



Clinical trial results:

Pilot/Phase IIa Trial to Investigate the Effect of ESN364 in Early Postmenopausal Women Suffering From Hot Flashes

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2015-002578-20 |
| Trial protocol | BE |
| Global end of trial date | 06 October 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 18 November 2023 |
| First version publication date | 15 November 2017 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | ESN364-HF-204 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05419908 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Ogeda S.A. |
| Sponsor organisation address | 47 Rue Adrienne Bolland, Gosselies, Belgium, 6047 |
| Public contact | Clinical Trial Disclosure, Ogeda S.A., astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Ogeda S.A., 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 | 06 October 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 October 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of ESN364 on the severity and frequency of hot flashes (HF) in early postmenopausal women suffering from HF, in terms of changes in weekly Hot Flash Score (HFS) from baseline to Week 12.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95) and with applicable local requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 21 September 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 87 |
| Worldwide total number of subjects | 87 |
| EEA total number of subjects | 87 |

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) | 87 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Postmenopausal women participants between 40 to 65 years of age who had hot flashes (HF) and who met the inclusion criteria and none of the exclusion criteria were enrolled in this study.

Pre-assignment

Screening details:

Prior to randomization, participants had a screening period during which a minimum 7-day collection of baseline HF frequency and severity assessments were performed.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Participants received fezolinetant matching placebo capsules orally, twice daily (BID) for a period of 12 weeks.

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

Dosage and administration details:

Participants received 90 mg of placebo orally twice a day for 12 weeks.

| | |
|------------------|--------------|
| Arm title | Fezolinetant |
|------------------|--------------|

Arm description:

Participants received 90 milligrams (mg) fezolinetant capsules orally, BID for a period of 12 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ESN364 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 90 mg of ESN364 orally twice a day for 12 weeks.

| Number of subjects in period 1 | Placebo | Fezolinetant |
|---|---------|--------------|
| Started | 44 | 43 |
| Completed | 40 | 40 |
| Not completed | 4 | 3 |
| Consent withdrawn by subject | 2 | - |
| Miscellaneous | 1 | 1 |
| Subject didn't Fulfill all Eligibility Criteria | 1 | - |
| Serious Adverse Event | - | 2 |

Baseline characteristics

Reporting groups

| | |
|--|--------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received fezolinetant matching placebo capsules orally, twice daily (BID) for a period of 12 weeks. | |
| Reporting group title | Fezolinetant |
| Reporting group description: Participants received 90 milligrams (mg) fezolinetant capsules orally, BID for a period of 12 weeks. | |

| Reporting group values | Placebo | Fezolinetant | Total |
|--|------------------|------------------|-------|
| Number of subjects | 44 | 43 | 87 |
| Age categorical Units: Subjects | | | |
| Age Continuous Units: Years arithmetic mean standard deviation | 53.7 ± 4.25 | 53.3 ± 4.03 | - |
| Sex: Female, Male Units: Subjects | | | |
| Female | 44 | 43 | 87 |
| Male | 0 | 0 | 0 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 44 | 42 | 86 |
| More than one race | 0 | 1 | 1 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | 2 |
| Not Hispanic or Latino | 42 | 42 | 84 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Weekly General Hot Flash Score | | | |
| The HF Score was calculated as follows (number of mild HF/day × 1) + (number of moderate HF/day × 2) + (number of severe HF/day × 3). Higher scores indicate worse symptoms. There is no maximum score since the score was participant-dependent for both number and severity. | | | |
| Units: Score on a scale arithmetic mean standard deviation | 25.76 ± 10.26 | 28.76 ± 13.39 | - |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received fezolinetant matching placebo capsules orally, twice daily (BID) for a period of 12 weeks. | |
| Reporting group title | Fezolinetant |
| Reporting group description: Participants received 90 milligrams (mg) fezolinetant capsules orally, BID for a period of 12 weeks. | |

Primary: Change From Baseline to Week 12 in The Weekly General Hot Flash Score

| | |
|---|---|
| End point title | Change From Baseline to Week 12 in The Weekly General Hot Flash Score |
| End point description: The HF score (based on severity and frequency) was calculated as: (number of mild HF/day × 1) + (number of moderate HF/day × 2) + (number of severe HF/day × 3) Severity of HFs is clinically defined as follows: Mild: sensation of heat without sweating/dampness. If at night, participant didn't wake up but later notices damp sheets or clothing. Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed). Higher scores indicate worse symptoms. There is no maximum score since the score was participant dependent for both number and severity. | |
| End point type | Primary |
| End point timeframe: Baseline and Week 12 Intent-to-treat (ITT) population (included all randomized participants who received at least one dose of the study medication and who had post-baseline efficacy data) with available data at specified time point. | |

| End point values | Placebo | Fezolinetant | | |
|---|--------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: score on a scale | | | | |
| arithmetic mean (confidence interval 95%) | -12.19 (-16.55 to -7.83) | -26.51 (-30.83 to -22.18) | | |

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: analysis of covariance (ANCOVA) | |

| | |
|---|------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[1] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -12.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.89 |
| upper limit | -7.79 |

Notes:

[1] - Least square (LS) mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly hot flash score as covariate. P-value of the t-statistic testing whether there is a treatment difference.

Secondary: Change From Baseline in The Weekly Hot Flash Severity Score at Weeks 4, 8 and 12 (Method 1)

| | |
|-----------------|---|
| End point title | Change From Baseline in The Weekly Hot Flash Severity Score at Weeks 4, 8 and 12 (Method 1) |
|-----------------|---|

End point description:

HF Severity Score by method 1 takes into account the number and severity of moderate and severe HF occurred during a given time period & was calculated as follows HF Severity score = [(No. of moderate HF/day × 2) + (No. of severe HF/day × 3)]/(number of moderate HF + No. of severe HF). Severity of HFs was clinically defined as follows: Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot & was sweating and needed to take action (e.g. removing layers of clothes, open the window, or get out of bed). Higher scores indicate worse symptoms. There is no maximum score since the score was participant-dependent for both number & severity. ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|---|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: score on a scale | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | -0.294 (-0.473 to -0.116) | -1.428 (-1.718 to -1.138) | | |
| Week 8 (n=41, n=40) | -0.608 (-0.899 to -0.318) | -1.557 (-1.858 to -1.257) | | |
| Week 12 (n=40, n=40) | -0.534 (-0.798 to -0.270) | -1.656 (-1.937 to -1.376) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|------------------------|
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[2] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.134 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.466 |
| upper limit | -0.802 |

Notes:

[2] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly hot flash score as covariate. P-value of the t-statistic testing whether there is a treatment difference.

| Statistical analysis title | Statistical Analysis 3 |
|---|------------------------|
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[3] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.122 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.504 |
| upper limit | -0.741 |

Notes:

[3] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly hot flash score as covariate. P-value of the t-statistic testing whether there is a treatment difference.

| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|------------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[4] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.948 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.362 |
| upper limit | -0.535 |

Notes:

[4] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly hot flash score as covariate. P-value of the t-statistic testing whether there is a treatment difference.

Secondary: Change From Baseline in The Weekly Hot Flash Severity Score at Weeks 4, 8 and 12 (Method 2)

| | |
|-----------------|---|
| End point title | Change From Baseline in The Weekly Hot Flash Severity Score at Weeks 4, 8 and 12 (Method 2) |
|-----------------|---|

End point description:

The HF Severity Score by method 2 takes into account moderate and severe HF during a given time period and was calculated as follows

HF Severity score = [(number of moderate HF/day × 2) + (number of severe HF/day × 3)]

The severity of HFs was clinically defined as follows:

- Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).

Higher scores indicate worse symptoms. There is no maximum score since the score was participant-dependent for both number and severity.

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|---|--------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: score on a scale | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | -9.55 (-12.73 to -6.36) | -25.26 (-29.64 to -20.89) | | |
| Week 8 (n=41, n=41) | -11.91 (-15.72 to -8.10) | -25.71 (-30.15 to -21.27) | | |
| Week 12 (n=40, n=40) | -12.14 (-16.62 to -7.65) | -26.61 (-31.06 to -22.17) | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: Week 4 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[5] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -13.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.02 |
| upper limit | -9.54 |

Notes:

[5] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly hot flash score as covariate. P-value of the t-statistic testing whether there is a treatment difference.

| | |
|--|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: Week 12 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[6] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -12.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17 |
| upper limit | -7.83 |

Notes:

[6] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly hot flash score as covariate. P-value of the t-statistic testing whether there is a treatment difference.

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Week 8 | |

| | |
|---|------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[7] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -11.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.3 |
| upper limit | -7.27 |

Notes:

[7] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly hot flash score as covariate. P-value of the t-statistic testing whether there is a treatment difference.

Secondary: Change From Baseline in The Weekly Mild, Moderate and Severe Hot Flash Frequency at Weeks 4, 8 and 12

| | |
|-----------------|---|
| End point title | Change From Baseline in The Weekly Mild, Moderate and Severe Hot Flash Frequency at Weeks 4, 8 and 12 |
|-----------------|---|

End point description:

The weekly HF frequency was calculated as number of mild, moderate and severe hot flashes over the week.

- Mild: sensation of heat without sweating/dampness. If at night, participant didn't wake up but later notices damp sheets or clothing.
- Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).

Higher number of hot flashes is worse.

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|---|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: HF's per day | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | -26.4 (-35.2 to -17.5) | -72.3 (-82.7 to -61.8) | | |
| Week 8 (n=41, n=40) | -32.9 (-43.2 to -22.7) | -73.3 (-83.8 to -62.8) | | |
| Week 12 (n=40, n=40) | -35.6 (-46.7 to -24.5) | -75.3 (-86.4 to -64.3) | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: Week 4 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[8] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -39.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -50.5 |
| upper limit | -29.1 |

Notes:

[8] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as factor. P-value of the t-statistic testing whether there is a treatment difference.

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: Week 8 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[9] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -35.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -47.9 |
| upper limit | -23 |

Notes:

[9] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as factor. P-value of the t-statistic testing whether there is a treatment difference.

| | |
|--|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: Week 12 | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[10] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -47.9 |
| upper limit | -22.1 |

Notes:

[10] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as factor. P-value of the t-statistic testing whether there is a treatment difference.

Secondary: Percentage of Participants With $\geq 70\%$ Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12

| | |
|-----------------|--|
| End point title | Percentage of Participants With $\geq 70\%$ Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12 |
|-----------------|--|

End point description:

HF score (based on severity and frequency) was calculated as: (No. of mild HF/day \times 1) + (No. of moderate HF/day \times 2) + (No. of severe HF/day \times 3) Severity of HFs is clinically defined as follows: Mild: sensation of heat without sweating/dampness. If at night, participant didn't wake up but later notices damp sheets or clothing. Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g. removing layers of clothes, open the window, or get out of bed). Higher scores indicate worse symptoms. There is no maximum score since the score was participant-dependent for both number and severity. ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|-----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | 22.7 (10.34 to 35.11) | 87.8 (77.79 to 97.82) | | |
| Week 8 (n=41, n=40) | 39.0 (24.09 to 53.96) | 87.5 (77.25 to 97.75) | | |
| Week 12 (n=40, n=40) | 42.5 (27.18 to 57.82) | 95.0 (88.25 to 100.00) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[11] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 65.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 49.15 |
| upper limit | 81 |

Notes:

[11] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[12] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 52.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 35.76 |
| upper limit | 69.24 |

Notes:

[12] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[13] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 48.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 30.37 |
| upper limit | 66.59 |

Notes:

[13] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

Secondary: Percentage of Participants With $\geq 80\%$ Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12

| | |
|-----------------|--|
| End point title | Percentage of Participants With $\geq 80\%$ Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12 |
|-----------------|--|

End point description:

HF score (based on severity and frequency) was calculated as: (No. of mild HF/day \times 1) + (No. of moderate HF/day \times 2) + (No. of severe HF/day \times 3) Severity of HFs is clinically defined as follows: Mild: sensation of heat without sweating/dampness. If at night, participant didn't wake up but later notices damp sheets or clothing. Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g. removing layers of clothes, open the window, or get out of bed). Higher scores indicate worse symptoms. There is no maximum score since the score was participant-dependent for both number and severity. ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | 9.1 (0.60 to 17.59) | 78.0 (65.38 to 90.72) | | |
| Week 8 (n=41, n=40) | 26.8 (13.27 to 40.39) | 77.5 (64.56 to 90.44) | | |
| Week 12 (n=40, n=40) | 30.0 (15.80 to 44.20) | 87.5 (77.25 to 97.75) | | |

Statistical analyses

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

Statistical analysis description:

Week 4

| | |
|-------------------|------------------------|
| Comparison groups | Placebo v Fezolinetant |
|-------------------|------------------------|

| | |
|---|----------------------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 ^[14] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 53.7 |
| upper limit | 84.21 |

Notes:

[14] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[15] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 50.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 31.93 |
| upper limit | 69.42 |

Notes:

[15] - Likelihood-ratio test based 95% confidence interval of the percentage difference

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[16] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 57.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 39.99 |
| upper limit | 75.01 |

Notes:

[16] - Likelihood-ratio test based 95% confidence interval of the percentage difference

Secondary: Percentage of Participants With $\geq 90\%$ Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12

| | |
|-----------------|--|
| End point title | Percentage of Participants With $\geq 90\%$ Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12 |
|-----------------|--|

End point description:

HF score (based on severity and frequency) was calculated as: (No. of mild HF/day \times 1) + (No. of moderate HF/day \times 2) + (No. of severe HF/day \times 3) Severity of HFs is clinically defined as follows: Mild: sensation of heat without sweating/dampness. If at night, participant didn't wake up but later notices damp sheets or clothing. Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g. removing layers of clothes, open the window, or get out of bed). Higher scores indicate worse symptoms. There is no maximum score since the score was participant-dependent for both number and severity. ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|-----------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | 6.8 (0.00 to 14.27) | 61.0 (46.04 to 75.91) | | |
| Week 8 (n=41, n=40) | 12.2 (2.18 to 22.21) | 60.0 (44.82 to 75.18) | | |
| Week 12 (n=40, n=40) | 15.0 (3.93 to 26.07) | 62.5 (47.50 to 77.50) | | |

Statistical analyses

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

Statistical analysis description:

Week 4

| | |
|---|----------------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[17] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 54.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 37.47 |
| upper limit | 70.84 |

Notes:

[17] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[18] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 47.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.86 |
| upper limit | 66.14 |

Notes:

[18] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[19] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 47.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 29.62 |
| upper limit | 65.99 |

Notes:

[19] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

Secondary: Percentage of Participants With $\geq 50\%$ Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to Weeks 4, 8 and 12

| | |
|-----------------|--|
| End point title | Percentage of Participants With $\geq 50\%$ Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to |
|-----------------|--|

End point description:

The weekly HF frequency of moderate and severe HF was calculated as number of moderate and severe HF over the week.

- Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).

Higher number of HF indicates worse symptoms.

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|-----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | 45.5 (30.74 to 60.17) | 95.1 (88.53 to 100.00) | | |
| Week 8 (n=41, n=40) | 53.7 (38.39 to 68.92) | 97.5 (92.66 to 100.00) | | |
| Week 12 (n=40, n=40) | 55.0 (39.58 to 70.42) | 97.5 (92.66 to 100.00) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|----------------------------------|
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[20] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 49.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 33.54 |
| upper limit | 65.79 |

Notes:

[20] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[21] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 42.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 26.34 |
| upper limit | 58.66 |

Notes:

[21] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[22] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 43.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 27.83 |
| upper limit | 59.85 |

Notes:

[22] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

Secondary: Percentage of Participants With $\geq 70\%$ Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to Weeks 4, 8 and 12

| | |
|-----------------|--|
| End point title | Percentage of Participants With $\geq 70\%$ Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to Weeks 4, 8 and 12 |
|-----------------|--|

End point description:

The weekly HF frequency of moderate and severe HF was calculated as number of moderate and severe HF over the week.

- Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).

Higher number of HF indicates worse symptoms.

ITT population with available data at specified time point.

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4, 8 and 12 | |

| End point values | Placebo | Fezolinetant | | |
|-----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | 25.0 (12.21 to 37.79) | 87.8 (77.79 to 97.82) | | |
| Week 8 (n=41, n=40) | 46.3 (31.08 to 61.61) | 92.5 (84.34 to 100.00) | | |
| Week 12 (n=40, n=40) | 40.0 (24.82 to 55.18) | 97.5 (92.66 to 100.00) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[23] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 62.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 46.56 |
| upper limit | 79.05 |

Notes:

[23] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|----------------------------------|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[24] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 57.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 41.57 |
| upper limit | 73.43 |

Notes:

[24] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[25] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 46.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.85 |
| upper limit | 63.47 |

Notes:

[25] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

Secondary: Percentage of Participants With $\geq 90\%$ Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to Weeks 4, 8 and 12

| | |
|-----------------|--|
| End point title | Percentage of Participants With $\geq 90\%$ Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to Weeks 4, 8 and 12 |
|-----------------|--|

End point description:

The weekly HF frequency of moderate and severe HF was calculated as number of moderate and severe HF over the week.

- Moderate: 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: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).

Higher number of HF indicates worse symptoms.

ITT population with available data at specified time point.

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4, 8 and 12 | |

| End point values | Placebo | Fezolinetant | | |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 41 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 4 (n=44, n=41) | 6.8 (0.00 to 14.27) | 68.3 (54.05 to 82.54) | | |
| Week 8 (n=41, n=40) | 24.4 (11.25 to 37.54) | 67.5 (52.99 to 82.01) | | |
| Week 12 (n=40, n=40) | 20.0 (7.60 to 32.40) | 72.5 (58.66 to 86.34) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|----------------------------------|
| Statistical analysis description: Week 4 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[26] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 61.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 45.4 |
| upper limit | 77.55 |

Notes:

[26] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| Statistical analysis title | Statistical Analysis 3 |
|--|----------------------------------|
| Statistical analysis description: Week 12 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[27] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 52.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 33.92 |
| upper limit | 71.08 |

Notes:

[27] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[28] |
| Method | Likelihood-Ratio Chi-Square Test |
| Parameter estimate | Percentage Difference |
| Point estimate | 43.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 23.53 |
| upper limit | 62.69 |

Notes:

[28] - Likelihood-ratio test based 95% confidence interval of the percentage difference.

Secondary: Change From Baseline in Hot Flash Related Daily Interference Scale (HFRDIS) Score at Weeks 4, 8 and 12

| | |
|--|--|
| End point title | Change From Baseline in Hot Flash Related Daily Interference Scale (HFRDIS) Score at Weeks 4, 8 and 12 |
| End point description: | |
| <p>The HFRDIS was a 10-item scale which measured a woman's perceptions of the degree to which HF interfere with 9 daily life activities (work, social activities, leisure, sleep, mood, concentration, relations with others, sexuality, enjoying life); the 10th item measures interference with overall quality of life. This scale was modeled after items on the Brief Pain Inventory and Brief Fatigue Inventory both of which assessed the extent to which pain or fatigue interfere with daily life. Participants were asked to rate the extent to which HF had interfered with each item during the previous 4-week time interval using a 0 (do not interfere) to 10 (completely interfere) scale. Overall mean score was calculated as sum of items/number of available items. Higher score indicate a higher interference.</p> | |
| ITT population with available data at specified time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4, 8 and 12 | |

| End point values | Placebo | Fezolinetant | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 41 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Work (n=42, n=41) | -1.7 (± 2.93) | -4.6 (± 2.65) | | |
| Week 8: Work (n=39, n=39) | -2.4 (± 2.80) | -5.0 (± 2.38) | | |
| Week 12: Work (n=39, n=39) | -2.3 (± 2.58) | -4.6 (± 2.68) | | |
| Week 4: Social Activities (n=42, n=41) | -1.6 (± 2.53) | -4.3 (± 2.48) | | |
| Week 8: Social Activities (n=39, n=39) | -1.9 (± 2.85) | -4.7 (± 2.37) | | |
| Week 12: Social Activities (n=39, n=39) | -1.8 (± 2.51) | -4.3 (± 2.35) | | |
| Week 4: Leisure Activities (n=42, n=41) | -1.6 (± 2.63) | -4.0 (± 2.51) | | |
| Week 8: Leisure Activities (n=39, n=39) | -1.7 (± 2.72) | -4.2 (± 2.50) | | |
| Week 12: Leisure Activities (n=39, n=39) | -2.0 (± 2.52) | -3.8 (± 3.08) | | |
| Week 4: Sleep (n=42, n=41) | -2.5 (± 2.93) | -5.2 (± 2.77) | | |
| Week 8: Sleep (n=39, n=39) | -3.2 (± 3.29) | -5.7 (± 2.37) | | |
| Week 12: Sleep (n=39, n=39) | -3.3 (± 3.01) | -5.8 (± 2.43) | | |
| Week 4: Mood (n=42, n=41) | -2.3 (± 2.49) | -4.0 (± 2.85) | | |
| Week 8: Mood (n=39, n=39) | -2.3 (± 2.86) | -4.4 (± 2.84) | | |
| Week 12: Mood (n=39, n=39) | -2.5 (± 2.56) | -4.3 (± 2.64) | | |
| Week 4: Concentration (n=42, n=41) | -1.6 (± 2.68) | -3.9 (± 2.57) | | |
| Week 8: Concentration (n=39, n=39) | -1.6 (± 3.06) | -4.1 (± 2.59) | | |
| Week 12: Concentration (n=39, n=39) | -1.9 (± 3.17) | -4.0 (± 2.47) | | |
| Week 4: Relations With Others (n=42, n=41) | -2.1 (± 2.93) | -3.3 (± 2.45) | | |
| Week 8: Relations With Others (n=39, n=39) | -1.8 (± 3.02) | -3.5 (± 2.70) | | |
| Week 12: Relations With Others (n=39, n=39) | -1.8 (± 3.16) | -3.3 (± 2.67) | | |
| Week 4: Sexuality (n=42, n=41) | -1.9 (± 2.88) | -3.0 (± 3.49) | | |
| Week 8: Sexuality (n=39, n=39) | -1.8 (± 3.48) | -3.2 (± 3.76) | | |
| Week 12: Sexuality (n=39, n=39) | -1.7 (± 2.84) | -3.4 (± 3.86) | | |
| Week 4: Enjoyment of Life (n=42, n=41) | -1.6 (± 2.86) | -3.6 (± 2.65) | | |
| Week 8: Enjoyment of Life (n=39, n=39) | -1.5 (± 3.15) | -3.9 (± 2.59) | | |
| Week 12: Enjoyment of Life (n=39, n=39) | -1.6 (± 3.38) | -3.7 (± 2.42) | | |
| Week 4: Overall Quality of Life (n=42, n=41) | -1.4 (± 2.43) | -3.8 (± 2.87) | | |
| Week 8: Overall Quality of Life (n=39, n=39) | -1.5 (± 3.01) | -4.5 (± 1.92) | | |
| Week 12: Overall Quality of Life (n=39, n=39) | -1.6 (± 3.05) | -4.6 (± 2.16) | | |
| Week 4: Overall Mean Score (n=42, n=41) | -1.84 (± 1.922) | -3.97 (± 2.141) | | |
| Week 8: Overall Mean Score (n=39, n=39) | -1.98 (± 2.439) | -4.33 (± 1.945) | | |
| Week 12: Overall Mean Score (n=39, n=39) | -2.05 (± 2.326) | -4.17 (± 2.067) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Week 4: Work | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[29] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.45 |
| upper limit | -1.6 |

Notes:

[29] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: | |
| Week 8: Social Activities | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[30] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.21 |
| upper limit | -1.47 |

Notes:

[30] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Week 4: Social Activities | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[31] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.33 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.19 |
| upper limit | -1.46 |

Notes:

[31] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

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

Statistical analysis description:

Week 8: Work

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[32] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.29 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.15 |
| upper limit | -1.42 |

Notes:

[32] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

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

Statistical analysis description:

Week 4: Leisure Activities

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[33] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.15 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.99 |
| upper limit | -1.31 |

Notes:

[33] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

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

Statistical analysis description:

Week 8: Leisure Activities

| | |
|-------------------|------------------------|
| Comparison groups | Placebo v Fezolinetant |
|-------------------|------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[34] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.19 |
| upper limit | -1.55 |

Notes:

[34] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Week 12: Leisure Activities | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[35] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.66 |
| upper limit | -0.62 |

Notes:

[35] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
| Statistical analysis description: | |
| Week 4: Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[36] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.08 |
| upper limit | -1.78 |

Notes:

[36] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 6 |
| Statistical analysis description: | |
| Week 12: Social Activities | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[37] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.09 |
| upper limit | -1.29 |

Notes:

[37] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Week 12: Work | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[38] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.03 |
| upper limit | -1.2 |

Notes:

[38] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 17 |
| Statistical analysis description: | |
| Week 8: Concentration | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[39] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.23 |
| Confidence interval | |
| level | Other: 94 % |
| sides | 2-sided |
| lower limit | -3.21 |
| upper limit | -1.25 |

Notes:

[39] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 16 |
| Statistical analysis description: | |
| Week 4: Concentration | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[40] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.86 |
| upper limit | -0.97 |

Notes:

[40] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 13 |
| Statistical analysis description: | |
| Week 4: Mood | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[41] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.67 |
| upper limit | -0.81 |

Notes:

[41] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 12 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 12: Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[42] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.67 |
| upper limit | -1.54 |

Notes:

[42] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 11 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 8: Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[43] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.86 |
| upper limit | -1.57 |

Notes:

[43] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 14 |
|-----------------------------------|-------------------------|
| Statistical analysis description: | |
| Week 8: Mood | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[44] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.09 |
| upper limit | -1.16 |

Notes:

[44] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
| Statistical analysis description: | |
| Week 12: Mood | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[45] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.69 |
| upper limit | -0.88 |

Notes:

[45] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 20 |
| Statistical analysis description: | |
| Week 8: Relations With others | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[46] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | -0.9 |

Notes:

[46] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 18 |
| Statistical analysis description: | |
| Week 12: Concentration | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[47] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.91 |
| upper limit | -0.88 |

Notes:

[47] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 22 |
| Statistical analysis description: | |
| Week 4: Sexuality | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.081 ^[48] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.25 |
| upper limit | 0.13 |

Notes:

[48] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 23 |
| Statistical analysis description: | |
| Week 8: Sexuality | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 ^[49] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 0 |

Notes:

[49] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 24 |
| Statistical analysis description: | |
| Week 12: Sexuality | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.026 ^[50] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.84 |
| upper limit | -0.19 |

Notes:

[50] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 25 |
| Statistical analysis description: | |
| Week 4: Enjoyment of Life | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[51] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.51 |
| upper limit | -0.79 |

Notes:

[51] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 26 |
|--|-------------------------|
| Statistical analysis description: Week 8: Enjoyment of Life | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [52] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.97 |
| upper limit | -1.18 |

Notes:

[52] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 27 |
|---|-------------------------|
| Statistical analysis description: Week 12: Enjoyment of Life | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [53] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.88 |
| upper limit | -0.78 |

Notes:

[53] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 21 |
|---|-------------------------|
| Statistical analysis description: Week 12: Relations With Others | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[54] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.66 |
| upper limit | -0.77 |

Notes:

[54] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 19 |
| Statistical analysis description: Week 4: Relations With Others | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 ^[55] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | -0.46 |

Notes:

[55] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 30 |
| Statistical analysis description: Week 12: Overall Quality of Life | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[56] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.31 |
| upper limit | -1.41 |

Notes:

[56] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 31 |
|---|-------------------------|
| Statistical analysis description: Week 4: Overall Mean Score | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[57] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.73 |
| upper limit | -1.23 |

Notes:

[57] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 32 |
|---|-------------------------|
| Statistical analysis description: Week 8: Overall Mean Score | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[58] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.02 |
| upper limit | -1.4 |

Notes:

[58] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| Statistical analysis title | Statistical Analysis 33 |
|--|-------------------------|
| Statistical analysis description: Week 12: Overall Mean Score | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[59] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.83 |
| upper limit | -1.13 |

Notes:

[59] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 29 |
| Statistical analysis description: Week 8: Overall Quality of Life | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[60] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.41 |
| upper limit | -1.61 |

Notes:

[60] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 28 |
| Statistical analysis description: Week 4: Overall Quality of Life | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[61] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -1.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.86 |
| upper limit | -0.97 |

Notes:

[61] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline weekly HFRDIS as covariate.

Secondary: Change From Baseline in Leeds Sleep Evaluation Questionnaire (LSEQ) at Weeks 4, 8 and 12

| | |
|-----------------|--|
| End point title | Change From Baseline in Leeds Sleep Evaluation Questionnaire (LSEQ) at Weeks 4, 8 and 12 |
|-----------------|--|

End point description:

The LSEQ was a 10-item self-rated questionnaire which assessed participants aspects of sleep and early morning behavior. The questions were grouped into 4 chronological areas: the ease of getting to sleep, the perceived quality of sleep, the ease of awaking from sleep, and the integrity of early morning behavior following wakefulness. The LSEQ was a visual analogue scale which requires respondents to place marks on a group of 10 cm lines, representing the changes they have experienced in a variety of symptoms since the beginning of treatment. Lines extends between extremes like "more difficult than usual" and "easier than usual". Responses are measured using a 100-mm scale and are averaged to provide a score for each domain.

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|---|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 41 | | |
| Units: millimeter (mm) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Getting to Sleep (n=43, n=41) | 1.017 (± 1.9195) | 2.283 (± 2.7364) | | |
| Week 8: Getting to Sleep (n=40, n=40) | 1.145 (± 1.7931) | 2.248 (± 2.5233) | | |
| Week 12: Getting to Sleep (n=39, n=39) | 1.282 (± 1.7761) | 2.094 (± 2.4419) | | |
| Week 4: Quality of Sleep (n=43, n=41) | 2.145 (± 2.6443) | 4.437 (± 4.0768) | | |
| Week 8: Quality of Sleep (n=39, n=40) | 2.378 (± 2.8160) | 4.703 (± 3.1971) | | |
| Week 12: Quality of Sleep (n=39, n=39) | 1.904 (± 2.7872) | 4.385 (± 3.4477) | | |
| Week 4: Awake Following Sleep (n=43, n=40) | 0.642 (± 2.0739) | 2.180 (± 3.0579) | | |
| Week 8: Awake Following Sleep (n=40, n=40) | 0.653 (± 2.5019) | 2.920 (± 3.0219) | | |
| Week 12: Awake Following Sleep (n=39, n=39) | 1.024 (± 2.6114) | 2.887 (± 3.1333) | | |
| Week 4: Behavior Following Wakening (n=43, n=41) | 1.173 (± 2.1743) | 2.513 (± 2.7919) | | |
| Week 8: Behavior Following Wakening (n=40, n=40) | 0.750 (± 2.6371) | 2.539 (± 2.7742) | | |
| Week 12: Behavior Following Wakening (n=39, n=39) | 1.203 (± 2.5185) | 2.233 (± 2.8190) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 4: Getting to Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[62] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.375 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.651 |
| upper limit | 2.1 |

Notes:

[62] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 8: Getting to Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[63] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.166 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.505 |
| upper limit | 1.827 |

Notes:

[63] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| Statistical analysis title | Statistical Analysis 3 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 12: Getting to Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 ^[64] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.895 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.19 |
| upper limit | 1.599 |

Notes:

[64] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

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

Statistical analysis description:

Week 4: Quality of Sleep

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[65] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.423 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.308 |
| upper limit | 3.539 |

Notes:

[65] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

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

Statistical analysis description:

Week 8: Quality of Sleep

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[66] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.291 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.31 |
| upper limit | 3.251 |

Notes:

[66] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

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

Statistical analysis description:

Week 12: Quality of Sleep

| | |
|-------------------|------------------------|
| Comparison groups | Placebo v Fezolinetant |
|-------------------|------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[67] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.433 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.334 |
| upper limit | 3.532 |

Notes:

[67] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 7 |
| Statistical analysis description: Week 4: Awake Following Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.059 ^[68] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.877 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.034 |
| upper limit | 1.789 |

Notes:

[68] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 8 |
| Statistical analysis description: Week 8: Awake Following Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[69] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.457 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.579 |
| upper limit | 2.335 |

Notes:

[69] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| Statistical analysis title | Statistical Analysis 9 |
|---|-------------------------|
| Statistical analysis description: Week 12: Awake Following Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.031 ^[70] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.113 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.107 |
| upper limit | 2.12 |

Notes:

[70] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| Statistical analysis title | Statistical Analysis 10 |
|---|-------------------------|
| Statistical analysis description: Week 4: Behaviour Following Wakening | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.008 ^[71] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.203 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.317 |
| upper limit | 2.088 |

Notes:

[71] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| Statistical analysis title | Statistical Analysis 11 |
|---|-------------------------|
| Statistical analysis description: Week 8: Behaviour Following Wakening | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[72] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.597 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.639 |
| upper limit | 2.556 |

Notes:

[72] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
| Statistical analysis description: Week 12: Behaviour Following Sleep | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.084 ^[73] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.842 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.116 |
| upper limit | 1.8 |

Notes:

[73] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline LSEQ as covariate.

Secondary: Change From Baseline in Greene Climacteric Scale (GCS) at Weeks 4, 8 and 12

| | |
|-----------------|---|
| End point title | Change From Baseline in Greene Climacteric Scale (GCS) at Weeks 4, 8 and 12 |
|-----------------|---|

End point description:

The GCS was a 21-item scale which provides a brief but comprehensive and valid measure of climacteric symptomatology. Each item was rated by the participant according to its severity using a four-point rating scale from 0 (none) to 3 (severe). The first 20 items of the scale combine into three main independent symptom measures: psychological symptoms (items 1 to 11; score 0 to 33), physical symptoms (items 12 to 18; score 0 to 21), and vasomotor symptoms (items 19 to 20; score 0 to 6), by summing up the individual item scores. Item 21 is a probe for sexual dysfunction (Loss of interest in sex). The total score ranges from 0 to 63. Higher scores indicate worse symptoms.

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 40 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Loss of Interest in Sex (n=41, n=40) | -0.4 (± 0.67) | -0.5 (± 0.88) | | |
| Week 8: Loss of interest in Sex (n=39, n=39) | -0.5 (± 0.85) | -0.7 (± 1.15) | | |
| Week 12: Loss of Interest in Sex (n=39, n=39) | -0.4 (± 0.75) | -0.6 (± 1.14) | | |
| Week 4: Psychological (n=41, n=39) | -2.3 (± 5.22) | -5.3 (± 5.97) | | |
| Week 8: Psychological (n=39, n=38) | -2.6 (± 5.31) | -6.7 (± 6.49) | | |
| Week 12: Psychological (n=38, n=39) | -2.9 (± 5.14) | -6.6 (± 6.03) | | |
| Week 4: Physical (n=39, n=38) | -2.1 (± 3.68) | -1.2 (± 2.71) | | |
| Week 8: Physical (n=37, n=38) | -1.9 (± 3.46) | -1.9 (± 3.09) | | |
| Week 12: Physical (n=38, n=37) | -2.4 (± 3.80) | -1.9 (± 3.32) | | |
| Week 4: Vasomotor (n=43, n=40) | -1.1 (± 1.79) | -3.3 (± 1.83) | | |
| Week 8: Vasomotor (n=39, n=39) | -1.7 (± 2.23) | -3.6 (± 1.48) | | |
| Week 12: Vasomotor (n=40, n=39) | -1.5 (± 2.31) | -3.6 (± 1.37) | | |
| Week 4: Total Symptom Score (n=37, n=35) | -5.5 (± 9.33) | -9.9 (± 9.24) | | |
| Week 8: Total Symptom Score (n=34, n=35) | -5.8 (± 8.89) | -13.1 (± 10.68) | | |
| Week 12: Total Symptom Score (n=36, n=35) | -6.3 (± 8.87) | -13.1 (± 10.04) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Week 4: Loss of Interest in Sex | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.881 ^[74] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.3 |

Notes:

[74] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| Statistical analysis title | Statistical Analysis 3 |
|---|-------------------------|
| Statistical analysis description: Week 12: Loss of Interest in Sex | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.301 ^[75] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.2 |

Notes:

[75] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| Statistical analysis title | Statistical Analysis 2 |
|--|-------------------------|
| Statistical analysis description: Week 8: Loss of Interest in Sex | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.383 ^[76] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.2 |

Notes:

[76] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| Statistical analysis title | Statistical Analysis 7 |
|---|------------------------|
| Statistical analysis description: Week 4: Physical | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.732 ^[77] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.9 |

Notes:

[77] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 6 |
| Statistical analysis description: | |
| Week 12: Psychological | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 ^[78] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.2 |
| upper limit | -1 |

Notes:

[78] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 5 |
| Statistical analysis description: | |
| Week 8: Psychological | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 ^[79] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.4 |
| upper limit | -1.2 |

Notes:

[79] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Week 4: Psychological | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 ^[80] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.5 |
| upper limit | -0.4 |

Notes:

[80] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 8 |
| Statistical analysis description: | |
| Week 8: Physical | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.282 ^[81] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 0.6 |

Notes:

[81] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 13 |
| Statistical analysis description: | |
| Week 4: Total Symptom Score | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.013 ^[82] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.2 |
| upper limit | -1 |

Notes:

[82] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Week 12: Physical | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.254 ^[83] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | 0.5 |

Notes:

[83] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
| Statistical analysis description: | |
| Week 4: Vasomotor | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[84] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | -1.4 |

Notes:

[84] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| Statistical analysis title | Statistical Analysis 11 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 8: Vasomotor | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[85] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | -1.1 |

Notes:

[85] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| Statistical analysis title | Statistical Analysis 12 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 12: Vasomotor | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[86] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.6 |
| upper limit | -1.3 |

Notes:

[86] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| Statistical analysis title | Statistical Analysis 14 |
|-----------------------------------|-------------------------|
| Statistical analysis description: | |
| Week 8: Total Symptom Score | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[87] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.7 |
| upper limit | -3.1 |

Notes:

[87] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
| Statistical analysis description: Week 12: Total Symptom Score | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[88] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.9 |
| upper limit | -2.8 |

Notes:

[88] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline GCS as covariate.

Secondary: Change From Baseline in Sheehan Disability Scale (SDS) at Weeks 4, 8 and 12

| | |
|-----------------|---|
| End point title | Change From Baseline in Sheehan Disability Scale (SDS) at Weeks 4, 8 and 12 |
|-----------------|---|

End point description:

The SDS was a composite of 3 self-rated items designed to measure the extent to which 3 major sectors in a participant's life are impaired by panic, anxiety, phobic, or depressive symptoms. The participant rates the extent to which his/her 1- work/school, 2- social life, and 3- family life are impaired by his/her symptoms on a 10-point visual analog scale. The 3 items could be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). Higher scores indicate significant functional impairment.

ITT population with available data at specified time point.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: Baseline and weeks 4, 8 and 12 | |

| End point values | Placebo | Fezolinetant | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 40 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week (Wk) 4: Work/School (n=35, n=38) | -1.3 (± 2.43) | -3.6 (± 2.78) | | |
| Week 8: Work/School (n=34, n=35) | -1.7 (± 2.56) | -4.4 (± 2.43) | | |
| Week 12: Work/School (n=35, n=36) | -1.8 (± 2.76) | -4.3 (± 2.47) | | |
| Week 4: Social Life (n=42, n=40) | -1.2 (± 2.35) | -3.3 (± 2.60) | | |
| Week 8: Social Life (n=39, n=40) | -1.3 (± 2.57) | -3.8 (± 2.79) | | |
| Week 12: Social Life (n=40, n=40) | -1.5 (± 2.55) | -3.6 (± 2.51) | | |
| Wk 4:Family Life/Home Responsibilities(n=42,n=40) | -1.5 (± 2.70) | -3.3 (± 2.97) | | |
| Wk 8:Family Life/Home Responsibilities(n=39,n=40) | -1.7 (± 2.64) | -4.0 (± 2.83) | | |
| Wk 12:Family Life/Home Responsibilities(n=40,n=40) | -1.7 (± 2.38) | -3.7 (± 2.65) | | |
| Week 4: Global Functional Impairment (n=35, n=38) | -3.7 (± 5.50) | -9.6 (± 6.99) | | |
| Week 8: Global Functional Impairment (n=34, n=35) | -4.5 (± 6.87) | -12.3 (± 6.42) | | |
| Week 12: Global Functional Impairment (n=35, n=36) | -4.8 (± 6.49) | -11.8 (± 6.35) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|-------------------------|
| Statistical analysis description: | |
| Week 4: Work/School | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[89] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | -0.8 |

Notes:

[89] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 8: Work/School

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[90] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | -1.3 |

Notes:

[90] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 8: Social Life

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[91] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | -1.1 |

Notes:

[91] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 4: Social Life

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[92] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | -0.6 |

Notes:

[92] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 12: Work/School

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[93] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.6 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | -0.8 |

Notes:

[93] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 12: Social Life

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[94] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.6 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | -0.7 |

Notes:

[94] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 4: Global Functional Impairment

| | |
|-------------------|------------------------|
| Comparison groups | Placebo v Fezolinetant |
|-------------------|------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[95] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | -2 |

Notes:

[95] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 4: Family Life/Home Responsibilities

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 ^[96] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | -0.4 |

Notes:

[96] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 8: Family Life/Home Responsibilities

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[97] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | -0.9 |

Notes:

[97] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

| Statistical analysis title | Statistical Analysis 9 |
|---|-------------------------|
| Statistical analysis description: Week 12: Family Life/Home Responsibilities | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[98] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | -0.7 |

Notes:

[98] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

| Statistical analysis title | Statistical Analysis 11 |
|---|-------------------------|
| Statistical analysis description: Week 8: Global Functional Impairment | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[99] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8 |
| upper limit | -3.6 |

Notes:

[99] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

| Statistical analysis title | Statistical Analysis 12 |
|--|-------------------------|
| Statistical analysis description: Week 12: Global Functional Impairment | |
| Comparison groups | Placebo v Fezolinetant |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[100] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.8 |
| upper limit | -2.8 |

Notes:

[100] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

Secondary: Change From Baseline in Sheehan Disability Scale (SDS) at Weeks 4, 8 and 12 (Days Lost and Days Unproductive)

| | |
|-----------------|---|
| End point title | Change From Baseline in Sheehan Disability Scale (SDS) at Weeks 4, 8 and 12 (Days Lost and Days Unproductive) |
|-----------------|---|

End point description:

The SDS was a composite of 3 self-rated items designed to measure the extent to which 3 major sectors in a participant's life are impaired by panic, anxiety, phobic, or depressive symptoms. The participant rates the extent to which his/her 1- work/school, 2- social life, and 3- family life are impaired by his/her symptoms. In addition to the 3 items, the participants were asked two questions

Days Lost: On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities?

Day Unproductive: On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced?

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and weeks 4, 8 and 12

| End point values | Placebo | Fezolinetant | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Days Lost (n=27, n=25) | -0.2 (± 1.27) | 0.0 (± 0.73) | | |
| Week 8: Days Lost (n=29, n=27) | -0.3 (± 0.81) | 0.0 (± 0.00) | | |
| Week 12: Days Lost (n=26, n=27) | -0.2 (± 1.18) | 0.0 (± 0.00) | | |
| Week 4: Days Unproductive (n=27, n=26) | -0.8 (± 2.83) | -1.7 (± 2.67) | | |
| Week 8: Days Unproductive (n=29, n=28) | -1.2 (± 3.10) | -2.0 (± 2.55) | | |
| Week 12: Days Unproductive (n=26, n=28) | -1.4 (± 2.82) | -2.2 (± 2.59) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--------------------------|
| Statistical analysis description: | |
| Week 4: Days Lost | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.936 ^[101] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 0.6 |

Notes:

[101] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------|
| Statistical analysis description: | |
| Week 8: Days Lost | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.884 ^[102] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.1 |

Notes:

[102] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

| Statistical analysis title | Statistical Analysis 6 |
|---|--------------------------|
| Statistical analysis description: | |
| Week 12: Days Unproductive | |
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 ^[103] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -0.8 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | 0 |

Notes:

[103] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 4: Days Unproductive

| | |
|---|--------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.052 ^[104] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -0.9 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 0 |

Notes:

[104] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 8: Days Unproductive

| | |
|---|-------------------------|
| Comparison groups | Placebo v Fezolinetant |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.06 ^[105] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -0.9 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | 0 |

Notes:

[105] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

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

Statistical analysis description:

Week 12: Days Lost

| | |
|-------------------|------------------------|
| Comparison groups | Placebo v Fezolinetant |
|-------------------|------------------------|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.124 ^[106] |
| Method | ANCOVA |
| Parameter estimate | LS Mean difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.1 |

Notes:

[106] - Least square mean difference versus placebo, obtained from an ANCOVA model with treatment group as fixed effect and baseline SDS as covariate.

Secondary: Change From Baseline in Plasma Concentration of Luteinizing Hormone (LH)

| | |
|-----------------|--|
| End point title | Change From Baseline in Plasma Concentration of Luteinizing Hormone (LH) |
|-----------------|--|

End point description:

Change From baseline in plasma concentration of LH was reported.

Safety population with available data at specified time point.

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

End point timeframe:

Baseline and week 4: pre-dose, week 8:pre-dose, week 12:pre-dose, week 12: 3h, follow-up (week 15)

| End point values | Placebo | Fezolinetant | | |
|--|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: international unit per liter (IU/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Pre-dose (n=43, n=42) | -2.34 (± 9.350) | -8.84 (± 10.865) | | |
| Week 8: Pre-dose (n=40, n=40) | -3.86 (± 9.838) | -9.46 (± 13.647) | | |
| Week 12: Pre-dose (n=40, n=40) | -4.61 (± 13.304) | -9.72 (± 12.834) | | |
| Week 12: 3 hours (h) (n=40, n=40) | -7.16 (± 13.009) | -21.78 (± 11.923) | | |
| Week 15 (n=43, n=42) | -6.16 (± 14.197) | -3.33 (± 11.742) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Follicle-Stimulating

Hormone (FSH)

| | |
|-----------------|--|
| End point title | Change From Baseline in Plasma Concentration of Follicle-Stimulating Hormone (FSH) |
|-----------------|--|

End point description:

Change From baseline in plasma concentration of FSH was reported.

Safety population with available data at specified time point.

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

End point timeframe:

Baseline and week 4: pre-dose, week 8:pre-dose, week 12:pre-dose, week 12:3h, follow-up (week 15)

| End point values | Placebo | Fezolinetant | | |
|--------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: IU/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Pre-dose (n=43, n=41) | -5.80 (± 19.430) | -3.44 (± 18.026) | | |
| Week 8: Pre-dose (n=40, n=40) | -6.60 (± 20.086) | -10.36 (± 23.943) | | |
| Week 12: Pre-dose (n=40, n=40) | -7.05 (± 19.978) | -10.51 (± 24.521) | | |
| Week 12: 3h (n=40, n=40) | -8.47 (± 19.159) | -19.48 (± 22.734) | | |
| Week 15 (n=43, n=42) | -6.50 (± 21.011) | -6.97 (± 22.273) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Estradiol (E2)

| | |
|-----------------|--|
| End point title | Change From Baseline in Plasma Concentration of Estradiol (E2) |
|-----------------|--|

End point description:

Change From baseline in plasma concentration of E2 was reported.

Safety population with available data at specified time point.

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

End point timeframe:

Baseline and week 4: pre-dose, week 8:pre-dose, week 12:pre-dose, week 12:3h, follow-up (week 15)

| End point values | Placebo | Fezolinetant | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: Picomoles per liter (pmol/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Pre-dose (n=43, n=42) | 18.4 (± 140.36) | -7.3 (± 75.13) | | |
| Week 8: Pre-dose (n=40, n=40) | 26.0 (± 157.18) | 1.0 (± 71.78) | | |
| Week 12: Pre-dose (n=40, n=40) | 32.3 (± 101.87) | 25.5 (± 108.27) | | |
| Week 12: 3h (n=40, n=40) | 26.0 (± 100.33) | 11.5 (± 77.68) | | |
| Week 15 (n=43, n=42) | 37.0 (± 167.37) | 27.9 (± 188.18) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Sex Hormone-Binding Globulin (SHBG)

| | |
|-----------------|---|
| End point title | Change From Baseline in Plasma Concentration of Sex Hormone-Binding Globulin (SHBG) |
|-----------------|---|

End point description:

Change From baseline in plasma concentration of SHBG was reported.

Safety population with available data at specified time point.

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

End point timeframe:

Baseline and week 4: pre-dose, week 8:pre-dose, week 12:pre-dose, week 12:3h, follow-up (week 15)

| End point values | Placebo | Fezolinetant | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: Nanomoles per liter (nmol/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Pre-dose (n=43, n=41) | 0.61 (± 16.260) | -0.47 (± 11.986) | | |
| Week 8: Pre-dose (n=40, n=40) | 5.10 (± 20.713) | -1.37 (± 12.186) | | |
| Week 12: Pre-dose (n=40, n=40) | 1.75 (± 18.090) | 0.36 (± 15.165) | | |
| Week 12: 3h (n=40, n=40) | 1.56 (± 18.658) | -1.49 (± 16.406) | | |
| Week 15 (n=43, n=42) | 1.92 (± 16.341) | -0.86 (± 13.540) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Leptin

| | |
|-----------------|--|
| End point title | Change From Baseline in Plasma Concentration of Leptin |
|-----------------|--|

End point description:

Change From baseline in plasma concentration of leptin was reported.

Safety population with available data at specified time point.

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

End point timeframe:

Baseline and week 4: pre-dose, week 8:pre-dose, week 12:pre-dose, week 12:3h, follow-up (week 15)

| End point values | Placebo | Fezolinetant | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: nanogram per liter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Pre-dose (n=42, n=40) | 1.2436 (± 5.6269) | -2.2185 (± 6.9522) | | |
| Week 8: Pre-dose (n=40, n=40) | 1.6225 (± 7.5029) | -1.7090 (± 6.9716) | | |
| Week 12: Pre-dose (n=40, n=40) | 0.9668 (± 5.4301) | -0.4183 (± 11.0737) | | |
| Week 12: 3h (n=40, n=40) | -2.0755 (± 5.3193) | -4.2085 (± 8.5335) | | |
| Week 15 (n=43, n=42) | -0.9914 (± 14.6660) | -0.6031 (± 8.2519) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Insulin

| | |
|-----------------|---|
| End point title | Change From Baseline in Plasma Concentration of Insulin |
|-----------------|---|

End point description:

Change From baseline in plasma concentration of insulin was reported.

Safety population with available data at specified time point.

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

End point timeframe:

Baseline and week 4: pre-dose, week 8:pre-dose, week 12:pre-dose, week 12:3h, follow-up (week 15)

| End point values | Placebo | Fezolinetant | | |
|---|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: micro units per milliliter (µU/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Pre-dose (n=43, n=41) | -0.2767 (± 3.0971) | -0.7512 (± 3.8798) | | |
| Week 8: Pre-dose (n=40, nn=40) | 0.3525 (± 4.0903) | -0.5325 (± 3.6121) | | |
| Week 12: Pre-dose (n=40, n=40) | -0.0825 (± 3.1593) | 0.1300 (± 4.7942) | | |
| Week 12: 3h (n=40, n=40) | 16.3225 (± 19.0210) | 14.4950 (± 19.2787) | | |
| Week 15 (n=43, n=42) | 0.3256 (± 4.1132) | -0.1595 (± 3.1071) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of C-peptide

| | |
|-----------------|---|
| End point title | Change From Baseline in Plasma Concentration of C-peptide |
|-----------------|---|

End point description:

Change From baseline in plasma concentration of C-peptide was reported.

Safety population with available data at specified time point.

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

End point timeframe:

Baseline and week 4: pre-dose, week 8:pre-dose, week 12:pre-dose, week 12:3h, follow-up (week 15)

| End point values | Placebo | Fezolinetant | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Pre-dose (n=43, n=41) | -0.0465 (± 0.3978) | -0.1463 (± 0.5134) | | |
| Week 8: Pre-dose (n=40, n=40) | -0.0300 (± 0.5273) | -0.1175 (± 0.4750) | | |
| Week 12: Pre-dose (n=40, n=40) | -0.0750 (± 0.5212) | -0.0425 (± 0.7154) | | |
| Week 12: 3h (n=40, n=40) | 2.1325 (± 1.9976) | 2.2875 (± 2.1811) | | |

| | | | | |
|----------------------|-------------------------|-------------------------|--|--|
| Week 15 (n=43, n=42) | -0.0047 (\pm 0.6102) | -0.0095 (\pm 0.4023) | | |
|----------------------|-------------------------|-------------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Glycated hemoglobin (HBA1c)

| | |
|---|---|
| End point title | Change From Baseline in Plasma Concentration of Glycated hemoglobin (HBA1c) |
| End point description: Change From baseline in plasma concentration of HBA1c was reported. | |
| Safety population with available data at specified time point. | |
| End point type | Secondary |
| End point timeframe: Baseline and week 12 | |

| End point values | Placebo | Fezolinetant | | |
|--------------------------------------|----------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 39 | | |
| Units: Percentage of HBA1c | | | | |
| arithmetic mean (standard deviation) | -0.00050000 (\pm 0.003162278) | -0.002307692 (\pm 0.004845800) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AE's)

| | |
|--|---|
| End point title | Number of Participants with Adverse Events (AE's) |
| 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 & 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 in participant 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: An AE observed from first dose date up to end of study. Safety population. | |
| End point type | Secondary |

End point timeframe:

From first dose of study drug until end of the study (Up to week 15)

Treatment (trt)

| End point values | Placebo | Fezolinetant | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 43 | | |
| Units: participants | | | | |
| At least one TEAE | 35 | 29 | | |
| At least one serious TEAE | 1 | 0 | | |
| At least one TEAE leading to death | 0 | 0 | | |
| At least one severe TEAE | 0 | 0 | | |
| At least 1 TEAE for which trt permanently stopped | 0 | 2 | | |
| At least 1 TEAE that was considered trt related | 11 | 13 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Bone Alkaline Phosphatase (BALP) at Week 12

| | |
|-----------------|---|
| End point title | Change From Baseline in Plasma Concentration of Bone Alkaline Phosphatase (BALP) at Week 12 |
|-----------------|---|

End point description:

Change from baseline in plasma concentration of BALP was reported.

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and week 12

| End point values | Placebo | Fezolinetant | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: microgram per milliliter (ug/mL) | | | | |
| arithmetic mean (standard deviation) | 2.9 (± 5.43) | 1.7 (± 3.19) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Carboxy-terminal Telopeptide of Type I Collagen (CTX) at Week 12

| | |
|-----------------|--|
| End point title | Change From Baseline in Plasma Concentration of Carboxy-terminal Telopeptide of Type I Collagen (CTX) at Week 12 |
|-----------------|--|

End point description:

Change from baseline in plasma concentration of CTX was reported.

ITT population with available data at specified time point.

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

End point timeframe:

Baseline and week 12

| End point values | Placebo | Fezolinetant | | |
|--------------------------------------|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | -0.021 (\pm 0.1278) | 0.001 (\pm 0.1356) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until end of the study (Up to week 15)

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

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
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| Dictionary version | 18.0 |
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Reporting groups

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|-----------------------|--------------|
| Reporting group title | Fezolinetant |
|-----------------------|--------------|

Reporting group description:

Participants received 90 mg fezolinetant capsules orally, BID for a period of 12 weeks.

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|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received fezolinetant matching placebo capsules orally, BID for a period of 12 weeks.

| Serious adverse events | Fezolinetant | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 44 (2.27%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Fezolinetant | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 43 (41.86%) | 18 / 44 (40.91%) | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | 2 / 44 (4.55%) | |
| occurrences (all) | 3 | 2 | |
| Nervous system disorders | | | |

| | | | |
|--|--|--|--|
| Headache subjects affected / exposed occurrences (all) | 7 / 43 (16.28%) 10 | 6 / 44 (13.64%) 10 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 0 / 44 (0.00%) 0 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | 0 / 44 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 0 / 43 (0.00%) 0 | 3 / 44 (6.82%) 3 3 / 44 (6.82%) 3 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 3 / 43 (6.98%) 3 | 4 / 44 (9.09%) 4 1 / 44 (2.27%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 10 December 2015 | The overall reason for the revision is to liberalize the participant selection criteria to facilitate recruitment, and to allow for a lower number of subjects to be included in the interim analysis. For a detailed overview of the changes, please refer to the Protocol Amendment section of the full CSR. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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Notes: