	May 18, 2015
Health Authority:	United States: Food and Drug Administration

TO TOP

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