



Clinical trial results:

A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-003529-27 |
| Trial protocol | GB LV CZ HU |
| Global end of trial date | 23 April 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 18 April 2022 |
| First version publication date | 18 April 2022 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 2693-CL-0302 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04003142 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Astellas Pharma Global Development, Inc |
| Sponsor organisation address | 1 Astellas Way, Northbrook, IL, United States, 60062 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 23 April 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of fezolinetant vs placebo on the frequency and severity of moderate to severe VMS.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 10 July 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 33 |
| Country: Number of subjects enrolled | Czechia: 14 |
| Country: Number of subjects enrolled | Latvia: 14 |
| Country: Number of subjects enrolled | Poland: 108 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | United States: 323 |
| Worldwide total number of subjects | 501 |
| EEA total number of subjects | 144 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|--|-----|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 496 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Postmenopausal women participants 40 to 65 years of age who had moderate to severe VMS & seeking treatment or relief for VMS associated with menopause, confirmed as menopausal, had to have 7 to 8 moderate to severe VMS per day within the 10 days prior to randomization & who met the inclusion criteria & none of the exclusion criteria were enrolled.

Pre-assignment

Screening details:

Prior to randomization, participants had a screening period during which a minimum 10-day collection of baseline VMS frequency and severity assessments were performed.

Period 1

| | |
|------------------------------|--------------------------------------|
| Period 1 title | Double-blind Period (DBP) (12 weeks) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Double-blind Period: Placebo |

Arm description:

Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, once daily (QD) up to week 12 during double-blind treatment period.

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

Dosage and administration details:

Participants received fezolinetant matching placebo orally, QD.

| | |
|------------------|---|
| Arm title | Double-blind Period: Fezolinetant 30 mg |
|------------------|---|

Arm description:

Participants received fezolinetant 30 mg (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD up to week 12 during double-blind treatment period.

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

Dosage and administration details:

Participants received fezolinetant 30 mg orally, QD.

| | |
|------------------|---|
| Arm title | Double-blind Period: Fezolinetant 45 mg |
|------------------|---|

Arm description:

Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD up to week 12 during double-blind treatment period.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------|
| Investigational medicinal product name | Fezolinetant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received fezolinetant 45 mg orally, QD.

| Number of subjects in period 1 | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg |
|--------------------------------|---------------------------------|--|--|
| Started | 168 | 166 | 167 |
| Treated | 167 | 166 | 167 |
| Completed | 151 | 152 | 155 |
| Not completed | 17 | 14 | 12 |
| Adverse event, non-fatal | 1 | 1 | 2 |
| Protocol Deviation | 1 | 5 | - |
| Miscellaneous | 2 | 1 | 2 |
| Lost to follow-up | 2 | 1 | 2 |
| Withdrawal by subject | 11 | 6 | 6 |

Period 2

| | |
|------------------------------|----------------------------------|
| Period 2 title | Extension Period (EP) (40 weeks) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | No |
| Arm title | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg |

Arm description:

Participants received fezolinetant 30 mg (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 30 mg orally, QD from week 13 up to Week 52 during extension treatment period.

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

Dosage and administration details:

Participants received fezolinetant 30 mg orally, QD.

| | |
|------------------|--|
| Arm title | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg |
|------------------|--|

Arm description:

Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 45 mg orally, QD from week 13 up to Week 52 during extension treatment period.

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

Dosage and administration details:

Participants received fezolinetant 45 mg orally, QD

| | |
|------------------|--|
| Arm title | Double-blind Period:Placebo/Extension Period:Fezolinetant 30mg |
|------------------|--|

Arm description:

Participants who received placebo during double-blind treatment period were re-randomized to receive fezolinetant 30 mg orally, QD from week 13 up to week 52 during extension treatment period.

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

Dosage and administration details:

Participants received fezolinetant 30 mg orally, QD.

| | |
|------------------|--|
| Arm title | Double-blind Period:Placebo/Extension Period:Fezolinetant 45mg |
|------------------|--|

Arm description:

Participants who received placebo during double-blind treatment period were re-randomized to receive fezolinetant 45 mg orally, QD from week 13 up to week 52 during extension treatment period.

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

Dosage and administration details:

Participants received fezolinetant 45 mg orally, QD

| Number of subjects in period 2 | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg | Double-blind Period:Placebo/Ext ension Period:Fezolinetant |
|---------------------------------------|---|---|---|
| Started | 152 | 154 | 76 |
| Completed | 125 | 132 | 63 |
| Not completed | 27 | 22 | 13 |
| Adverse event, serious fatal | - | - | - |
| Adverse event, non-fatal | 4 | 4 | 2 |
| Protocol Deviation | - | 2 | - |
| Miscellaneous | 4 | 1 | - |

| | | | |
|-----------------------|----|----|---|
| Lost to follow-up | 2 | 1 | 2 |
| Withdrawal by subject | 17 | 14 | 9 |

| Number of subjects in period 2 | Double-blind Period:Placebo/Extension Period:Fezolinetant |
|---------------------------------------|---|
| Started | 75 |
| Completed | 63 |
| Not completed | 12 |
| Adverse event, serious fatal | 1 |
| Adverse event, non-fatal | 3 |
| Protocol Deviation | - |
| Miscellaneous | 2 |
| Lost to follow-up | 1 |
| Withdrawal by subject | 5 |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Double-blind Period: Placebo |
| Reporting group description: Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, once daily (QD) up to week 12 during double-blind treatment period. | |
| Reporting group title | Double-blind Period: Fezolinetant 30 mg |
| Reporting group description: Participants received fezolinetant 30 mg (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD up to week 12 during double-blind treatment period. | |
| Reporting group title | Double-blind Period: Fezolinetant 45 mg |
| Reporting group description: Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD up to week 12 during double-blind treatment period. | |

| Reporting group values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg |
|---------------------------|------------------------------|---|---|
| Number of subjects | 168 | 166 | 167 |
| Age categorical Units: | | | |

| | | | |
|--|---------------|---------------|---------------|
| Age Continuous Units: Years arithmetic mean standard deviation | 54.6 ± 4.6 | 53.9 ± 4.9 | 54.3 ± 5.4 |
| Sex: Female, Male Units: Participants | | | |
| Female | 168 | 166 | 167 |
| Male | 0 | 0 | 0 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 1 |
| Asian | 1 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 31 | 35 | 33 |
| White | 135 | 131 | 132 |
| More than one race | 1 | 0 | 1 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 33 | 34 | 41 |
| Not Hispanic or Latino | 134 | 132 | 126 |
| Unknown or Not Reported | 1 | 0 | 0 |
| Severity of Moderate and Severe VMS per 24 hours | | | |
| Severity of moderate to severe VMS per day was calculated as follows: [(number of moderate VMS × 2) + (number of severe VMS × 3)]/number of daily moderate/severe VMS. Higher score indicates greater severity. Baseline was the weighted average of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization | | | |
| Units: Score on a scale | | | |

| | | | |
|--|--------|--------|--------|
| arithmetic mean | 2.43 | 2.45 | 2.39 |
| standard deviation | ± 0.34 | ± 0.35 | ± 0.36 |
| Frequency of Moderate and Severe VMS per 24 hours | | | |
| The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization. | | | |
| Units: VMS per day | | | |
| arithmetic mean | 11.59 | 11.23 | 11.79 |
| standard deviation | ± 5.02 | ± 4.88 | ± 8.26 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 501 | | |
| Age categorical | | | |
| Units: | | | |

| | | | |
|--|-----|--|--|
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 501 | | |
| Male | 0 | | |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | | |
| Asian | 1 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 99 | | |
| White | 398 | | |
| More than one race | 2 | | |
| Unknown or Not Reported | 0 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 108 | | |
| Not Hispanic or Latino | 392 | | |
| Unknown or Not Reported | 1 | | |
| Severity of Moderate and Severe VMS per 24 hours | | | |
| Severity of moderate to severe VMS per day was calculated as follows: [(number of moderate VMS × 2) + (number of severe VMS × 3)]/number of daily moderate/severe VMS. Higher score indicates greater severity. Baseline was the weighted average of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization | | | |
| Units: Score on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Frequency of Moderate and Severe VMS per 24 hours | | | |
| The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization. | | | |
| Units: VMS per day | | | |
| arithmetic mean | | | |

| | | | |
|--------------------|---|--|--|
| standard deviation | - | | |
|--------------------|---|--|--|

| |
|--|
| |
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End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Double-blind Period: Placebo |
| Reporting group description: Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, once daily (QD) up to week 12 during double-blind treatment period. | |
| Reporting group title | Double-blind Period: Fezolinetant 30 mg |
| Reporting group description: Participants received fezolinetant 30 mg (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD up to week 12 during double-blind treatment period. | |
| Reporting group title | Double-blind Period: Fezolinetant 45 mg |
| Reporting group description: Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD up to week 12 during double-blind treatment period. | |
| Reporting group title | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg |
| Reporting group description: Participants received fezolinetant 30 mg (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 30 mg orally, QD from week 13 up to Week 52 during extension treatment period. | |
| Reporting group title | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg |
| Reporting group description: Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 45 mg orally, QD from week 13 up to Week 52 during extension treatment period. | |
| Reporting group title | Double-blind Period:Placebo/Extension Period:Fezolinetant 30mg |
| Reporting group description: Participants who received placebo during double-blind treatment period were re-randomized to receive fezolinetant 30 mg orally, QD from week 13 up to week 52 during extension treatment period. | |
| Reporting group title | Double-blind Period:Placebo/Extension Period:Fezolinetant 45mg |
| Reporting group description: Participants who received placebo during double-blind treatment period were re-randomized to receive fezolinetant 45 mg orally, QD from week 13 up to week 52 during extension treatment period. | |
| Subject analysis set title | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received fezolinetant 30 mg (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 30 mg orally, QD from week 13 up to Week 52 during extension treatment period. | |
| Subject analysis set title | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 45 mg orally, QD from week 13 up to Week 52 during extension treatment period. | |

Primary: Change From Baseline in The Mean Frequency of Moderate to Severe VMS at Week 4

| | |
|-----------------|--|
| End point title | Change From Baseline in The Mean Frequency of Moderate to Severe VMS at Week 4 |
|-----------------|--|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and week 4

Analysis Population: Full analysis set (FAS) (consisted of all randomized participants who took at least 1 dose of study intervention) with available data at specified time point.

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 151 | 155 | 155 | |
| Units: VMS per day | | | | |
| least squares mean (standard error) | -3.72 (± 0.33) | -5.53 (± 0.33) | -6.26 (± 0.33) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.001 ^[2] |
| Method | MMRM |
| Parameter estimate | Least squares (LS) Mean difference |
| Point estimate | -1.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.73 |
| upper limit | -0.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.46 |

Notes:

[1] - Least squares Mean (LSM), Standard error (SE), Confidence interval (CI), Mixed model repeated measures (MMRM), Change from Baseline (CFB), Dependent variable (dv), Treatment (tr), Week (wk), Baseline (bl), Weight (wt)

[2] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[3] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.45 |
| upper limit | -1.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.46 |

Notes:

[3] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 ^[4] |
| Method | Hochberg |

Notes:

[4] - Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 4 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[5] |
| Method | Hochberg |

Notes:

[5] - Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level.

Primary: Change From Baseline in The Mean Frequency of Moderate to Severe VMS at Week 12

| | |
|--|---|
| End point title | Change From Baseline in The Mean Frequency of Moderate to Severe VMS at Week 12 |
| End point description: | |
| <p>The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization.</p> <p>Analysis Population: FAS population with available data at specified time point.</p> | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and week 12 | |

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 140 | 133 | 145 | |
| Units: VMS per day | | | | |
| least squares mean (standard error) | -4.97 (± 0.39) | -6.83 (± 0.39) | -7.50 (± 0.39) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 273 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[6] |
| Method | MMRM |
| Parameter estimate | LSMean Difference |
| Point estimate | -1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.94 |
| upper limit | -0.78 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.55 |

Notes:

[6] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[7] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | -1.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.55 |

Notes:

[7] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 273 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[8] |
| Method | Hochberg |

Notes:

[8] - Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level

Primary: Change From Baseline in The Mean Severity of Moderate to Severe VMS at Week 4

| | |
|-----------------|---|
| End point title | Change From Baseline in The Mean Severity of Moderate to Severe VMS at Week 4 |
|-----------------|---|

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows:

$[(\text{number of mild hot flashes per day} \times 1) + (\text{number of moderate hot flashes per day} \times 2) + (\text{number of severe hot flashes per day} \times 3)] / \text{Total number of daily mild/moderate/severe hot flashes}$

Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Severity was zero for participants that had no mild or moderate or severe VMS. Higher scores indicates greater severity.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline and week 4 | |

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|---------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 151 | 155 | 155 | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -0.32 (± 0.05) | -0.47 (± 0.05) | -0.61 (± 0.05) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.021 ^[9] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | -0.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.06 |

Notes:

[9] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| Statistical analysis title | Statistical Analysis 2 |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[10] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | -0.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.06 |

Notes:

[10] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 ^[11] |
| Method | Hochberg |

Notes:

[11] - Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 4 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[12] |
| Method | Hochberg |

Notes:

[12] - Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level

Primary: Change From Baseline in The Mean Severity of Moderate to Severe VMS at Week 12

| | |
|-----------------|--|
| End point title | Change From Baseline in The Mean Severity of Moderate to Severe VMS at Week 12 |
|-----------------|--|

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows:

$$[(\text{number of mild hot flashes per day} \times 1) + (\text{number of moderate hot flashes per day} \times 2) + (\text{number of severe hot flashes per day} \times 3)] / \text{Total number of daily mild/moderate/severe hot flashes}$$

Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed).

Severity was zero for participants that had no mild or moderate or severe VMS. Higher scores indicates greater severity.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline and week 12 | |

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 140 | 133 | 145 | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -0.48 (± 0.06) | -0.64 (± 0.06) | -0.77 (± 0.06) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 273 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 ^[13] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[13] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| Statistical analysis title | Statistical Analysis 2 |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[14] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | -0.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[14] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 273 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 ^[15] |
| Method | Hochberg |

Notes:

[15] - Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 4 |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[16] |
| Method | Hochberg |

Notes:

[16] - Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level

Secondary: Change From Baseline in The Mean Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) Total Score at Week 12

| | |
|-----------------|--|
| End point title | Change From Baseline in The Mean Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) Total Score at Week 12 |
|-----------------|--|

End point description:

The PROMIS SD SF 8b assesses self-reported sleep disturbance over the past 7 days and includes perceptions of restless sleep; satisfaction with sleep; refreshing sleep; difficulties sleeping, getting to sleep or staying asleep; amount of sleep; and sleep quality. Because it assesses the participants experience of sleep disturbance, the measure does not focus on specific sleep-disorder symptoms or ask patients to report objective measures of sleep (e.g., total amount of sleep, time to fall asleep and amount of wakefulness during sleep). Responses to each of the 8 items range from 1 (no disturbed sleep) to 5 (disturbed sleep), and the range of possible summed raw scores is 8 to 40. Higher scores on the PROMIS SD SF 8b indicate more of the disturbed sleep.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 143 | 139 | 145 | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -3.4 (± 0.5) | -4.1 (± 0.5) | -5.5 (± 0.5) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 282 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.381 ^[17] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 0.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

Notes:

[17] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| Statistical analysis title | Statistical Analysis 2 |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 288 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.007 ^[18] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | -0.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

Notes:

[18] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

Secondary: Change from Baseline in The Mean Frequency of Moderate, and Severe VMS to Each Study Week Up to Week 12

| | |
|-----------------|---|
| End point title | Change from Baseline in The Mean Frequency of Moderate, and Severe VMS to Each Study Week Up to Week 12 |
|-----------------|---|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 1, 2, 3, 5, 6, 7, 8, 9, 10, 11

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 166 | 164 | 158 | |
| Units: VMS per day | | | | |
| least squares mean (standard error) | | | | |
| Week 1 (n = 166, 164, 158) | -2.32 (± 0.28) | -3.62 (± 0.29) | -4.03 (± 0.29) | |
| Week 2 (n = 159, 160, 156) | -3.06 (± 0.32) | -4.82 (± 0.32) | -5.03 (± 0.32) | |
| Week 3 (n = 156, 157, 156) | -3.56 (± 0.32) | -5.29 (± 0.32) | -5.95 (± 0.32) | |
| Week 5 (n = 152, 152, 154) | -4.05 (± 0.34) | -5.89 (± 0.34) | -6.71 (± 0.34) | |
| Week 6 (n = 152, 146, 149) | -4.25 (± 0.33) | -6.03 (± 0.33) | -6.91 (± 0.33) | |
| Week 7 (n = 149, 143, 147) | -4.44 (± 0.35) | -6.24 (± 0.35) | -6.78 (± 0.35) | |
| Week 8 (n = 148, 143, 154) | -4.48 (± 0.37) | -6.25 (± 0.37) | -6.86 (± 0.37) | |
| Week 9 (n = 145, 140, 148) | -4.88 (± 0.38) | -6.54 (± 0.38) | -7.39 (± 0.38) | |
| Week 10 (n = 139, 138, 149) | -4.83 (± 0.38) | -6.74 (± 0.38) | -7.47 (± 0.38) | |
| Week 11 (n = 138, 142, 149) | -4.90 (± 0.38) | -6.76 (± 0.38) | -7.46 (± 0.37) | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Week 1

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[19] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.09 |
| upper limit | -0.51 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4 |

Notes:

[19] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 1

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[20] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.51 |
| upper limit | -0.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4 |

Notes:

[20] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 2

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[21] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.65 |
| upper limit | -0.87 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.45 |

Notes:

[21] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 2

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[22] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.86 |
| upper limit | -1.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.45 |

Notes:

[22] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[23] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.63 |
| upper limit | -0.84 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.46 |

Notes:

[23] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[24] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.29 |
| upper limit | -1.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.46 |

Notes:

[24] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 5

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[25] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.79 |
| upper limit | -0.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.48 |

Notes:

[25] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 5

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[26] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.61 |
| upper limit | -1.72 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.48 |

Notes:

[26] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 6

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[27] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.71 |
| upper limit | -0.85 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.47 |

Notes:

[27] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[28] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.59 |
| upper limit | -1.73 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.47 |

Notes:

[28] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[29] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.77 |
| upper limit | -0.83 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.49 |

Notes:

[29] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[30] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | -1.37 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.49 |

Notes:

[30] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[31] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.79 |
| upper limit | -0.74 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.52 |

Notes:

[31] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[32] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | -1.35 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.52 |

Notes:

[32] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[33] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.71 |
| upper limit | -0.59 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.54 |

Notes:

[33] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[34] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.57 |
| upper limit | -1.45 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.54 |

Notes:

[34] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 17 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[35] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.96 |
| upper limit | -0.86 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.54 |

Notes:

[35] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[36] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.69 |
| upper limit | -1.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.53 |

Notes:

[36] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[37] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.91 |
| upper limit | -0.81 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.53 |

Notes:

[37] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[38] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -2.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.61 |
| upper limit | -1.52 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.53 |

Notes:

[38] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

Secondary: Change from Baseline in The Mean Severity of Moderate, and Severe VMS to Each Study Week Up to Week 12

| | |
|-----------------|--|
| End point title | Change from Baseline in The Mean Severity of Moderate, and Severe VMS to Each Study Week Up to Week 12 |
|-----------------|--|

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows:

$$[(\text{number of mild hot flashes per day} \times 1) + (\text{number of moderate hot flashes per day} \times 2) + (\text{number of severe hot flashes per day} \times 3)] / \text{Total number of daily mild/moderate/severe hot flashes}$$

Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed).

Severity was zero for participants that had no mild or moderate or severe VMS. Higher scores indicates greater severity.

Analysis Population: FAS population with available data at specified time point.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 1, 2, 3, 5, 6, 7, 8, 9, 10, 11 | |

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 166 | 164 | 158 | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 1 (n = 166, 164, 158) | -0.18 (± 0.03) | -0.32 (± 0.03) | -0.34 (± 0.03) | |
| Week 2 (n = 159, 160, 156) | -0.24 (± 0.04) | -0.41 (± 0.04) | -0.42 (± 0.04) | |
| Week 3 (n = 156, 157, 156) | -0.31 (± 0.04) | -0.42 (± 0.04) | -0.54 (± 0.04) | |
| Week 5 (n = 152, 152, 154) | -0.37 (± 0.05) | -0.53 (± 0.05) | -0.66 (± 0.05) | |
| Week 6 (n = 152, 146, 149) | -0.37 (± 0.05) | -0.55 (± 0.05) | -0.65 (± 0.05) | |
| Week 7 (n = 149, 143, 147) | -0.42 (± 0.05) | -0.58 (± 0.05) | -0.70 (± 0.05) | |
| Week 8 (n = 148, 143, 154) | -0.43 (± 0.05) | -0.56 (± 0.05) | -0.69 (± 0.05) | |
| Week 9 (n = 145, 140, 148) | -0.46 (± 0.06) | -0.59 (± 0.06) | -0.74 (± 0.06) | |
| Week 10 (n = 139, 138, 149) | -0.45 (± 0.06) | -0.64 (± 0.06) | -0.76 (± 0.06) | |
| Week 11 (n = 138, 142, 149) | -0.46 (± 0.06) | -0.67 (± 0.06) | -0.77 (± 0.06) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[39] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | -0.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.04 |

Notes:

[39] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[40] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | -0.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.04 |

Notes:

[40] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 2 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[41] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | -0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.05 |

Notes:

[41] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 2

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[42] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | -0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.05 |

Notes:

[42] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.067 ^[43] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.06 |

Notes:

[43] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[44] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | -0.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.06 |

Notes:

[44] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 5

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 ^[45] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | -0.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

Notes:

[45] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 5

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[46] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | -0.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

Notes:

[46] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 6

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.012 ^[47] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | -0.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

Notes:

[47] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[48] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | -0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

Notes:

[48] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03 ^[49] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | -0.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

Notes:

[49] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[50] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | -0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

Notes:

[50] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 ^[51] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[51] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[52] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | -0.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[52] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.109 ^[53] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[53] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[54] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | -0.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[54] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 17 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 ^[55] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | -0.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[55] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[56] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | -0.15 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[56] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.012 ^[57] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.37 |
| upper limit | -0.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[57] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[58] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | -0.15 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[58] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

Secondary: Mean Percent Change in The Frequency of Moderate And Severe VMS From Baseline to Each Study Week Up to Week 12

| | |
|-----------------|--|
| End point title | Mean Percent Change in The Frequency of Moderate And Severe VMS From Baseline to Each Study Week Up to Week 12 |
|-----------------|--|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-------------------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 166 | 164 | 158 | |
| Units: Percent change | | | | |
| least squares mean (standard error) | | | | |
| Week 1 (n = 166, 164, 158) | -20.82 (± 2.42) | -32.98 (± 2.43) | -36.50 (± 2.45) | |
| Week 2 (n = 159, 160, 156) | -29.21 (± 2.69) | -43.82 (± 2.69) | -45.16 (± 2.71) | |
| Week 3 (n = 156, 157, 156) | -33.17 (± 2.76) | -48.68 (± 2.75) | -53.42 (± 2.76) | |
| Week 4 (n = 151, 155, 155) | -34.72 (± 2.78) | -51.06 (± 2.77) | -56.37 (± 2.77) | |

| | | | | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Week 5 (n = 152, 152, 154) | -37.88 (± 2.75) | -53.50 (± 2.75) | -60.76 (± 2.74) | |
| Week 6 (n = 152, 146, 149) | -39.64 (± 2.73) | -54.42 (± 2.73) | -62.30 (± 2.73) | |
| Week 7 (n = 149, 143, 147) | -40.91 (± 2.84) | -55.88 (± 2.84) | -62.38 (± 2.83) | |
| Week 8 (n = 148, 143, 154) | -41.84 (± 2.86) | -56.22 (± 2.86) | -62.42 (± 2.84) | |
| Week 9 (n = 145, 140, 148) | -45.87 (± 2.88) | -58.01 (± 2.88) | -65.60 (± 2.86) | |
| Week 10 (n = 139, 138, 149) | -45.58 (± 2.83) | -59.98 (± 2.82) | -65.68 (± 2.81) | |
| Week 11 (n = 138, 142, 149) | -45.41 (± 2.88) | -60.37 (± 2.87) | -65.56 (± 2.86) | |
| Week 12 (n = 140, 133, 145) | -46.91 (± 2.87) | -60.55 (± 2.87) | -65.85 (± 2.85) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[59] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -12.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.9 |
| upper limit | -5.43 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.43 |

Notes:

[59] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|--|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[60] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -15.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.44 |
| upper limit | -8.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.44 |

Notes:

[60] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 2

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[61] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -14.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.09 |
| upper limit | -7.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.81 |

Notes:

[61] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 2

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[62] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -15.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.45 |
| upper limit | -8.45 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.82 |

Notes:

[62] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[63] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -15.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.16 |
| upper limit | -7.86 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.89 |

Notes:

[63] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[64] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -20.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.91 |
| upper limit | -12.59 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.9 |

Notes:

[64] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 4

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[65] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -16.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.04 |
| upper limit | -8.63 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.92 |

Notes:

[65] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 4

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[66] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -21.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.36 |
| upper limit | -13.94 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.92 |

Notes:

[66] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 5

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[67] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -15.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.27 |
| upper limit | -7.98 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.89 |

Notes:

[67] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 5

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[68] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -22.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.52 |
| upper limit | -15.24 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.89 |

Notes:

[68] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[69] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -14.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.38 |
| upper limit | -7.19 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.87 |

Notes:

[69] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[70] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -22.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.25 |
| upper limit | -15.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.86 |

Notes:

[70] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[71] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -14.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.86 |
| upper limit | -7.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.01 |

Notes:

[71] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[72] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -21.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.34 |
| upper limit | -13.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.01 |

Notes:

[72] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[73] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -14.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.33 |
| upper limit | -6.43 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.05 |

Notes:

[73] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[74] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -20.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.5 |
| upper limit | -12.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.03 |

Notes:

[74] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 17 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 ^[75] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -12.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.14 |
| upper limit | -4.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.07 |

Notes:

[75] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[76] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -19.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.71 |
| upper limit | -11.755 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.06 |

Notes:

[76] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[77] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -14.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.25 |
| upper limit | -6.54 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4 |

Notes:

[77] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[78] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -20.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.93 |
| upper limit | -12.27 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.98 |

Notes:

[78] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[79] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -14.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.96 |
| upper limit | -6.96 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.07 |

Notes:

[79] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[80] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -20.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.13 |
| upper limit | -12.18 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.06 |

Notes:

[80] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 23 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[81] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -13.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.62 |
| upper limit | -5.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.07 |

Notes:

[81] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 24 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 12

| | |
|-------------------|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
|-------------------|--|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 324 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[82] |
| Method | MMRM |
| Parameter estimate | LSMean difference |
| Point estimate | -18.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.89 |
| upper limit | -10.98 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.05 |

Notes:

[82] - LSM, SE, CI, & p-values come from MMRM analysis of covariance model with CFB as dv & trt group, wk & smoking status as factors, with bl measurement & bl wt as covariates, as well as an interaction of trt by wk & interaction of bl measurement by wk.

Secondary: Number of Participants With Percent Reduction of $\geq 50\%$ in the Mean Frequency of Moderate and Severe VMS From Baseline to Each Study Week Up to Week 12

| | |
|-----------------|--|
| End point title | Number of Participants With Percent Reduction of $\geq 50\%$ in the Mean Frequency of Moderate and Severe VMS From Baseline to Each Study Week Up to Week 12 |
|-----------------|--|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization. Participant has $\geq 50\%$ reduction from baseline to each post baseline week for the frequency of moderate to severe VMS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

Analysis Population: FAS population with available data at specified time point.

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-----------------------------|---------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 166 | 167 | |
| Units: Participants | | | | |
| Week 1 | 28 | 46 | 58 | |
| Week 2 | 39 | 71 | 71 | |
| Week 3 | 48 | 81 | 89 | |
| Week 4 | 44 | 84 | 88 | |
| Week 5 | 54 | 84 | 98 | |
| Week 6 | 53 | 81 | 95 | |

| | | | | |
|---------|----|----|-----|--|
| Week 7 | 55 | 84 | 92 | |
| Week 8 | 56 | 81 | 103 | |
| Week 9 | 64 | 84 | 98 | |
| Week 10 | 62 | 85 | 103 | |
| Week 11 | 60 | 94 | 105 | |
| Week 12 | 71 | 84 | 101 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 ^[83] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.881 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.11 |
| upper limit | 3.233 |

Notes:

[83] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[84] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.645 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.585 |
| upper limit | 4.498 |

Notes:

[84] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| Statistical analysis title | Statistical Analysis 3 |
|---|--|
| Statistical analysis description: Week 2 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[85] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.464 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.535 |
| upper limit | 4.001 |

Notes:

[85] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| Statistical analysis title | Statistical Analysis 4 |
|---|--|
| Statistical analysis description: Week 2 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[86] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.464 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.534 |
| upper limit | 4.004 |

Notes:

[86] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| Statistical analysis title | Statistical Analysis 5 |
|---|--|
| Statistical analysis description: Week 3 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[87] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.367 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.502 |
| upper limit | 3.762 |

Notes:

[87] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 6 |
| Statistical analysis description: | |
| Week 3 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[88] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.894 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.835 |
| upper limit | 4.609 |

Notes:

[88] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 7 |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[89] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.902 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.829 |
| upper limit | 4.657 |

Notes:

[89] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 4

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[90] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.218 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.025 |
| upper limit | 5.172 |

Notes:

[90] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 5

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[91] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.153 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.375 |
| upper limit | 3.394 |

Notes:

[91] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 5

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[92] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.074 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.957 |
| upper limit | 4.878 |

Notes:

[92] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[93] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.31 |
| upper limit | 3.228 |

Notes:

[93] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[94] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.908 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.856 |
| upper limit | 4.599 |

Notes:

[94] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[95] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.113 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.349 |
| upper limit | 3.332 |

Notes:

[95] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[96] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.594 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.653 |
| upper limit | 4.104 |

Notes:

[96] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 ^[97] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.891 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.21 |
| upper limit | 2.973 |

Notes:

[97] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

Statistical analysis title

Statistical Analysis 16

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[98] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.314 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.108 |
| upper limit | 5.265 |

Notes:

[98] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

Statistical analysis title

Statistical Analysis 17

Statistical analysis description:

Week 9

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.027 ^[99] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.646 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 2.566 |

Notes:

[99] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[100] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.347 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.507 |
| upper limit | 3.683 |

Notes:

[100] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 ^[101] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.792 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.153 |
| upper limit | 2.799 |

Notes:

[101] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[102] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.819 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.805 |
| upper limit | 4.441 |

Notes:

[102] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[103] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.357 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.513 |
| upper limit | 3.699 |

Notes:

[103] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[104] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.131 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.999 |
| upper limit | 4.95 |

Notes:

[104] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 23 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.152 ^[105] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.373 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.891 |
| upper limit | 2.122 |

Notes:

[105] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 24 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[106] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.09 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.351 |
| upper limit | 3.252 |

Notes:

[106] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

Secondary: Number of Participants With Mean Percent Reduction of 100% in The Mean Frequency of Moderate, and Severe VMS From Baseline to Each Study Week Up to Week 12

| | |
|--|---|
| End point title | Number of Participants With Mean Percent Reduction of 100% in The Mean Frequency of Moderate, and Severe VMS From Baseline to Each Study Week Up to Week 12 |
| End point description: | |
| The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization. Participant has 100% reduction from baseline to each post baseline week for the frequency of moderate to severe VMS. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 | |
| Analysis Population: FAS population with available data at specified time point. | |

| End point values | Double-blind Period: Placebo | Double-blind Period: Fezolinetant 30 mg | Double-blind Period: Fezolinetant 45 mg | |
|-----------------------------|------------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 166 | 167 | |
| Units: Participants | | | | |
| Week 1 | 1 | 1 | 3 | |
| Week 2 | 3 | 8 | 4 | |
| Week 3 | 5 | 4 | 11 | |
| Week 4 | 3 | 10 | 17 | |
| Week 5 | 3 | 12 | 11 | |
| Week 6 | 9 | 12 | 17 | |
| Week 7 | 9 | 13 | 18 | |
| Week 8 | 10 | 17 | 22 | |
| Week 9 | 9 | 14 | 18 | |
| Week 10 | 11 | 17 | 25 | |
| Week 11 | 9 | 15 | 28 | |
| Week 12 | 9 | 15 | 25 | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.951 ^[107] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.915 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.036 |
| upper limit | 23.464 |

Notes:

[107] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 1 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.362 ^[108] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.889 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.364 |
| upper limit | 58.864 |

Notes:

[108] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 2 | |
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.138 ^[109] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.775 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.785 |
| upper limit | 12.87 |

Notes:

[109] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 2

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.704 ^[110] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.342 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.291 |
| upper limit | 6.914 |

Notes:

[110] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.741 ^[111] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.798 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.194 |
| upper limit | 3.079 |

Notes:

[111] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 3

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.134 ^[112] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.292 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.809 |
| upper limit | 7.443 |

Notes:

[112] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 4

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.062 ^[113] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.474 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.039 |
| upper limit | 15.712 |

Notes:

[113] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 4

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 ^[114] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 6.184 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.025 |
| upper limit | 26.875 |

Notes:

[114] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Week 5

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.028 ^[115] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.217 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.305 |
| upper limit | 18.806 |

Notes:

[115] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 5

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.044 ^[116] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.802 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.157 |
| upper limit | 17.075 |

Notes:

[116] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.519 ^[117] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.342 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.551 |
| upper limit | 3.382 |

Notes:

[117] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 6

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.117 ^[118] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.961 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.863 |
| upper limit | 4.741 |

Notes:

[118] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.393 ^[119] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.471 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.612 |
| upper limit | 3.687 |

Notes:

[119] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 7

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.086 ^[120] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.087 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.923 |
| upper limit | 5.043 |

Notes:

[120] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.168 ^[121] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.774 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.798 |
| upper limit | 4.143 |

Notes:

[121] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 8

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03 ^[122] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.374 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.112 |
| upper limit | 5.41 |

Notes:

[122] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 17 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.287 ^[123] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.605 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.681 |
| upper limit | 3.971 |

Notes:

[123] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 9

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.08 ^[124] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.108 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.936 |
| upper limit | 5.076 |

Notes:

[124] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.247 ^[125] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.599 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 3.636 |

Notes:

[125] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 10

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 ^[126] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.481 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.201 |
| upper limit | 5.441 |

Notes:

[126] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.212 ^[127] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.728 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.744 |
| upper limit | 4.236 |

Notes:

[127] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 11

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[128] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.536 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.666 |
| upper limit | 8.207 |

Notes:

[128] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 23 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 30 mg |
| Number of subjects included in analysis | 333 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.225 ^[129] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.701 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.733 |
| upper limit | 4.169 |

Notes:

[129] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 24 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | Double-blind Period: Placebo v Double-blind Period: Fezolinetant 45 mg |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 ^[130] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.049 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.42 |
| upper limit | 7.125 |

Notes:

[130] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms at baseline as a covariate.

Secondary: Change from Baseline in The Mean Frequency of Moderate, and Severe VMS at Week 24

| | |
|-----------------|---|
| End point title | Change from Baseline in The Mean Frequency of Moderate, and Severe VMS at Week 24 |
|-----------------|---|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed). Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 24 weeks of fezolinetant exposure (week 36 for arms Placebo/Fezolinetant 30 mg and Placebo/Fezolinetant 45 mg)

| End point values | Double-blind Period:Placebo/ Extension Period:Fezoline tant 30mg | Double-blind Period:Placebo/ Extension Period:Fezoline tant 45mg | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 62 | 60 | 131 | 134 |
| Units: VMS per day | | | | |
| arithmetic mean (standard deviation) | -9.01 (± 5.80) | -7.08 (± 5.40) | -7.86 (± 4.21) | -7.96 (± 4.53) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in The Mean Severity of Moderate, and Severe VMS at Week 24

| | |
|-----------------|--|
| End point title | Change from Baseline in The Mean Severity of Moderate, and Severe VMS at Week 24 |
|-----------------|--|

End point description:

Severity of moderate to severe VMS per day at post baseline visit was calculated as follows:

[(number of mild hot flashes per day x 1) + (number of moderate hot flashes per day x 2) + (number of severe hot flashes per day x 3)]/Total number of daily mild/moderate/severe hot flashes

Moderate VMS was defined as sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed).

Severity was zero for participants that had no mild or moderate or severe VMS. Higher scores indicates greater severity.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 24 weeks of fezolinetant exposure (week 36 for arms Placebo/Fezolinetant 30 mg and Placebo/Fezolinetant 45 mg)

| End point values | Double-blind Period:Placebo/ Extension Period:Fezoline tant 30mg | Double-blind Period:Placebo/ Extension Period:Fezoline tant 45mg | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 62 | 60 | 131 | 134 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | -0.78 (± 0.85) | -0.95 (± 0.77) | -0.85 (± 0.88) | -0.90 (± 0.80) |

Statistical analyses

Secondary: Number of Participants in Each Category of Patient's Global Impression of Change (PGIC) in VMS at Each Visit

| | |
|-----------------|---|
| End point title | Number of Participants in Each Category of Patient's Global Impression of Change (PGIC) in VMS at Each Visit ^[131] |
|-----------------|---|

End point description:

The PGI is comprised of 2 companion 1-item PRO measures analogous to the Clinical Global Impression (CGI) scales. These measures provide brief, stand-alone global assessments prior to and after initiating a study medication. Patient-perceived change from the initiation of treatment (PGI-C)-VMS is used to evaluate meaningful within-person changes over time in VMS. This measure provides patient-perceived change from the initiation of treatment.

The PGI-C VMS asks: "Compared to the beginning of this study, how would you rate your HFs/night sweats now?" Subject ratings range from (1) much better to (7) much worse. Participant ratings range from 1=much better, 2= moderately better, 3= a little better, 4= no change, 5= a little worse, 6= moderately worse, 7= much worse.

Analysis Population: FAS population with available data at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 4, 12, 16, 20, 24, 28, 32, 36, 40, 44, 52 of fezolinetant exposure (weeks 16, 24, 28, 32, 36, 40, 44, 48 and 52 for arms Placebo/Fezolinetant 30 mg and Placebo/Fezolinetant 45 mg)

Notes:

[131] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There was no pre-specified statistical analysis for this endpoint.

| End point values | Double-blind Period: Placebo | Double-blind Period:Placebo/ Extension Period:Fezoline tant 30mg | Double-blind Period:Placebo/ Extension Period:Fezoline tant 45mg | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg |
|--|---------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 151 | 67 | 69 | 155 |
| Units: Participants | | | | |
| Week 4: Much better (n = 151, 0, 3, 155, 159) | 25 | 0 | 2 | 61 |
| Week 4: Moderately better (n=151, 0, 3, 155, 159) | 23 | 0 | 0 | 21 |
| Week 4: A little better (n=151, 0, 3, 155, 159) | 46 | 0 | 1 | 42 |
| Week 4: No change (n = 151, 0, 3, 155, 159) | 43 | 0 | 0 | 29 |
| Week 4: A little worse (n = 151, 0, 3, 155, 159) | 6 | 0 | 0 | 2 |
| Week 4: Moderately worse (n=151, 0, 3, 155, 159) | 6 | 0 | 0 | 0 |
| Week 4: Much worse (n = 151, 0, 3, 155, 159) | 2 | 0 | 0 | 0 |
| Week 12: Much better (n = 144, 67, 69, 145, 149) | 35 | 40 | 30 | 68 |
| Week 12: Moderately better (n=144, 67, 69, 145, 149) | 24 | 11 | 18 | 25 |
| Week 12: A little better (n=144, 67, 69, 145, 149) | 36 | 11 | 10 | 29 |
| Week 12: No change (n = 144, 67, 69, 145, 149) | 39 | 4 | 4 | 19 |

| | | | | |
|---|-------|---|---|----|
| Week 12:A little worse(n = 144, 67, 69, 145, 149) | 6 | 1 | 4 | 1 |
| Week 12:Moderately worse(n=144, 67, 69, 145, 149) | 2 | 0 | 1 | 2 |
| Week 12: Much worse(n=144, 67, 69, 145, 149) | 2 | 0 | 2 | 1 |
| Week 16: Much better(n =NA,0, 0, 1, 2,) | 99999 | 0 | 0 | 0 |
| Week 16:Moderately better(n =NA,0, 0, 1, 2,) | 99999 | 0 | 0 | 0 |
| Week 16: A little better(n =NA,0, 0, 1, 2,) | 99999 | 0 | 0 | 0 |
| Week 16: No change(n =NA,0, 0, 1, 2,) | 99999 | 0 | 0 | 0 |
| Week 16: A little worse(n =NA,0, 0, 1, 2,) | 99999 | 0 | 0 | 0 |
| Week 16:Moderately worse(n =NA,0, 0, 1, 2,) | 99999 | 0 | 0 | 0 |
| Week 16: Much worse(n =NA,0, 0, 1, 2,) | 99999 | 0 | 0 | 0 |
| Week 20: Much better (n =NA,0, 0,2,0) | 99999 | 0 | 0 | 0 |
| Week 20:Moderately better(n =NA,0, 0,2,0) | 99999 | 0 | 0 | 0 |
| Week 20: A little better (n =NA,0, 0,2,0) | 99999 | 0 | 0 | 0 |
| Week 20: No change (n =NA,0, 0,2,0) | 99999 | 0 | 0 | 1 |
| Week 20: A little worse (n =NA,0, 0,2,0) | 99999 | 0 | 0 | 0 |
| Week 20: Moderately worse(n =NA,0, 0,2,0) | 99999 | 0 | 0 | 0 |
| Week 20: Much worse (n =NA,0, 0,2,0) | 99999 | 0 | 0 | 0 |
| Week 24: Much better (n = NA,1, 0, 134, 139) | 99999 | 0 | 0 | 68 |
| Week 24:Moderately better(n = NA,1, 0, 134, 139) | 99999 | 1 | 0 | 31 |
| Week 24: A little better(n = NA,1, 0, 134, 139) | 99999 | 0 | 0 | 22 |
| Week 24: No change (n = NA,1, 0, 134, 139) | 99999 | 0 | 0 | 9 |
| Week 24: A little worse(n = NA,1, 0, 134, 139) | 99999 | 0 | 0 | 1 |
| Week 24:Moderately worse (n = NA,1, 0, 134, 139) | 99999 | 0 | 0 | 2 |
| Week 24: Much worse (n = NA,1, 0, 134, 139) | 99999 | 0 | 0 | 1 |
| Week 28: Much better (n = NA,1, 0,1,1) | 99999 | 1 | 0 | 1 |
| Week 28: Moderately better (n = NA,1, 0,1,1) | 99999 | 0 | 0 | 0 |
| Week 28: A little better (n = NA,1, 0,1,1) | 99999 | 0 | 0 | 0 |
| Week 28: No change (n = NA,1, 0,1,1) | 99999 | 0 | 0 | 0 |
| Week 28: A little worse (n = NA,1, 0,1,1) | 99999 | 0 | 0 | 0 |
| Week 28:Moderately worse (n = NA,1, 0,1,1) | 99999 | 0 | 0 | 0 |
| Week 28: Much worse (n = NA,1, 0,1,1) | 99999 | 0 | 0 | 0 |
| Week 32: Much better (n =NA, 0, 0,0,1) | 99999 | 0 | 0 | 0 |
| Week 32:Moderately better(n =NA, 0, 0,0,1) | 99999 | 0 | 0 | 0 |
| Week 32: A little better(n =NA, 0, 0,0,1) | 99999 | 0 | 0 | 0 |

| | | | | |
|---|-------|-------|-------|----|
| Week 32: No change(n =NA, 0, 0,0,1) | 99999 | 0 | 0 | 0 |
| Week 32: A little worse(n =NA, 0, 0,0,1) | 99999 | 0 | 0 | 0 |
| Week 32: Moderately worse(n =NA, 0, 0,0,1) | 99999 | 0 | 0 | 0 |
| Week 32: Much worse(n =NA, 0, 0,0,1) | 99999 | 0 | 0 | 0 |
| Week 36: Much better (n =NA, 0, 0,1, 0,) | 99999 | 0 | 0 | 0 |
| Week 36: Moderately better (n =NA, 0, 0,1, 0,) | 99999 | 0 | 0 | 1 |
| Week 36: A little better(n =NA, 0, 0,1, 0,) | 99999 | 0 | 0 | 0 |
| Week 36: No change(n =NA, 0, 0,1, 0,) | 99999 | 0 | 0 | 0 |
| Week 36: A little worse(n =NA, 0, 0,1, 0,) | 99999 | 0 | 0 | 0 |
| Week 36: Moderately worse(n =NA, 0, 0,1, 0,) | 99999 | 0 | 0 | 0 |
| Week 36: Much worse(n =NA, 0, 0,1, 0,) | 99999 | 0 | 0 | 0 |
| Week 40: Much better (n = NA,55, 54,0, 0) | 99999 | 33 | 31 | 0 |
| Week 40: Moderately better(n = NA,55, 54,0, 0) | 99999 | 14 | 13 | 0 |
| Week 40: A little better(n = NA,55, 54,0, 0) | 99999 | 5 | 8 | 0 |
| Week 40: No change(n = NA,55, 54,0, 0) | 99999 | 3 | 2 | 0 |
| Week 40: A little worse(n = NA,55, 54,0, 0) | 99999 | 0 | 0 | 0 |
| Week 40: Moderately worse(n = NA,55, 54,0, 0) | 99999 | 0 | 0 | 0 |
| Week 40: Much worse(n = NA,55, 54,0, 0) | 99999 | 0 | 0 | 0 |
| Week 44: Much better (n = NA, NA, NA,2, 0,) | 99999 | 99999 | 99999 | 2 |
| Week 44: Moderately better(n = NA, NA, NA,2, 0,) | 99999 | 99999 | 99999 | 0 |
| Week 44: A little better (n = NA, NA, NA,2, 0,) | 99999 | 99999 | 99999 | 0 |
| Week 44: No change(n = NA, NA, NA,2, 0,) | 99999 | 99999 | 99999 | 0 |
| Week 44: A little worse(n = NA, NA, NA,2, 0,) | 99999 | 99999 | 99999 | 0 |
| Week 44: Moderately worse(n = NA, NA, NA,2, 0,) | 99999 | 99999 | 99999 | 0 |
| Week 44: Much worse(n = NA, NA, NA,2, 0,) | 99999 | 99999 | 99999 | 0 |
| Week 52: Much better (n = NA, NA, NA,107, 116) | 99999 | 99999 | 99999 | 60 |
| Week 52: Moderately better(n = NA, NA, NA,107, 116) | 99999 | 99999 | 99999 | 25 |
| Week 52: A little better(n = NA, NA, NA,107, 116) | 99999 | 99999 | 99999 | 14 |
| Week 52: No change(n = NA, NA, NA,107, 116) | 99999 | 99999 | 99999 | 4 |
| Week 52: A little worse(n = NA, NA, NA,107, 116) | 99999 | 99999 | 99999 | 1 |
| Week 52: Moderately worse(n=NA, NA, NA,107,116) | 99999 | 99999 | 99999 | 1 |
| Week 52: Much worse(n = NA, NA, NA,107, 116) | 99999 | 99999 | 99999 | 2 |

| | | | | |
|--|--|--|--|--|
| End point values | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 150 | | | |
| Units: Participants | | | | |
| Week 4: Much better (n = 151, 0, 3, 155, 159) | 68 | | | |
| Week 4: Moderately better (n=151, 0, 3, 155, 159) | 32 | | | |
| Week 4: A little better (n=151, 0, 3, 155, 159) | 42 | | | |
| Week 4: No change (n = 151, 0, 3, 155, 159) | 16 | | | |
| Week 4: A little worse (n = 151, 0, 3, 155, 159) | 0 | | | |
| Week 4: Moderately worse (n=151, 0, 3, 155, 159) | 0 | | | |
| Week 4: Much worse (n = 151, 0, 3, 155, 159) | 1 | | | |
| Week 12: Much better (n = 144, 67, 69, 145, 149) | 71 | | | |
| Week 12: Moderately better (n=144, 67, 69, 145, 149) | 37 | | | |
| Week 12: A little better (n=144, 67, 69, 145, 149) | 32 | | | |
| Week 12: No change (n = 144, 67, 69, 145, 149) | 8 | | | |
| Week 12: A little worse (n = 144, 67, 69, 145, 149) | 1 | | | |
| Week 12: Moderately worse (n=144, 67, 69, 145, 149) | 0 | | | |
| Week 12: Much worse (n=144, 67, 69, 145, 149) | 0 | | | |
| Week 16: Much better (n = NA, 0, 0, 1, 2,) | 2 | | | |
| Week 16: Moderately better (n = NA, 0, 0, 1, 2,) | 0 | | | |
| Week 16: A little better (n = NA, 0, 0, 1, 2,) | 0 | | | |
| Week 16: No change (n = NA, 0, 0, 1, 2,) | 0 | | | |
| Week 16: A little worse (n = NA, 0, 0, 1, 2,) | 0 | | | |
| Week 16: Moderately worse (n = NA, 0, 0, 1, 2,) | 0 | | | |
| Week 16: Much worse (n = NA, 0, 0, 1, 2,) | 0 | | | |
| Week 20: Much better (n = NA, 0, 0, 2, 0) | 0 | | | |
| Week 20: Moderately better (n = NA, 0, 0, 2, 0) | 0 | | | |
| Week 20: A little better (n = NA, 0, 0, 2, 0) | 0 | | | |
| Week 20: No change (n = NA, 0, 0, 2, 0) | 0 | | | |
| Week 20: A little worse (n = NA, 0, 0, 2, 0) | 0 | | | |

| | | | | |
|--|----|--|--|--|
| Week 20: Moderately worse(n =NA,0, 0,2,0) | 0 | | | |
| Week 20: Much worse (n =NA,0, 0,2,0) | 0 | | | |
| Week 24: Much better (n = NA,1, 0, 134, 139) | 76 | | | |
| Week 24:Moderately better(n = NA,1, 0, 134, 139) | 33 | | | |
| Week 24: A little better(n = NA,1, 0, 134, 139) | 22 | | | |
| Week 24: No change (n = NA,1, 0, 134, 139) | 4 | | | |
| Week 24: A little worse(n = NA,1, 0, 134, 139) | 3 | | | |
| Week 24:Moderately worse (n = NA,1, 0, 134, 139) | 1 | | | |
| Week 24: Much worse (n = NA,1, 0, 134, 139) | 0 | | | |
| Week 28: Much better (n = NA,1, 0,1,1) | 0 | | | |
| Week 28: Moderately better (n = NA,1, 0,1,1) | 0 | | | |
| Week 28: A little better (n = NA,1, 0,1,1) | 0 | | | |
| Week 28: No change (n = NA,1, 0,1,1) | 0 | | | |
| Week 28: A little worse (n = NA,1, 0,1,1) | 0 | | | |
| Week 28:Moderately worse (n = NA,1, 0,1,1) | 0 | | | |
| Week 28: Much worse (n = NA,1, 0,1,1) | 1 | | | |
| Week 32: Much better (n =NA, 0, 0,0,1) | 1 | | | |
| Week 32:Moderately better(n =NA, 0, 0,0,1) | 0 | | | |
| Week 32: A little better(n =NA, 0, 0,0,1) | 0 | | | |
| Week 32: No change(n =NA, 0, 0,0,1) | 0 | | | |
| Week 32: A little worse(n =NA, 0, 0,0,1) | 0 | | | |
| Week 32:Moderately worse(n =NA, 0, 0,0,1) | 0 | | | |
| Week 32: Much worse(n =NA, 0, 0,0,1) | 0 | | | |
| Week 36: Much better (n =NA, 0, 0,1, 0,) | 0 | | | |
| Week 36: Moderately better (n =NA, 0, 0,1, 0,) | 0 | | | |
| Week 36: A little better(n =NA, 0, 0,1, 0,) | 0 | | | |
| Week 36: No change(n =NA, 0, 0,1, 0,) | 0 | | | |
| Week 36: A little worse(n =NA, 0, 0,1, 0,) | 0 | | | |
| Week 36: Moderately worse(n =NA, 0, 0,1, 0,) | 0 | | | |
| Week 36: Much worse(n =NA, 0, 0,1, 0,) | 0 | | | |
| Week 40: Much better (n = NA,55, 54,0, 0) | 0 | | | |
| Week 40:Moderately better(n = NA,55, 54,0, 0) | 0 | | | |
| Week 40: A little better(n = NA,55, 54,0, 0) | 0 | | | |
| Week 40: No change(n = NA,55, 54,0, 0) | 0 | | | |

| | | | | |
|--|----|--|--|--|
| Week 40: A little worse(n = NA,55, 54,0, 0) | 0 | | | |
| Week 40:Moderately worse(n = NA,55, 54,0, 0) | 0 | | | |
| Week 40: Much worse(n = NA,55, 54,0, 0) | 0 | | | |
| Week 44: Much better (n = NA, NA, NA,2, 0,) | 0 | | | |
| Week 44:Moderately better(n = NA, NA, NA,2, 0,) | 0 | | | |
| Week 44: A little better (n = NA, NA, NA,2, 0,) | 0 | | | |
| Week 44: No change(n = NA, NA, NA,2, 0,) | 0 | | | |
| Week 44: A little worse(n = NA, NA, NA,2, 0,) | 0 | | | |
| Week 44:Moderately worse(n = NA, NA, NA,2, 0,) | 0 | | | |
| Week 44: Much worse(n = NA, NA, NA,2, 0,) | 0 | | | |
| Week 52: Much better (n = NA, NA, NA,107, 116) | 77 | | | |
| Week 52:Moderately better(n = NA, NA, NA,107, 116) | 22 | | | |
| Week 52: A little better(n = NA, NA, NA,107, 116) | 13 | | | |
| Week 52: No change(n = NA, NA, NA,107, 116) | 2 | | | |
| Week 52: A little worse(n = NA, NA, NA,107, 116) | 0 | | | |
| Week 52:Moderately worse(n=NA, NA, NA,107,116) | 0 | | | |
| Week 52: Much worse(n = NA, NA, NA,107, 116) | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

| | |
|---|---|
| End point title | Number of Participants With Adverse Events ^[132] |
| End point description: | |
| An AE is any untoward medical occurrence in a participant administered a study drug, & which does not necessarily have to have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with use of a medicinal product (mp) whether or not considered related to the mp. An AE is considered "serious" if it results in death, is life-threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, Results in congenital anomaly or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, hospitalization for treatment/observation/examination caused by AE is to be considered as serious, discontinuation due to increases in liver enzymes, other medically important events. TEAE was defined as an AE observed from first dose date up to 21 days after last dose. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose date up to 21 days after last dose (to 55 weeks) | |
| Analysis Population: Safety analysis set consisted of all randomized participants who took at least 1 dose of study intervention. | |

Notes:

[132] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There was no pre-specified statistical analysis for this endpoint.

| End point values | Double-blind Period: Placebo | Double-blind Period: Placebo/ Extension Period: Fezolinetant 30mg | Double-blind Period: Placebo/ Extension Period: Fezolinetant 45mg | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg |
|--|---------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 167 | 76 | 75 | 166 |
| Units: Participants | | | | |
| Treatment Emergent Adverse Events (TEAE) | 54 | 43 | 45 | 107 |
| Drug-related TEAE | 11 | 8 | 8 | 33 |
| Serious TEAE | 0 | 2 | 4 | 9 |
| Drug-related serious TEAE | 0 | 0 | 1 | 0 |
| TEAE leading to death | 0 | 0 | 1 | 0 |
| Drug-related TEAE leading to death | 0 | 0 | 0 | 0 |
| TEAE leading to withdrawal of treatment | 1 | 2 | 3 | 4 |
| Drug-related TEAE leading to withdrawal of trt | 0 | 1 | 2 | 1 |
| Death | 0 | 0 | 1 | 0 |

| End point values | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg | | | |
|--|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 167 | | | |
| Units: Participants | | | | |
| Treatment Emergent Adverse Events (TEAE) | 106 | | | |
| Drug-related TEAE | 30 | | | |
| Serious TEAE | 8 | | | |
| Drug-related serious TEAE | 1 | | | |
| TEAE leading to death | 0 | | | |
| Drug-related TEAE leading to death | 0 | | | |
| TEAE leading to withdrawal of treatment | 7 | | | |
| Drug-related TEAE leading to withdrawal of trt | 6 | | | |
| Death | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose date up to 21 days after last dose (to 55 weeks)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|-------|
| Dictionary version | v23.0 |
|--------------------|-------|

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Double-blind Period: Placebo |
|-----------------------|------------------------------|

Reporting group description:

Participants received fezolinetant matching placebo (two fezolinetant matching placebo tablets) orally, once daily (QD) up to week 12 during double-blind treatment period.

| | |
|-----------------------|---|
| Reporting group title | Double-blind : Placebo/Extension : Fezolinetant 45 mg |
|-----------------------|---|

Reporting group description:

Participants who received placebo during double-blind treatment period were re-randomized to receive fezolinetant 45 mg orally, QD from week 13 up to week 52 during extension treatment period.

| | |
|-----------------------|---|
| Reporting group title | Double-blind : Placebo/Extension : Fezolinetant 30 mg |
|-----------------------|---|

Reporting group description:

Participants who received placebo during double-blind treatment period were re-randomized to receive fezolinetant 30 mg orally, QD from week 13 up to week 52 during extension treatment period.

| | |
|-----------------------|--|
| Reporting group title | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg |
|-----------------------|--|

Reporting group description:

Participants received fezolinetant 30 mg (one 30 mg fezolinetant tablet and one placebo tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 30 mg orally, QD from week 13 up to Week 52 during extension treatment period.

| | |
|-----------------------|--|
| Reporting group title | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg |
|-----------------------|--|

Reporting group description:

Participants received fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD up to week 12 during double-blind treatment period followed by fezolinetant 45 mg (one 30 mg tablet and one 15 mg tablet) orally, QD from week 13 up to Week 52 during extension treatment period.

| Serious adverse events | Double-blind Period: Placebo | Double-blind : Placebo/Extension : Fezolinetant 45 mg | Double-blind : Placebo/Extension : Fezolinetant 30 mg |
|---|------------------------------|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 4 / 75 (5.33%) | 2 / 76 (2.63%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive breast carcinoma | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Keratoacanthoma | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 75 (1.33%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 75 (1.33%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb traumatic amputation | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 75 (1.33%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Posterior tibial nerve injury | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|----------------|----------------|
| Skin laceration | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary dyskinesia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 75 (1.33%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 75 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 166 (5.42%) | 8 / 167 (4.79%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive breast carcinoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Keratoacanthoma | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb traumatic amputation | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posterior tibial nerve injury | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal haemorrhage | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary dyskinesia | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 166 (0.00%) | 1 / 167 (0.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 2 / 166 (1.20%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 166 (0.60%) | 0 / 167 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Double-blind Period: Placebo | Double-blind : Placebo/Extension : Fezolinetant 45 mg | Double-blind : Placebo/Extension : Fezolinetant 30 mg |
|--|---------------------------------|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 6 / 167 (3.59%) | 12 / 75 (16.00%) | 10 / 76 (13.16%) |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 167 (0.00%) 0 | 5 / 75 (6.67%) 6 | 1 / 76 (1.32%) 1 |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 1 / 167 (0.60%) 1 | 0 / 75 (0.00%) 0 | 4 / 76 (5.26%) 4 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 4 / 167 (2.40%) 4 | 4 / 75 (5.33%) 5 | 1 / 76 (1.32%) 1 |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) | 1 / 167 (0.60%) 1 | 3 / 75 (4.00%) 3 | 4 / 76 (5.26%) 4 |

| Non-serious adverse events | Double-blind: Fezolinetant 30 mg/Extension: Fezolinetant 30 mg | Double-blind: Fezolinetant 45 mg/Extension: Fezolinetant 45 mg | |
|--|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 20 / 166 (12.05%) | 34 / 167 (20.36%) | |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 2 / 166 (1.20%) 2 | 3 / 167 (1.80%) 3 | |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 3 / 166 (1.81%) 3 | 7 / 167 (4.19%) 7 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 8 / 166 (4.82%) 9 | 12 / 167 (7.19%) 14 | |
| Infections and infestations | | | |

| | | | |
|--|----------------------|------------------------|--|
| COVID-19 subjects affected / exposed occurrences (all) | 8 / 166 (4.82%) 8 | 15 / 167 (8.98%) 15 | |
|--|----------------------|------------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 17 May 2019 | <p>The changed included:</p> <p>The study title is updated to convey that the second phase of the study is a non-controlled extension period.</p> <p>The number of subjects to be enrolled is increased from 300 to 450, and the sample size justification parameters are updated to reflect a possible 20% discontinuation rate instead of a 32% rate.</p> <p>An additional treatment arm is added to include a 45 mg dose of fezolinetant.</p> <p>The schedule of assessments is updated to include a mammogram at week 52/end of treatment/early discontinuation and an endometrial biopsy following study discontinuation. Further details are provided regarding the circumstances under which these procedures are performed.</p> <p>The screening serology panel is updated to include testing for antibody against hepatitis B antigen and antibody to hepatitis B core antigen.</p> <p>The dose rationale is updated with additional information about Study ESN364_HF_205 and results regarding the potential for drug-induced liver injury.</p> <p>The length of time prior to screening in which a normal/negative or not clinically significant mammogram may have been performed is increased to within 12 months of trial enrollment.</p> <p>The schedule of assessments is updated to include 2 additional study visits (2b and 5b).</p> <p>The schedule of assessments and pharmacokinetics assessment sections are updated to include the addition of blood draws for pharmacokinetic analysis in subjects with a signal of elevated transaminases who are returning for a repeat hepatic abnormality testing blood draw.</p> <p>Details are added for the reporting of drug-induced liver damage and it is clarified that such events are to be characterized as serious adverse events (SAEs).</p> <p>The statistical analysis is updated to accommodate inclusion of a second dosing cohort.</p> |

| | |
|--------------|--|
| 01 July 2020 | <p>The changes included:</p> <p>Inclusion criterion #4 was updated to remove with or without hysterectomy from the bilateral oophorectomy screening criteria. Inclusion criteria #8 and #10 are aligned to account for the exclusion of subjects who have had a hysterectomy. Inclusion criterion #9 is updated to specify that the endometrial biopsy obtained at screening must be considered evaluable; this criterion is now required for all subjects.</p> <p>Alternate measures that may be implemented due to site closures related to the COVID-19 pandemic are added to the protocol. These include telemedicine conferences (by telephone), home healthcare services, and laboratory assessments performed at local laboratories. It is noted that subjects who screen fail due to a COVID-19 pandemic study suspension and have an evaluable endometrial biopsy will not require a repeat biopsy if they rescreen.</p> <p>Exclusion criteria #6 and #7 are updated so that they apply to all subjects, not just subjects with a uterus, and the exception for endometrial thickness less than 4 mm is removed from exclusion criterion #7. Exclusion criterion #20 is added to exclude subjects who have had partial or full hysterectomies.</p> <p>Language is added to specify that the screening endometrial biopsy must be evaluable. Retest biopsies may only be performed for insufficient material or unevaluable biopsies, and a maximum of one retest biopsy during screening is allowed. It is noted that subjects will be allowed into the study based on the primary endometrial result/diagnosis, but a second and tertiary diagnosis will also be reported.</p> <p>Adverse events (AEs) of abuse liability, depression, wakefulness and effect on memory are added to the protocol as AEs of special interest. AEs of liver test elevation are clarified.</p> <p>Category 2 results of secondary or tertiary screening endometrial biopsy diagnosis are added to the list of reasons for subject discontinuation.</p> |
| 01 July 2020 | <p>The exploratory endpoint of "Mean score on the PGI-C in VMS from baseline to each visit" is re-categorized as a secondary endpoint.</p> <p>Language is added to instruct sites about daily diary compliance.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported