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Dose-Finding Safety and Efficacy Trial of Org 50081 (Esmirtazapine) in the Treatment of Vasomotor Symptoms (177001/P06472/MK-8265-013)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

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

ClinicalTrials.gov Identifier:
NCT00535288

First received: September 24, 2007
Last updated: May 27, 2015
Last verified: May 2015
History of Changes

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Purpose

To investigate efficacy and safety of 4 doses of esmirtazapine, compared to placebo, in the treatment of moderate to severe hot flushes (vasomotor symptoms) associated with the menopause. Co-primary efficacy endpoints are the frequency and severity of hot flushes after 4 and 12 weeks as compared to Baseline.

Condition	Intervention	Phase
Postmenopausal Symptoms Menopause Vasomotor Symptoms	Drug: Esmirtazapine Drug: Placebo	Phase 3

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

Official Title: A Multicenter, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Four Different Doses of Org 50081 in the Treatment of Moderate to Severe Vasomotor Symptoms Associated With the Menopause

Resource links provided by NLM:

MedlinePlus related topics: Menopause

U.S. FDA Resources

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

Primary Outcome Measures:

- Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4
  [Time Frame: Baseline and Week 4] [Designated as safety issue: No]

  Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on an electronic diary card (LogPad®) on a daily basis during screening and treatment. Frequency Score A was based on the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (last observation carried forward, or LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

- Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4
  [Time Frame: Baseline and Week 4] [Designated as safety issue: No]

  Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score A was calculated as the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of moderate and severe hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

- Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12
  [Time Frame: Baseline and Week 12] [Designated as safety issue: No]

  Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on a LogPad on a daily basis during screening and treatment. Frequency Score A was based on the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

- Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12
  [Time Frame: Baseline and Week 12] [Designated as safety issue: No]

  Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score A was calculated as the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of moderate and severe hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

Secondary Outcome Measures:

- Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) by Week Excluding Weeks 4 and 12 [Time Frame: Baseline and Up to Week 12] [Designated as safety issue: No]

  Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on a LogPad on a daily basis during screening and treatment. Frequency Score A was based on the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

- Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) by Week Excluding Weeks 4 and 12 [Time Frame: Baseline and up to Week 12] [Designated as safety issue: No]

  Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score A was calculated as the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of moderate and severe hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

- Change From Baseline in Average Daily Moderate/Severe Composite Score (Composite Score A) by Week [Time Frame: Baseline and up to

Week 12] [Designated as safety issue: No]

Composite Score A was calculated as Severity Score A x Frequency Score A.

- Change From Baseline in Average Daily Frequency of Mild to Severe Vasomotor Symptoms (Frequency Score B) by Week [Time Frame: Baseline and up to Week 12] [Designated as safety issue: No]

  Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on a LogPad on a daily basis during screening and treatment. Frequency Score B was based on the number of mild hot flushes + the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

- Change From Baseline in Average Daily Severity of Mild to Severe Vasomotor Symptoms (Severity Score B) by Week [Time Frame: Baseline and up to Week 12] [Designated as safety issue: No]

  Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score B was calculated as the number of mild hot flushes + the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of all hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.

- Change From Baseline in Average Daily Mild to Severe Composite Symptoms Score (Composite Score B) by Week [Time Frame: Baseline and up to Week 12] [Designated as safety issue: No]

  Composite Score B was calculated as Severity Score B x Frequency Score B.

- Total Number of Responders by Week [Time Frame: Up to 12 weeks] [Designated as safety issue: No]

  A participant was defined as a (hot flush) responder for a study week if a reduction of at least 50% for average daily frequency of moderate/severe vasomotor symptoms (hot flushes) (Frequency Score A) compared to Baseline was recorded. A study week was taken into account if at least 4 days were completely observed. The last observation was carried forward if there were less than 4 complete days observed. In cases where Week 1 did not have 4 days that were completely observed, the participant was considered a non-responder. An LOCF approach was used.

- Total Number of Remitters by Week [Time Frame: Up to 12 weeks] [Designated as safety issue: No]

  A participant was defined as a (hot flush) remitter for a study week if at most one moderate/severe vasomotor symptom per day on average was recorded. A study week was taken into account if at least 4 days were completely observed. The last observation was carried forward if there were less than 4 complete days observed. In cases where Week 1 did not have 4 days that were completely observed, the participant was considered a non-remitter.

- Change From Baseline in Women's Health Questionnaire (WHQ) Sleep Problems Symptoms Domain Score at Week 12 [Time Frame: Baseline and Week 12] [Designated as safety issue: No]

  The WHQ is a 36-item, user-friendly, and rapid way of assessing nine domains of physical and emotional health for mid-aged women. Participants self-administered the WHQ questionnaire; scoring is based on a 4-point scale as follows: 'Yes definitely=1', 'Yes sometimes=2', 'No not much=3' and 'No not at all=4'. Each score is transformed to a value '1' for scores '1' and '2' and to a value '0' for scores '3' and '4'. Sleep problems encompass Items 1, 11, and 29 of the 36 total items. The transformed sums of items 1, 11, and 29 were divided by 3 to get the score; therefore, the domain ranges from 0 to 1, where lower values are better.

- Change From Baseline in WHQ Vasomotor Symptoms Domain Score at Week 12 [Time Frame: Baseline and Week 12] [Designated as safety issue: No]

  The WHQ is a 36-item, user-friendly, and rapid way of assessing nine domains of physical and emotional health for mid-aged women. Participants self-administered the WHQ questionnaire; scoring is based on a 4-point scale as follows: 'Yes definitely=1', 'Yes sometimes=2', 'No not much=3' and 'No not at all=4'. Each score is transformed to a value '1' for scores '1' and '2' and to a value '0' for scores '3' and '4'. Vasomotor symptoms encompass Items 19 and 27 of the 36 total items. The transformed sums of items 19+27 are divided by 2 to get the score; therefore, the domain ranges from 0 to 1, where lower values are better.

Enrollment:	946
Study Start Date:	September 2004

Study Completion Date: January 2006
Primary Completion Date: January 2006 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Placebo Comparator: Placebo Participants receive encapsulated tablets, orally, once daily (QD) for up to 12 weeks.	Drug: Placebo Encapsulated placebo tablets in Swedish Orange hard gelatin DB-B capsules for blinding purposes. Encapsulated tablets were administered orally once daily in the evening prior to sleep for 12 weeks.
Experimental: Esmirtazapine 2.25 mg Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.	Drug: Esmirtazapine Four different doses (2.25, 4.5, 9.0, and 18 mg) encapsulated esmirtazapine tablets in Swedish Orange hard gelatin DB-B capsules for blinding purposes. Encapsulated tablets were administered orally once daily in the evening prior to sleep for 12 weeks. Other Names: • Esmirtazapine maleate • SCH 900265 • Org 50081
Experimental: Esmirtazapine 4.5 mg Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.	Drug: Esmirtazapine Four different doses (2.25, 4.5, 9.0, and 18 mg) encapsulated esmirtazapine tablets in Swedish Orange hard gelatin DB-B capsules for blinding purposes. Encapsulated tablets were administered orally once daily in the evening prior to sleep for 12 weeks. Other Names: • Esmirtazapine maleate • SCH 900265 • Org 50081
Experimental: Esmirtazapine 9 mg Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.	Drug: Esmirtazapine Four different doses (2.25, 4.5, 9.0, and 18 mg) encapsulated esmirtazapine tablets in Swedish Orange hard gelatin DB-B capsules for blinding purposes. Encapsulated tablets were administered orally once daily in the evening prior to sleep for 12 weeks. Other Names: • Esmirtazapine maleate • SCH 900265 • Org 50081
Experimental: Esmirtazapine 18 mg Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.	Drug: Esmirtazapine Four different doses (2.25, 4.5, 9.0, and 18 mg) encapsulated esmirtazapine tablets in Swedish Orange hard gelatin DB-B capsules for blinding purposes. Encapsulated tablets were administered orally once daily in the evening prior to sleep for 12 weeks. Other Names: • Esmirtazapine maleate • SCH 900265 • Org 50081

Detailed Description:

The most direct treatment of hot flushes may be by means of 5-HT2A receptor antagonist. Mirtazapine is a potent blocker of 5-HT2A receptors and was found to be effective in reducing the number and intensity of hot flushes in preliminary trials. Also several Selective Serotonin Reuptake Inhibitors (SSRIs) and other similar compounds have been investigated to manage hot flushes, confirming the role of the serotonergic system. In the present trial, the efficacy and safety of four different doses of esmirtazapine compared to placebo were investigated in women with moderate to severe vasomotor symptoms associated with the menopause. The primary objective of this trial was to demonstrate superior efficacy in at least one of the four doses of esmirtazapine as compared to placebo on the four following co-primary endpoints: 1) the mean change from baseline in average daily frequency of moderate and severe vasomotor symptoms at Week 4; 2) the mean change from baseline in average daily frequency of moderate and severe vasomotor symptoms at Week 12; 3) the mean change from baseline in average daily severity of moderate and severe vasomotor symptoms at Week 4; 4) the mean change from baseline in average daily severity of moderate and severe vasomotor symptoms at

Week 12. The number and severity of hot flushes was recorded by means of electronic diary by the subjects.

Eligibility

Ages Eligible for Study:	40 Years to 65 Years
Genders Eligible for Study:	Female
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Postmenopausal women, defined as:
  - 12 months of spontaneous amenorrhea;
  - OR 6 months of spontaneous amenorrhea with serum Follicle Stimulating Hormone (FSH) levels >40 mIU/mL;
  - OR 6 weeks post surgical bilateral oophorectomy with or without hysterectomy.
- Be ≥ 40 and ≤ 65 years of age;
- Have a body mass index (BMI) ≥ 18 and ≤ 32 kg/m^2;
- Minimum of 7 moderate to severe hot flushes per day or 50 per week, as quantified from daily diary recordings during at least 7 days preceding randomization to trial medication;
- Able to handle the electronic diary device after training and having at least 80% compliance on complete daily diary entries during the period prior to randomization;
- Give voluntary written Informed Consent (IC) after the scope and nature of the investigation had been explained, before screening evaluations.

Exclusion Criteria:

- History or presence of any malignancy, except non-melanoma skin cancers;
- Any clinically unstable or uncontrolled renal, hepatic, endocrine, respiratory, hematological, neurological, cardiovascular or cerebrovascular disease that would put the subject at safety risk or mask measure of efficacy;
- History of seizures or epilepsy;
- History or presence of clinically significant depression or other psychiatric disorder which, in the opinion of the investigator, might compromise or confound the subject's participation in the trial;
- Abnormal clinically relevant vaginal bleeding;
- Any clinically relevant (opinion of investigator) abnormal finding during physical, gynecological and breast examination at screening;
- Abnormal, clinically significant results of mammography;
- Abnormal cervical smear test results (corresponding to Pap III and higher, including Low-Grade Squamous Intraepithelial Lesion (LSIL), High-Grade Squamous Intraepithelial Lesion (HSIL), Cervical Intraepithelial Neoplasia (CIN) 1 and higher);
- Hematological or biochemical values at screening outside the reference ranges considered clinically relevant in the opinion of the investigator;
- High Blood Pressure (BP);
- Use of any drug product containing estrogens, progestins, androgens or tibolone prior to screening (and up to and including randomization) within a pre-specified period;
- Any of the following treatments within the last 4 weeks prior to screening (and up to and including randomization):
  - tricyclic antidepressants, Serotonin Noradrenergic Reuptake Inhibitors (SNRIs), SSRIs, Monoamine Oxidase (MAO)-inhibitors, mirtazapine
  - antianxiety drugs, antipsychotics
  - coumarin-derivatives
  - α-adrenergic agents
  - β-blockers
  - dopamine agonists/antagonists
  - opiates, barbiturates
  - raloxifene
  - homeopathic menopausal preparations or other preparations intended to treat climacteric or Central Nervous System (CNS) symptoms
  - hepatic microsomal enzyme-inducing drugs or drugs known to affect or interfere with the pharmacokinetics of mirtazapine;
- Any condition or disease that could affect or interfere with the pharmacokinetics of mirtazapine;
- Subjects sensitive to trial medication or its components;
- Use of any investigational drug and/or participation in another clinical trial within the last eight weeks prior to screening;
- History of alcohol and/or drug abuse within the last two years prior to screening.

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: NCT00535288

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:	NCT00535288 History of Changes
Other Study ID Numbers:	P06472 White Moonstone 177001
Study First Received:	September 24, 2007
Results First Received:	June 16, 2014
Last Updated:	May 27, 2015
Health Authority:	United States: Food and Drug Administration Belgium: Federal Agency for Medicinal Products and Health Products Brazil: Ministry of Health Canada: Health Canada Czech Republic: State Institute for Drug Control Denmark: Danish Medicines Agency Hungary: National Institute of Pharmacy Netherlands: Medicines Evaluation Board (MEB) Norway: Norwegian Medicines Agency Slovakia: State Institute for Drug Control Spain: Spanish Agency of Medicines Switzerland: Swissmedic United Kingdom: Medicines and Healthcare Products Regulatory Agency

ClinicalTrials.gov processed this record on April 20, 2016

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Dose-Finding Safety and Efficacy Trial of Org 50081 (Esmirtazapine) in the Treatment of Vasomotor Symptoms (177001/P06472/MK-8265-013)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
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ClinicalTrials.gov Identifier:
NCT00535288

First received: September 24, 2007
Last updated: May 27, 2015
Last verified: May 2015
History of Changes

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Results First Received: June 16, 2014

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Conditions:	Postmenopausal Symptoms Menopause Vasomotor Symptoms
Interventions:	Drug: Esmirtazapine Drug: Placebo

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
946 participants were randomly assigned in this study, however, one participant assigned to placebo never received treatment and one

participant assigned to placebo actually received esmirtazapine 18 mg and is included in that group for all study analyses.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, once daily (QD) for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.

Participant Flow: Overall Study

	Placebo	Esmirtazapine 2.25 mg	Esmirtazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg
STARTED	314 [1]	162	160	151	158 [2]
COMPLETED	260	130	127	122	116
NOT COMPLETED	54	32	33	29	42
Adverse Event	20	19	25	20	30
Lost to Follow-up	0	3	0	0	0
Lack of Efficacy	26	3	4	4	7
Unwilling to cooperate	6	6	3	3	4
Not specified	2	1	1	2	1

[1] 2 participants randomized to receive placebo did not receive placebo
[2] One participant randomized to receive placebo received esmirtazapine 18 mg.

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
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.

Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.
Total	Total of all reporting groups

Baseline Measures

	Placebo	Esmirtazapine 2.25 mg	Esmirtazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg	Total
Number of Participants [units: participants]	314	162	160	151	158	945
Age [units: Years] Mean (Standard Deviation)	53.5 (4.9)	53.8 (5.0)	53.7 (4.8)	54.7 (4.6)	53.5 (4.7)	53.8 (4.8)
Gender [units: Participants]						
Female	314	162	160	151	158	945
Male	0	0	0	0	0	0

Outcome Measures

Hide All Outcome Measures

1. Primary: Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4 [Time Frame: Baseline and Week 4]

Measure Type	Primary
Measure Title	Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4
Measure Description	Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on an electronic diary card (LogPad®) on a daily basis during screening and treatment. Frequency Score A was based on the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (last observation carried forward, or LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and Week 4
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, once daily (QD) for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12

	weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	Esmirtazapine 2.25 mg	Esmirtazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4 [units: Events per day] Mean (Standard Deviation)					
Baseline	**12.1 (5.1)**	**12.2 (5.1)**	**12.6 (4.7)**	**12.3 (4.4)**	**11.5 (4.7)**
Week 4	**-3.8 (4.5)**	**-5.1 (4.1)**	**-5.7 (4.8)**	**-5.3 (3.8)**	**-5.6 (4.4)**

Statistical Analysis 1 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 2.25 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-1.2
95% Confidence Interval	-2.2 to -0.2

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 4.5 mg
Method [2]	ANCOVA

P Value [3]	<0.01
Difference between least squares means [4]	-1.7
95% Confidence Interval	-2.7 to -0.7

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 3 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 9 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-1.4
95% Confidence Interval	-2.4 to -0.4

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 4 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 18 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-1.9
95% Confidence Interval	-2.9 to -0.9

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate
[4]	Other relevant estimation information:
	No text entered.

2. Primary: Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4 [Time Frame: Baseline and Week 4]

Measure Type	Primary
Measure Title	Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4
Measure Description	Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score A was calculated as the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of moderate and severe hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and Week 4
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	**Esmirtazapine**	**Esmirtazapine**	**Esmirtazapine**	**Esmirtazapine**

		2.25 mg	4.5 mg	9 mg	18 mg
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4 [units: Severity score] Mean (Standard Deviation)					
Baseline	**2.45 (0.30)**	**2.45 (0.30)**	**2.45 (0.32)**	**2.46 (0.30)**	**2.40 (0.27)**
Week 4	**-0.07 (0.20)**	**-0.14 (0.23)**	**-0.13 (0.23)**	**-0.15 (0.24)**	**-0.15 (0.23)**

Statistical Analysis 1 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 2.25 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-0.07
95% Confidence Interval	-0.12 to -0.01

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 4.5 mg
Method [2]	ANCOVA
P Value [3]	0.02
Difference between least squares means [4]	-0.06
95% Confidence Interval	-0.11 to -0.01

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity

[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 3 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 9 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-0.07
95% Confidence Interval	-0.13 to -0.02

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 4 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 4

Groups [1]	Placebo vs. Esmirtazapine 18 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-0.08
95% Confidence Interval	-0.14 to -0.03

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

3. Primary: Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12 [Time Frame: Baseline and Week 12]

Measure Type	Primary
Measure Title	Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12
Measure Description	Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on a LogPad on a daily basis during screening and treatment. Frequency Score A was based on the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, once daily QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12 [units: Events per day] Mean (Standard Deviation)					
Baseline	**12.1 (5.1)**	**12.2 (5.1)**	**12.6 (4.7)**	**12.3 (4.4)**	**11.5 (4.7)**
Week 12	**-4.2 (5.3)**	**-5.2 (4.6)**	**-6.0 (4.9)**	**-5.8 (4.3)**	**-6.0 (4.6)**

Statistical Analysis 1 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 2.25 mg
Method [2]	ANCOVA
P Value [3]	0.08
Difference between least squares means [4]	-1.0
95% Confidence Interval	-2.1 to 0.1

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 4.5 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-1.6
95% Confidence Interval	-2.7 to -0.5

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 3 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 9 mg
Method [2]	ANCOVA

P Value [3]	<0.01
Difference between least squares means [4]	-1.5
95% Confidence Interval	-2.7 to -0.4

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 4 for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 18 mg
Method [2]	ANCOVA
P Value [3]	<0.01
Difference between least squares means [4]	-2.0
95% Confidence Interval	-3.1 to -0.9

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline frequency
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

4. Primary: Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12 [Time Frame: Baseline and Week 12]

Measure Type	Primary
Measure Title	Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12
Measure Description	Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with

	sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score A was calculated as the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of moderate and severe hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12 [units: Severity score] Mean (Standard Deviation)					
Baseline	**2.45 (0.30)**	**2.45 (0.30)**	**2.45 (0.32)**	**2.46 (0.30)**	**2.40 (0.27)**
Week 12	**-0.08 (0.26)**	**-0.15 (0.27)**	**-0.13 (0.27)**	**-0.13 (0.26)**	**-0.15 (.026)**

Statistical Analysis 1 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 2.25 mg
Method [2]	ANCOVA
P Value [3]	0.07
Difference between least squares means [4]	-0.06

95% Confidence Interval	-0.12 to 0.00

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 4.5 mg
Method [2]	ANCOVA
P Value [3]	0.24
Difference between least squares means [4]	-0.05
95% Confidence Interval	-0.11 to 0.02

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 3 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 9 mg
Method [2]	ANCOVA
P Value [3]	0.29
Difference between least squares means [4]	-0.04
95% Confidence Interval	-0.11 to 0.02

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity

[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 4 for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) at Week 12

Groups [1]	Placebo vs. Esmirtazapine 18 mg
Method [2]	ANCOVA
P Value [3]	0.02
Difference between least squares means [4]	-0.07
95% Confidence Interval	-0.14 to -0.01

[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:
	Factors for treatment group and (pooled) center and a covariate for the baseline severity
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Confidence intervals and p-values were adjusted by (2-sided) Dunnett many-to-one comparison at 0.05 overall Type 1 error rate.
[4]	Other relevant estimation information:
	No text entered.

5. Secondary: Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) by Week Excluding Weeks 4 and 12 [Time Frame: Baseline and Up to Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) by Week Excluding Weeks 4 and 12
Measure Description	Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on a LogPad on a daily basis during screening and treatment. Frequency Score A was based on the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and Up to Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the

number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	Esmirtazapine 2.25 mg	Esmirtazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) by Week Excluding Weeks 4 and 12 [units: Events per day] Mean (Standard Deviation)					
Baseline	**12.10 (5.10)**	**12.19 (5.07)**	**12.56 (4.66)**	**12.30 (4.39)**	**11.52 (4.67)**
Week 1	**-2.21 (3.37)**	**-3.20 (3.35)**	**-4.08 (3.79)**	**-3.63 (2.89)**	**-4.18 (3.83)**
Week 2	**-3.25 (4.08)**	**-4.72 (3.85)**	**-5.19 (4.59)**	**-4.88 (3.24)**	**-5.39 (3.96)**
Week 3	**-3.71 (4.39)**	**-4.82 (4.08)**	**-5.68 (4.74)**	**-5.13 (3.68)**	**-5.59 (4.05)**
Week 5	**-3.90 (4.82)**	**-5.29 (4.28)**	**-5.83 (4.72)**	**-5.50 (3.79)**	**-5.54 (4.48)**
Week 6	**-4.02 (4.90)**	**-5.41 (4.43)**	**-5.96 (4.79)**	**-5.58 (3.89)**	**-5.62 (4.71)**
Week 7	**-4.11 (4.96)**	**-5.33 (4.30)**	**-6.10 (4.87)**	**-5.69 (4.28)**	**-5.93 (4.63)**
Week 8	**-4.04 (5.05)**	**-5.19 (4.49)**	**-6.14 (4.72)**	**-5.86 (4.52)**	**-5.72 (4.36)**
Week 9	**-4.11 (5.18)**	**-5.15 (4.65)**	**-6.23 (4.90)**	**-5.96 (4.39)**	**-5.95 (4.77)**
Week 10	**-4.11 (5.42)**	**-5.18 (4.54)**	**-5.97 (4.79)**	**-6.00 (4.36)**	**-6.11 (4.66)**
Week 11	**-4.20 (5.38)**	**-5.30 (4.65)**	**-6.03 (4.86)**	**-5.86 (4.34)**	**-5.91 (4.57)**

No statistical analysis provided for Change From Baseline in Average Daily Frequency of Moderate/Severe Vasomotor Symptoms (Frequency Score A) by Week Excluding Weeks 4 and 12

6. Secondary: Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) by Week Excluding Weeks 4 and 12 [Time Frame: Baseline and up to Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) by Week Excluding Weeks 4 and 12
Measure Description	Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score A was calculated as the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of moderate and severe hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and up to Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) by Week Excluding Weeks 4 and 12 [units: Severity score] Mean (Standard Deviation)					
Baseline	**2.447 (0.301)**	**2.451 (0.297)**	**2.449 (0.315)**	**2.460 (0.296)**	**2.400 (0.274)**
Week 1	**-0.045 (0.124)**	**-0.081 (0.153)**	**-0.085 (0.151)**	**-0.085 (0.159)**	**-0.108 (0.150)**

Week 2	**-0.063 (0.172)**	**-0.117 (0.199)**	**-0.111 (0.212)**	**-0.140 (0.200)**	**-0.136 (0.178)**
Week 3	**-0.071 (0.195)**	**-0.133 (0.214)**	**-0.119 (0.214)**	**-0.150 (0.200)**	**-0.137 (0.240)**
Week 5	**-0.080 (0.215)**	**-0.141 (0.233)**	**-0.123 (0.227)**	**-0.154 (0.225)**	**-0.151 (0.232)**
Week 6	**-0.075 (0.215)**	**-0.136 (0.246)**	**-0.127 (0.234)**	**-0.140 (0.236)**	**-0.152 (0.245)**
Week 7	**-0.088 (0.233)**	**-0.144 (0.236)**	**-0.131 (0.260)**	**-0.140 (0.253)**	**-0.144 (0.257)**
Week 8	**-0.082 (0.239)**	**-0.142 (0.242)**	**-0.124 (0.270)**	**-0.139 (0.254)**	**-0.133 (0.247)**
Week 9	**-0.083 (0.242)**	**-0.142 (0.257)**	**-0.137 (0.260)**	**-0.130 (0.265)**	**-0.144 (0.246)**
Week 10	**-0.084 (0.255)**	**-0.147 (0.261)**	**-0.125 (0.263)**	**-0.141 (0.258)**	**-0.162 (0.252)**
Week 11	**-0.078 (0.261)**	**-0.159 (0.273)**	**-0.130 (0.273)**	**-0.124 (0.257)**	**-0.156 (0.257)**

No statistical analysis provided for Change From Baseline in Average Daily Severity of Moderate/Severe Vasomotor Symptoms (Severity Score A) by Week Excluding Weeks 4 and 12

7. Secondary: Change From Baseline in Average Daily Moderate/Severe Composite Score (Composite Score A) by Week [Time Frame: Baseline and up to Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in Average Daily Moderate/Severe Composite Score (Composite Score A) by Week
Measure Description	Composite Score A was calculated as Severity Score A x Frequency Score A.
Time Frame	Baseline and up to Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description

Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	Esmirtazapine 2.25 mg	Esmirtazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Moderate/Severe Composite Score (Composite Score A) by Week [units: Composite score] Mean (Standard Deviation)					
Baseline	**30.19 (15.42)**	**30.41 (14.56)**	**31.03 (12.98)**	**30.40 (11.81)**	**27.87 (12.56)**
Week 1	**-5.65 (8.99)**	**-8.48 (9.10)**	**-10.28 (9.19)**	**-9.43 (7.84)**	**-10.63 (9.63)**
Week 2	**-8.28 (10.93)**	**-12.32 (10.18)**	**-12.98 (11.36)**	**-12.70 (8.75)**	**-13.54 (9.89)**
Week 3	**-9.46 (11.92)**	**-12.63 (11.09)**	**-14.22 (11.88)**	**-13.39 (9.82)**	**-13.89 (10.28)**
Week 4	**-9.79 (12.39)**	**-13.18 (11.29)**	**-14.42 (11.88)**	**-13.70 (10.28)**	**-13.72 (11.38)**
Week 5	**-9.96 (13.19)**	**-13.65 (11.77)**	**-14.47 (11.65)**	**-14.16 (10.09)**	**-13.72 (11.33)**
Week 6	**-10.22 (13.40)**	**-13.89 (11.88)**	**-14.84 (11.92)**	**-14.24 (10.26)**	**-13.95 (12.05)**
Week 7	**-10.42 (13.49)**	**-13.73 (11.66)**	**-15.11 (12.32)**	**-14.42 (11.23)**	**-14.72 (11.87)**
Week 8	**-10.20 (13.71)**	**-13.31 (11.98)**	**-15.19 (11.93)**	**-14.73 (11.56)**	**-14.08 (11.21)**
Week 9	**-10.30 (14.06)**	**-13.20 (12.54)**	**-15.40 (12.18)**	**-14.93 (11.20)**	**-14.67 (12.30)**
Week 10	**-10.26 (14.77)**	**-13.30 (12.34)**	**-14.76 (12.07)**	**-15.03 (11.24)**	**-15.08 (12.09)**
	-10.53	**-13.58**	**-14.92**	**-14.58**	**14.57**

Week 11	**(14.73)**	**(12.61)**	**(12.41)**	**(11.28)**	**(11.85)**
Week 12	**-10.42 (14.56)**	**-13.25 (12.52)**	**-14.88 (12.49)**	**-14.36 (11.17)**	**-14.71 (12.17)**

No statistical analysis provided for Change From Baseline in Average Daily Moderate/Severe Composite Score (Composite Score A) by Week

8. Secondary: Change From Baseline in Average Daily Frequency of Mild to Severe Vasomotor Symptoms (Frequency Score B) by Week [Time Frame: Baseline and up to Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in Average Daily Frequency of Mild to Severe Vasomotor Symptoms (Frequency Score B) by Week
Measure Description	Participants recorded the frequency (number) of vasomotor symptoms (hot flushes) on a LogPad on a daily basis during screening and treatment. Frequency Score B was based on the number of mild hot flushes + the number of moderate hot flushes + the number of severe hot flushes in one day. Baseline average was derived from, at most, 7 completely observed pre-treatment days. Weekly averages during treatment were calculated if at least 4 days with non-missing data were completely observed; if less than 4 days were completely observed, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and up to Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Frequency of Mild to Severe Vasomotor Symptoms (Frequency Score B) by Week [units: Events per day]					

Mean (Standard Deviation)					
Baseline	13.29 (5.35)	13.48 (5.35)	13.66 (4.96)	13.41 (4.61)	13.00 (6.09)
Week 1	-2.22 (3.41)	-3.24 (3.23)	-3.81 (3.33)	-3.57 (2.96)	-4.16 (4.69)
Week 2	-3.35 (4.17)	-4.81 (4.03)	-5.19 (4.46)	-4.79 (3.28)	-5.50 (4.75)
Week 3	-3.83 (4.46)	-5.05 (4.15)	-5.66 (4.74)	-5.08 (3.72)	-5.79 (4.88)
Week 4	-3.97 (4.63)	-5.37 (4.14)	-6.01 (4.80)	-5.38 (3.98)	-5.85 (5.30)
Week 5	-4.06 (4.91)	-5.61 (4.46)	-6.13 (4.81)	-5.57 (4.03)	-5.90 (5.31)
Week 6	-4.25 (4.86)	-5.82 (4.51)	-6.32 (4.89)	-5.75 (4.11)	-5.89 (5.24)
Week 7	-4.27 (4.85)	-5.69 (4.36)	-6.47 (4.89)	-5.90 (4.45)	-6.15 (5.18)
Week 8	-4.19 (4.94)	-5.54 (4.50)	-6.51 (4.72)	-6.06 (4.55)	-6.03 (4.73)
Week 9	-4.30 (5.06)	-5.47 (4.71)	-6.59 (4.79)	-6.08 (4.51)	-6.26 (5.26)
Week 10	-4.29 (5.39)	-5.59 (4.73)	-6.36 (4.81)	-6.18 (4.46)	-6.35 (5.05)
Week 11	-4.43 (5.42)	-5.68 (4.83)	-6.45 (4.91)	-6.08 (4.48)	-6.28 (4.98)
Week 12	-4.40 (5.44)	-5.63 (4.71)	-6.45 (4.96)	-6.10 (4.48)	-6.32 (4.99)

No statistical analysis provided for Change From Baseline in Average Daily Frequency of Mild to Severe Vasomotor Symptoms (Frequency Score B) by Week

9. Secondary: Change From Baseline in Average Daily Severity of Mild to Severe Vasomotor Symptoms (Severity Score B) by Week [Time Frame: Baseline and up to Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in Average Daily Severity of Mild to Severe Vasomotor Symptoms (Severity Score B) by Week
Measure Description	Participants recorded the severity of hot flushes on a LogPad on a daily basis during screening and treatment. The severity of hot flushes was defined as: mild (sensation of heat without sweating); moderate (sensation of heat with sweating, able to continue activity); and severe (sensation of heat with sweating, causing cessation of activity). Severity Score B was calculated as the number of mild hot flushes + the number of moderate hot flushes x 2 + the number of severe hot flushes x 3, divided by the total number of all hot flushes per week. If no hot flushes were experienced, this was to be recorded as 'no sensation of heat'. Baseline values were based on, at most, 7 completely observed pre-treatment days. If less than 4 days were completely observed during treatment, the averages of the previous week were carried forward (LOCF). If the number of days observed in Week 1 were not sufficient, baseline values were carried forward.
Time Frame	Baseline and up to Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	Esmirtazapine 2.25 mg	Esmirtazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Severity of Mild to Severe Vasomotor Symptoms (Severity Score B) by Week [units: Severity score] Mean (Standard Deviation)					
Baseline	**2.332 (0.369)**	**2.331 (0.375)**	**2.349 (0.373)**	**2.350 (0.347)**	**2.270 (0.332)**
Week 1	**-0.080 (0.220)**	**-0.132 (0.246)**	**-0.167 (0.245)**	**-0.140 (0.245)**	**-0.192 (0.273)**
Week 2	**-0.111 (0.291)**	**-0.210 (0.342)**	**-0.223 (0.341)**	**-0.225 (0.341)**	**-0.250 (0.312)**
Week 3	**-0.121 (0.307)**	**-0.217 (0.373)**	**-0.246 (0.400)**	**-0.240 (0.337)**	**-0.272 (0.389)**
Week 4	**-0.113 (0.312)**	**-0.224 (0.409)**	**-0.240 (0.388)**	**-0.249 (0.387)**	**-0.273 (0.411)**
Week 5	**-0.124 (0.354)**	**-0.234 (0.411)**	**-0.228 (0.403)**	**-0.254 (0.368)**	**-0.266 (0.409)**
Week 6	**-0.121 (0.360)**	**-0.222 (0.429)**	**-0.214 (0.386)**	**-0.245 (0.396)**	**-0.275 (0.436)**
Week 7	**-0.142 (0.389)**	**-0.234 (0.433)**	**-0.232 (0.444)**	**-0.242 (0.424)**	**-0.287 (0.460)**

Week 8	**-0.139 (0.408)**	**-0.251 (0.440)**	**-0.234 (0.467)**	**-0.251 (0.447)**	**-0.273 (0.463)**
Week 9	**-0.136 (0.408)**	**-0.245 (0.438)**	**-0.256 (0.454)**	**-0.256 (0.462)**	**-0.292 (0.474)**
Week 10	**-0.143 (0.431)**	**-0.244 (0.452)**	**-0.257 (0.465)**	**-0.257 (0.467)**	**-0.307 (0.460)**
Week 11	**-0.149 (0.439)**	**-0.260 (0.467)**	**-0.245 (0.463)**	**-0.224 (0.459)**	**-0.308 (0.477)**
Week 12	**-0.152 (0.457)**	**-0.255 (0.471)**	**-0.240 (0.465)**	**-0.210 (0.450)**	**-0.280 (0.472)**

No statistical analysis provided for Change From Baseline in Average Daily Severity of Mild to Severe Vasomotor Symptoms (Severity Score B) by Week

10. Secondary: Change From Baseline in Average Daily Mild to Severe Composite Symptoms Score (Composite Score B) by Week [Time Frame: Baseline and up to Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in Average Daily Mild to Severe Composite Symptoms Score (Composite Score B) by Week
Measure Description	Composite Score B was calculated as Severity Score B x Frequency Score B.
Time Frame	Baseline and up to Week 12
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally, QD for up to 12 weeks

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**

Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Change From Baseline in Average Daily Mild to Severe Composite Symptoms Score (Composite Score B) by Week [units: Composite score] Mean (Standard Deviation)					
Baseline	**31.39 (15.37)**	**31.70 (14.47)**	**32.13 (12.91)**	**31.51 (11.80)**	**29.35 (13.55)**
Week 1	**-5.66 (8.94)**	**-8.53 (8.85)**	**-10.01 (8.60)**	**-9.37 (7.74)**	**-10.61 (10.31)**
Week 2	**-8.38 (10.91)**	**-12.40 (10.12)**	**-12.98 (11.05)**	**-12.60 (8.58)**	**-13.64 (10.46)**
Week 3	**-9.57 (11.88)**	**-12.86 (10.89)**	**-14.40 (11.69)**	**-13.34 (9.69)**	**-14.09 (10.80)**
Week 4	**-9.93 (12.36)**	**-13.48 (11.06)**	**-14.69 (11.89)**	**-13.75 (10.24)**	**-14.01 (11.91)**
Week 5	**-10.12 (13.13)**	**-13.96 (11.65)**	**014.78 (11.54)**	**-14.22 (10.12)**	**-14.08 (11.82)**
Week 6	**-10.45 (13.24)**	**-14.29 (11.65)**	**-15.19 (11.83)**	**-14.40 (10.30)**	**-14.21 (12.22)**
Week 7	**-10.58 (13.23)**	**-14.09 (11.45)**	**-15.48 (12.16)**	**-14.63 (11.18)**	**-14.93 (12.04)**
Week 8	**-10.34 (13.43)**	**-13.66 (11.73)**	**-15.56 (11.76)**	**-14.92 (11.38)**	**-14.40 (11.18)**
Week 9	**-10.49 (13.78)**	**-13.53 (12.33)**	**-15.77 (11.91)**	**-15.05 (11.09)**	**-14.98 (12.44)**
Week 10	**-10.44 (14.56)**	**-13.71 (12.27)**	**-15.15 (11.92)**	**-15.21 (11.11)**	**-15.32 (12.09)**
Week 11	**-10.76 (14.57)**	**-13.96 (12.53)**	**-15.34 (12.27)**	**-14.79 (11.16)**	**-14.95 (11.95)**
Week 12	**-10.66 (14.44)**	**-13.66 (12.32)**	**-15.32 (12.38)**	**-14.71 (11.11)**	**-15.04 (12.17)**

No statistical analysis provided for Change From Baseline in Average Daily Mild to Severe Composite Symptoms Score (Composite Score B) by Week

11. Secondary: Total Number of Responders by Week [Time Frame: Up to 12 weeks]

Measure Type	Secondary

Measure Title	Total Number of Responders by Week
Measure Description	A participant was defined as a (hot flush) responder for a study week if a reduction of at least 50% for average daily frequency of moderate/severe vasomotor symptoms (hot flushes) (Frequency Score A) compared to Baseline was recorded. A study week was taken into account if at least 4 days were completely observed. The last observation was carried forward if there were less than 4 complete days observed. In cases where Week 1 did not have 4 days that were completely observed, the participant was considered a non-responder. An LOCF approach was used.
Time Frame	Up to 12 weeks
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Total Number of Responders by Week [units: Participants]					
Week 1	**37**	**29**	**35**	**32**	**42**
Week 2	**56**	**49**	**60**	**48**	**65**
Week 3	**85**	**53**	**63**	**47**	**72**
Week 4	**76**	**58**	**70**	**52**	**71**
Week 5	**76**	**63**	**65**	**56**	**71**
Week 6	**84**	**67**	**70**	**55**	**69**
Week 7	**89**	**59**	**72**	**60**	**75**
Week 8	**93**	**65**	**73**	**66**	**72**
Week 9	**96**	**67**	**74**	**68**	**75**
Week 10	**97**	**65**	**73**	**67**	**77**
Week 11	**95**	**70**	**78**	**65**	**72**

Week 12	**99**	**70**	**75**	**65**	**77**

No statistical analysis provided for Total Number of Responders by Week

12. Secondary: Total Number of Remitters by Week [Time Frame: Up to 12 weeks]

Measure Type	Secondary
Measure Title	Total Number of Remitters by Week
Measure Description	A participant was defined as a (hot flush) remitter for a study week if at most one moderate/severe vasomotor symptom per day on average was recorded. A study week was taken into account if at least 4 days were completely observed. The last observation was carried forward if there were less than 4 complete days observed. In cases where Week 1 did not have 4 days that were completely observed, the participant was considered a non-remitter.
Time Frame	Up to 12 weeks
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, defined as all randomized participants who had at least one pre-baseline and at least one post-baseline average of the number of hot flushes in a week. An LOCF approach was used.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**
Number of Participants Analyzed [units: participants]	**283**	**146**	**144**	**134**	**138**
Total Number of Remitters by Week [units: Participants]					
Week 1	**3**	**2**	**7**	**2**	**2**
Week 2	**6**	**11**	**13**	**8**	**13**
Week 3	**8**	**15**	**16**	**7**	**17**
Week 4	**10**	**15**	**18**	**15**	**17**
Week 5	**13**	**18**	**16**	**12**	**17**

Week 6	**15**	**15**	**21**	**13**	**18**
Week 7	**19**	**19**	**22**	**16**	**21**
Week 8	**23**	**19**	**25**	**18**	**21**
Week 9	**24**	**19**	**25**	**19**	**26**
Week 10	**25**	**19**	**25**	**23**	**25**
Week 11	**25**	**22**	**23**	**21**	**28**
Week 12	**27**	**23**	**24**	**20**	**26**

No statistical analysis provided for Total Number of Remitters by Week

13. Secondary: Change From Baseline in Women's Health Questionnaire (WHQ) Sleep Problems Symptoms Domain Score at Week 12 [Time Frame: Baseline and Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in Women's Health Questionnaire (WHQ) Sleep Problems Symptoms Domain Score at Week 12
Measure Description	The WHQ is a 36-item, user-friendly, and rapid way of assessing nine domains of physical and emotional health for mid-aged women. Participants self-administered the WHQ questionnaire; scoring is based on a 4-point scale as follows: 'Yes definitely=1', 'Yes sometimes=2', 'No not much=3' and 'No not at all=4'. Each score is transformed to a value '1' for scores '1' and '2' and to a value '0' for scores '3' and '4'. Sleep problems encompass Items 1, 11, and 29 of the 36 total items. The transformed sums of items 1, 11, and 29 were divided by 3 to get the score; therefore, the domain ranges from 0 to 1, where lower values are better.
Time Frame	Baseline and Week 12
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.
All participants who received study drug and had valid answers recorded for the WHQ domain for sleep problems.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, once daily QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally, QD for up to 12 weeks
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.

Measured Values

	Placebo	**Esmirtazapine 2.25 mg**	**Esmirtazapine 4.5 mg**	**Esmirtazapine 9 mg**	**Esmirtazapine 18 mg**
Number of Participants Analyzed [units: participants]	**265**	**138**	**134**	**128**	**128**

Change From Baseline in Women's Health Questionnaire (WHQ) Sleep Problems Symptoms Domain Score at Week 12 [units: Score on a scale] Mean (Standard Deviation)					
Baseline	0.714 (0.291)	0.659 (0.321)	0.684 (0.298)	0.688 (0.270)	0.693 (0.260)
Week 12	-0.140 (0.325)	-0.232 (0.338)	-0.251 (0.336)	-0.224 (0.381)	-0.195 (0.328)

No statistical analysis provided for Change From Baseline in Women's Health Questionnaire (WHQ) Sleep Problems Symptoms Domain Score at Week 12

14. Secondary: Change From Baseline in WHQ Vasomotor Symptoms Domain Score at Week 12 [Time Frame: Baseline and Week 12]

Measure Type	Secondary
Measure Title	Change From Baseline in WHQ Vasomotor Symptoms Domain Score at Week 12
Measure Description	The WHQ is a 36-item, user-friendly, and rapid way of assessing nine domains of physical and emotional health for mid-aged women. Participants self-administered the WHQ questionnaire; scoring is based on a 4-point scale as follows: 'Yes definitely=1', 'Yes sometimes=2', 'No not much=3' and 'No not at all=4'. Each score is transformed to a value '1' for scores '1' and '2' and to a value '0' for scores '3' and '4'. Vasomotor symptoms encompass Items 19 and 27 of the 36 total items. The transformed sums of items 19+27 are divided by 2 to get the score; therefore, the domain ranges from 0 to 1, where lower values are better.
Time Frame	Baseline and Week 12
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.
All participants who received study drug and had valid answers recorded for the WHQ domain for vasomotor symptoms.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, QD for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally, QD for up to 12 weeks
Esmirtazapine 18mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.

Measured Values

	Placebo	Esmirtazapine 2.25 mg	Esmirtazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18mg
Number of Participants Analyzed [units: participants]	**265**	**138**	**134**	**128**	**128**

Change From Baseline in WHQ Vasomotor Symptoms Domain Score at Week 12 [units: Score on a scale] Mean (Standard Deviation)					
Baseline	0.983 (0.091)	0.989 (0.0873)	0.993 (0.061)	0.984 (0.087)	0.984 (0.087)
Week 12	-0.085 (0.260)	-0.196 (0.349)	-0.224 (0.381)	-0.117 (0.277)	-0.164 (0.314)

No statistical analysis provided for Change From Baseline in WHQ Vasomotor Symptoms Domain Score at Week 12

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Non-serious adverse events were collected up to 7 days after the last dose of study drug; serious adverse events were collected for up to 30 days after the last dose of study drug.
Additional Description	No text entered.

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, once daily (QD) for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmertazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.

Serious Adverse Events

	Placebo	Esmirtazapine 2.25 mg	Esmertazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg
Total, serious adverse events					
# participants affected / at risk	2/314 (0.64%)	1/162 (0.62%)	1/160 (0.63%)	3/151 (1.99%)	1/158 (0.63%)
Cardiac disorders					
Wolff-Parkinson-White Syndrome † [1]					
# participants affected / at risk	0/314 (0.00%)	0/162 (0.00%)	0/160 (0.00%)	1/151 (0.66%)	0/158 (0.00%)
# events	0	0	0	1	0
Gastrointestinal disorders					
Diverticular perforation † [1]					
# participants affected / at risk	0/314 (0.00%)	1/162 (0.62%)	0/160 (0.00%)	0/151 (0.00%)	0/158 (0.00%)

# events	0	1	0	0	0
General disorders					
Asthenia † 1					
# participants affected / at risk	0/314 (0.00%)	0/162 (0.00%)	0/160 (0.00%)	1/151 (0.66%)	0/158 (0.00%)
# events	0	0	0	1	0
Non-cardiac chest pain † 1					
# participants affected / at risk	0/314 (0.00%)	0/162 (0.00%)	0/160 (0.00%)	1/151 (0.66%)	0/158 (0.00%)
# events	0	0	0	1	0
Infections and infestations					
Diverticulitis † 1					
# participants affected / at risk	0/314 (0.00%)	0/162 (0.00%)	1/160 (0.63%)	0/151 (0.00%)	0/158 (0.00%)
# events	0	0	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Ovarian fibroma † 1					
# participants affected / at risk	0/314 (0.00%)	0/162 (0.00%)	0/160 (0.00%)	1/151 (0.66%)	0/158 (0.00%)
# events	0	0	0	1	0
Nervous system disorders					
Syncope vasovagal † 1					
# participants affected / at risk	1/314 (0.32%)	0/162 (0.00%)	0/160 (0.00%)	0/151 (0.00%)	1/158 (0.63%)
# events	1	0	0	0	1
Psychiatric disorders					
Nightmare † 1					
# participants affected / at risk	1/314 (0.32%)	0/162 (0.00%)	0/160 (0.00%)	0/151 (0.00%)	0/158 (0.00%)
# events	1	0	0	0	0
Suicidal ideation † 1					
# participants affected / at risk	1/314 (0.32%)	0/162 (0.00%)	0/160 (0.00%)	0/151 (0.00%)	0/158 (0.00%)
# events	1	0	0	0	0

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA 9.0

Other Adverse Events

Hide Other Adverse Events

Time Frame	Non-serious adverse events were collected up to 7 days after the last dose of study drug; serious adverse events were collected for up to 30 days after the last dose of study drug.
Additional Description	No text entered.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Placebo	Participants receive encapsulated tablets, orally, once daily (QD) for up to 12 weeks.
Esmirtazapine 2.25 mg	Participants receive esmirtazapine, 2.25 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmertazapine 4.5 mg	Participants receive esmirtazapine, 4.5 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 9 mg	Participants receive esmirtazapine, 9 mg, encapsulated tablets, orally QD for up to 12 weeks.
Esmirtazapine 18 mg	Participants receive esmirtazapine, 18 mg, encapsulated tablets, orally QD for up to 12 weeks.

Other Adverse Events

	Placebo	Esmirtazapine 2.25 mg	Esmertazapine 4.5 mg	Esmirtazapine 9 mg	Esmirtazapine 18 mg
Total, other (not including serious) adverse events					
# participants affected / at risk	**91/314 (28.98%)**	**71/162 (43.83%)**	**70/160 (43.75%)**	**58/151 (38.41%)**	**80/158 (50.63%)**
Gastrointestinal disorders					
Abdominal distension † 1					
# participants affected / at risk	**5/314 (1.59%)**	**2/162 (1.23%)**	**3/160 (1.88%)**	**4/151 (2.65%)**	**10/158 (6.33%)**
# events	**5**	**3**	**3**	**5**	**11**
Dry mouth † 1					
# participants affected / at risk	**6/314 (1.91%)**	**8/162 (4.94%)**	**7/160 (4.38%)**	**12/151 (7.95%)**	**9/158 (5.70%)**
# events	**6**	**9**	**7**	**12**	**10**
General disorders					
Fatigue † 1					
# participants affected / at risk	**9/314 (2.87%)**	**16/162 (9.88%)**	**26/160 (16.25%)**	**16/151 (10.60%)**	**23/158 (14.56%)**
# events	**10**	**18**	**28**	**19**	**25**
Oedema peripheral † 1					
# participants affected / at risk	**3/314 (0.96%)**	**9/162 (5.56%)**	**8/160 (5.00%)**	**3/151 (1.99%)**	**6/158 (3.80%)**
# events	**4**	**10**	**10**	**6**	**11**
Infections and infestations					
Influenza † 1					
# participants affected / at risk	**15/314 (4.78%)**	**9/162 (5.56%)**	**3/160 (1.88%)**	**6/151 (3.97%)**	**2/158 (1.27%)**
# events	**15**	**9**	**3**	**6**	**2**

Investigations					
Weight increased † 1					
# participants affected / at risk	**6/314 (1.91%)**	**7/162 (4.32%)**	**13/160 (8.13%)**	**11/151 (7.28%)**	**18/158 (11.39%)**
# events	**6**	**7**	**13**	**11**	**18**
Metabolism and nutrition disorders					
Increased appetite † 1					
# participants affected / at risk	**4/314 (1.27%)**	**8/162 (4.94%)**	**8/160 (5.00%)**	**10/151 (6.62%)**	**14/158 (8.86%)**
# events	**4**	**8**	**8**	**11**	**14**
Musculoskeletal and connective tissue disorders					
Arthralgia † 1					
# participants affected / at risk	**16/314 (5.10%)**	**6/162 (3.70%)**	**4/160 (2.50%)**	**3/151 (1.99%)**	**6/158 (3.80%)**
# events	**20**	**6**	**5**	**3**	**6**
Nervous system disorders					
Dizziness † 1					
# participants affected / at risk	**12/314 (3.82%)**	**8/162 (4.94%)**	**4/160 (2.50%)**	**5/151 (3.31%)**	**13/158 (8.23%)**
# events	**12**	**8**	**4**	**5**	**14**
Headache † 1					
# participants affected / at risk	**33/314 (10.51%)**	**14/162 (8.64%)**	**9/160 (5.63%)**	**5/151 (3.31%)**	**13/158 (8.23%)**
# events	**52**	**18**	**11**	**14**	**17**
Somnolence † 1					
# participants affected / at risk	**6/314 (1.91%)**	**19/162 (11.73%)**	**21/160 (13.13%)**	**11/151 (7.28%)**	**27/158 (17.09%)**
# events	**7**	**25**	**23**	**12**	**30**
Reproductive system and breast disorders					
Menopausal symptoms † 1					
# participants affected / at risk	**8/314 (2.55%)**	**5/162 (3.09%)**	**10/160 (6.25%)**	**6/151 (3.97%)**	**4/158 (2.53%)**
# events	**8**	**5**	**10**	**6**	**4**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA 9.0

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:
☑ 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.
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☐ Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

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Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00535288 History of Changes
Other Study ID Numbers:	P06472 White Moonstone (Other Identifier: Organon Protocol Name) 177001 (Other Identifier: Organon Protocol Number)
Study First Received:	September 24, 2007
Results First Received:	June 16, 2014
Last Updated:	May 27, 2015
Health Authority:	United States: Food and Drug Administration Belgium: Federal Agency for Medicinal Products and Health Products Brazil: Ministry of Health Canada: Health Canada Czech Republic: State Institute for Drug Control Denmark: Danish Medicines Agency Hungary: National Institute of Pharmacy Netherlands: Medicines Evaluation Board (MEB) Norway: Norwegian Medicines Agency Slovakia: State Institute for Drug Control Spain: Spanish Agency of Medicines Switzerland: Swissmedic United Kingdom: Medicines and Healthcare Products Regulatory Agency

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