



## Clinical trial results:

### A Phase 3b, Randomized, Double-blind, Placebo-controlled, 24-week Study to Assess the Efficacy and Safety of Fezolinetant in Menopausal Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) and Considered Unsuitable for Hormone Replacement Therapy Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2021-001685-38                         |
| Trial protocol           | CZ ES IT HU FI NL NO DE PL DK BE SK BG |
| Global end of trial date | 20 April 2023                          |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 31 March 2024 |
| First version publication date | 31 March 2024 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 2693-CL-0312 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT05033886 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Astellas Pharma Global Development, Inc. (APGD)  |
| Sponsor organisation address | 1 Astellas Way, Northbrook, Illinois, United States, 60062   |
| Public contact               | Clinical Trial Transparency, Astellas Pharma Global Development, Inc., 60062 8008887704, <a href="mailto:astellas.resultsdisclosure@astellas.com">astellas.resultsdisclosure@astellas.com</a>        |
| Scientific contact           | Clinical Trial Transparency, Astellas Pharma Global Development, Inc. (APGD), 60062 8008887704, <a href="mailto:astellas.resultsdisclosure@astellas.com">astellas.resultsdisclosure@astellas.com</a> |

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                       | 20 April 2023 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 20 April 2023 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of fezolinetant 45 milligram (mg) versus placebo on the frequency of moderate to severe Vasomotor Symptoms (VMS) from baseline to week 24

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 08 November 2021 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 5         |
| Country: Number of subjects enrolled | Canada: 86         |
| Country: Number of subjects enrolled | Czechia: 44        |
| Country: Number of subjects enrolled | Denmark: 32        |
| Country: Number of subjects enrolled | Finland: 4         |
| Country: Number of subjects enrolled | France: 2          |
| Country: Number of subjects enrolled | Germany: 23        |
| Country: Number of subjects enrolled | Italy: 5           |
| Country: Number of subjects enrolled | Hungary: 24        |
| Country: Number of subjects enrolled | Netherlands: 12    |
| Country: Number of subjects enrolled | Norway: 4          |
| Country: Number of subjects enrolled | Poland: 94         |
| Country: Number of subjects enrolled | Spain: 42          |
| Country: Number of subjects enrolled | Sweden: 13         |
| Country: Number of subjects enrolled | Türkiye: 16        |
| Country: Number of subjects enrolled | United Kingdom: 47 |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 453 |
| EEA total number of subjects       | 304 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 447 |
| From 65 to 84 years                       | 6   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Female participants aged  $\geq 40$  and  $\leq 65$  years suffering from moderate to severe VMS associated with menopause and unsuitable Hormone Replacement Therapy (HRT) and those who met inclusion criteria and none of the exclusion criteria were enrolled.

### Pre-assignment

Screening details:

Prior to randomization, participants had a screening period during which a maximum 21-day collection of baseline VMS frequency and severity assessments were performed. Participants were stratified by smoking status (Current versus former or never).

### 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          |
| <b>Arm title</b>             | Fezolinetant |

Arm description:

Participants received fezolinetant 45 milligrams (mg) (one 30 mg tablet and one 15 mg tablet) orally once daily for 24 weeks of treatment.

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

Dosage and administration details:

Tablet administered orally once daily for 24 weeks.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Participants received placebo matched to fezolinetant tablets orally once daily for 24 weeks of treatment.

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

Dosage and administration details:

Tablet administered orally once daily for 24 weeks.

| <b>Number of subjects in period 1</b> | Fezolinetant | Placebo |
|---------------------------------------|--------------|---------|
| Started                               | 227          | 226     |
| Completed                             | 202          | 185     |
| Not completed                         | 25           | 41      |
| Consent withdrawn by subject          | 19           | 33      |
| Adverse event, non-fatal              | 2            | 2       |
| Randomized but not treated            | 1            | -       |
| Miscellaneous                         | 2            | -       |
| Lost to follow-up                     | -            | 5       |
| Protocol deviation                    | 1            | 1       |

## Baseline characteristics

### Reporting groups

|  |              |
|--|--------------|
| Reporting group title  | Fezolinetant |
| Reporting group description:   |              |
| Participants received fezolinetant 45 milligrams (mg) (one 30 mg tablet and one 15 mg tablet) orally once daily for 24 weeks of treatment. |              |
| Reporting group title  | Placebo      |
| Reporting group description:   |              |
| Participants received placebo matched to fezolinetant tablets orally once daily for 24 weeks of treatment.                                 |              |

| Reporting group values   | Fezolinetant | Placebo | Total |
|--|--------------|---------|-------|
| Number of subjects   | 227          | 226     | 453   |
| Age categorical  |              |         |       |
| Units: Subjects  |              |         |       |
| Age  |              |         |       |
| Units: years   |              |         |       |
| arithmetic mean  | 54.9         | 54.1    |       |
| standard deviation   | ± 4.8        | ± 4.6   | -     |
| Sex  |              |         |       |
| Units: Subjects  |              |         |       |
| Female   | 227          | 226     | 453   |
| Race   |              |         |       |
| Units: Subjects  |              |         |       |
| Asian  | 1            | 5       | 6     |
| Black or African American  | 4            | 0       | 4     |
| Missing  | 0            | 2       | 2     |
| More Than One Race   | 3            | 0       | 3     |
| Other  | 1            | 1       | 2     |
| White  | 218          | 218     | 436   |
| Smoking status   |              |         |       |
| Current versus former or never smoking status was a stratification factor for randomization.   |              |         |       |
| Units: Subjects  |              |         |       |
| Current  | 36           | 35      | 71    |
| Former/Never   | 191          | 191     | 382   |
| Frequency of Moderate to Severe VMS per 24 hour  |              |         |       |
| The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. Baseline was the average number of moderate to severe VMS per 24 hours based on the non-missing values in the 10 days immediately prior to randomization. Number of participants analyzed is 226 and 226 for fezolinetant and placebo, respectively. One participant was randomized but was not included in the analysis as the participant did not receive study medication. |              |         |       |
| Units: VMS per day   |              |         |       |
| arithmetic mean  | 10.58        | 10.75   |       |
| standard deviation   | ± 3.57       | ± 4.08  | -     |

## End points

### End points reporting groups

|  |              |
|--|--------------|
| Reporting group title  | Fezolinetant |
| Reporting group description:<br>Participants received fezolinetant 45 milligrams (mg) (one 30 mg tablet and one 15 mg tablet) orally once daily for 24 weeks of treatment. |              |
| Reporting group title  | Placebo      |
| Reporting group description:<br>Participants received placebo matched to fezolinetant tablets orally once daily for 24 weeks of treatment.                                 |              |

### Primary: Mean change in the frequency of moderate to severe VMS from baseline at week 24

|  |   |
|--|---|
| End point title  | Mean change in the frequency of moderate to severe VMS from baseline at week 24 |
| End point description:<br>The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness but was able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. Full Analysis Set (FAS) (consisted of all randomized participants who received at least one dose of study intervention) with available data were analyzed. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline, week 24  |   |

| End point values                    | Fezolinetant    | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 176             | 164             |  |  |
| Units: VMS per day                  |                 |                 |  |  |
| least squares mean (standard error) | -8.13 (± 0.25)  | -6.20 (± 0.26)  |  |  |

### Statistical analyses

|   |                            |
|---|----------------------------|
| Statistical analysis title              | Statistical Analysis       |
| Comparison groups                       | Fezolinetant v Placebo     |
| Number of subjects included in analysis | 340                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | MMRM                       |
| Parameter estimate                      | LS mean difference         |
| Point estimate                          | -1.93                      |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -2.64                      |
| upper limit          | -1.22                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.36                       |

Notes:

[1] - The Least Square (LS) Means, standard error (SE) and p-values came from a Mixed Model Repeated Measures (MMRM) analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

### **Secondary: Mean change in the patient-reported sleep disturbance by the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b total score) from baseline at week 24**

|                 |  |
|-----------------|--|
| End point title | Mean change in the patient-reported sleep disturbance by the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b total score) from baseline at week 24 |
|-----------------|--|

End point description:

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

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

End point timeframe:

Baseline, week 24

| <b>End point values</b>             | Fezolinetant    | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 196             | 178             |  |  |
| Units: Score on scale               |                 |                 |  |  |
| least squares mean (standard error) | -7.0 (± 0.5)    | -4.5 (± 0.5)    |  |  |

### **Statistical analyses**

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis   |
| Comparison groups                 | Fezolinetant v Placebo |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 374                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | MMRM                       |
| Parameter estimate                      | LS mean difference         |
| Point estimate                          | -2.5                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -3.9                       |
| upper limit                             | -1.1                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.7                        |

Notes:

[2] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

### Secondary: Mean change in the severity of moderate to severe VMS from baseline at week 24

|                 |  |
|-----------------|--|
| End point title | Mean change in the severity of moderate to severe VMS from baseline at week 24 |
|-----------------|--|

End point description:

Severity of moderate to severe VMS per day was calculated as follows: [(number of moderate Hot Flashes (HFs) × 2) + (number of severe HFs/day × 3)]/number of daily moderate/severe HFs. Moderate VMS was defined as sensation of heat with sweating but able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, causing cessation of activity. Severity was zero for participants that had no moderate or severe VMS. Higher score indicated greater severity. A negative change indicated a reduction/improvement. FAS population with available data was analyzed.

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

End point timeframe:

Baseline, week 24

| End point values                    | Fezolinetant    | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 176             | 164             |  |  |
| Units: Score on scale               |                 |                 |  |  |
| least squares mean (standard error) | -1.01 (± 0.06)  | -0.62 (± 0.06)  |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis   |
| Comparison groups          | Fezolinetant v Placebo |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 340                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | MMRM                       |
| Parameter estimate                      | LS mean difference         |
| Point estimate                          | -0.39                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.57                      |
| upper limit                             | -0.21                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.09                       |

Notes:

[3] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

### Secondary: Mean change in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16 and 20

|                 |  |
|-----------------|--|
| End point title | Mean change in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16 and 20 |
|-----------------|--|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness but was able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. FAS population with available data was analyzed.

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

End point timeframe:

Baseline, weeks 1, 4, 8, 12, 16 and 20

| End point values                    | Fezolinetant    | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 225             | 223             |  |  |
| Units: VMS per day                  |                 |                 |  |  |
| least squares mean (standard error) |                 |                 |  |  |
| Week 1 (n= 225, 223)                | -4.56 (± 0.21)  | -2.36 (± 0.21)  |  |  |
| Week 4 (n= 217, 212)                | -6.79 (± 0.23)  | -4.50 (± 0.24)  |  |  |
| Week 8 (n= 208, 201)                | -7.41 (± 0.25)  | -5.44 (± 0.25)  |  |  |
| Week 12 (n= 203, 185)               | -7.65 (± 0.25)  | -5.69 (± 0.25)  |  |  |
| Week 16 (n= 190, 175)               | -7.70 (± 0.26)  | -5.81 (± 0.26)  |  |  |
| Week 20 (n= 184, 172)               | -8.07 (± 0.25)  | -5.90 (± 0.25)  |  |  |

## Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 1) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 448                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[4]</sup>    |
| P-value                                 | < 0.001                       |
| Method                                  | MMRM                          |
| Parameter estimate                      | LS mean difference            |
| Point estimate                          | -2.2                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -2.78                         |
| upper limit                             | -1.61                         |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.3                           |

Notes:

[4] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 20) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[5]</sup>     |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -2.17                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -2.87                          |
| upper limit                             | -1.48                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.35                           |

Notes:

[5] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 12) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[6]</sup>     |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -1.96                          |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -2.65                      |
| upper limit          | -1.26                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.35                       |

Notes:

[6] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 16) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[7]</sup>     |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -1.88                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -2.6                           |
| upper limit                             | -1.16                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.37                           |

Notes:

[7] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 4) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 448                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[8]</sup>    |
| P-value                                 | < 0.001                       |
| Method                                  | MMRM                          |
| Parameter estimate                      | LS mean difference            |
| Point estimate                          | -2.28                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -2.93                         |
| upper limit                             | -1.63                         |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.33                          |

Notes:

[8] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 8) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 448                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[9]</sup>    |
| P-value                                 | < 0.001                       |
| Method                                  | MMRM                          |
| Parameter estimate                      | LS mean difference            |
| Point estimate                          | -1.97                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -2.66                         |
| upper limit                             | -1.27                         |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.35                          |

Notes:

[9] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

## Secondary: Mean change in severity of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16 and 20

|                 |   |
|-----------------|---|
| End point title | Mean change in severity of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16 and 20 |
|-----------------|---|

End point description:

Severity of moderate to severe VMS per day was calculated as follows: [(number of moderate HFs × 2) + (number of severe HFs/day × 3)]/number of daily moderate/severe HFs. Moderate VMS was defined as sensation of heat with sweating/dampness but was able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, causing cessation of activity. Severity was zero for participants that had no moderate or severe VMS. Higher score indicated greater severity. A negative change indicated a reduction/improvement. FAS population with available data was analyzed.

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

End point timeframe:

Baseline, weeks 1, 4, 8, 12, 16 and 20

| End point values                    | Fezolinetant    | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 223             | 225             |  |  |
| Units: Score on scale               |                 |                 |  |  |
| least squares mean (standard error) |                 |                 |  |  |
| Week 1 (n= 223, 225)                | -0.34 (± 0.02)  | -0.17 (± 0.02)  |  |  |
| Week 4 (n= 217, 212)                | -0.66 (± 0.04)  | -0.30 (± 0.04)  |  |  |
| Week 8 (n= 208, 201)                | -0.83 (± 0.05)  | -0.52 (± 0.05)  |  |  |
| Week 12 (n= 203, 185)               | -0.87 (± 0.05)  | -0.57 (± 0.06)  |  |  |
| Week 16 (n= 190, 175)               | -0.90 (± 0.06)  | -0.62 (± 0.06)  |  |  |

|                       |                     |                     |  |  |
|-----------------------|---------------------|---------------------|--|--|
| Week 20 (n= 184, 172) | -0.98 ( $\pm$ 0.06) | -0.62 ( $\pm$ 0.06) |  |  |
|-----------------------|---------------------|---------------------|--|--|

## Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 1) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 448                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[10]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | MMRM                          |
| Parameter estimate                      | LS mean difference            |
| Point estimate                          | -0.17                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.23                         |
| upper limit                             | -0.1                          |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.03                          |

Notes:

[10] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 4) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 448                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[11]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | MMRM                          |
| Parameter estimate                      | LS mean difference            |
| Point estimate                          | -0.35                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.47                         |
| upper limit                             | -0.24                         |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.06                          |

Notes:

[11] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis (Week 8) |
|-----------------------------------|-------------------------------|

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Fezolinetant v Placebo      |
| Number of subjects included in analysis | 448                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[12]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | MMRM                        |
| Parameter estimate                      | LS mean difference          |
| Point estimate                          | -0.31                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.45                       |
| upper limit                             | -0.17                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.07                        |

Notes:

[12] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 12) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[13]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -0.3                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.45                          |
| upper limit                             | -0.15                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.08                           |

Notes:

[13] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 16) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[14]</sup>    |
| P-value                                 | = 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -0.28                          |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.45                      |
| upper limit          | -0.11                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.08                       |

Notes:

[14] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 20) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[15]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -0.36                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.53                          |
| upper limit                             | -0.19                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.09                           |

Notes:

[15] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

### **Secondary: Mean percent change in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24**

|                 |  |
|-----------------|--|
| End point title | Mean percent change in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24 |
|-----------------|--|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness but was able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. FAS population with available data was analyzed.

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

End point timeframe:

Baseline, weeks 1, 4, 8, 12, 16, 20 and 24



| End point values                    | Fezolinetant    | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 223             | 225             |  |  |
| Units: Percent Change               |                 |                 |  |  |
| least squares mean (standard error) |                 |                 |  |  |
| Week 1 (n= 223, 225)                | -41.19 (± 1.92) | -22.56 (± 1.91) |  |  |
| Week 4 (n= 217, 212)                | -63.01 (± 2.12) | -43.98 (± 2.13) |  |  |
| Week 8 (n= 208, 201)                | -69.27 (± 2.23) | -53.12 (± 2.25) |  |  |
| Week 12 (n= 203, 185)               | -71.18 (± 2.23) | -55.27 (± 2.28) |  |  |
| Week 16 (n= 190, 175)               | -71.75 (± 2.37) | -55.83 (± 2.43) |  |  |
| Week 20 (n= 184, 172)               | -75.49 (± 2.25) | -56.45 (± 2.32) |  |  |
| Week 24 (n= 176, 164)               | -75.66 (± 2.27) | -59.12 (± 2.34) |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis (Week 1) |
|---|-------------------------------|
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 448                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[16]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | MMRM                          |
| Parameter estimate                      | LS mean difference            |
| Point estimate                          | -18.62                        |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -23.95                        |
| upper limit                             | -13.3                         |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 2.71                          |

Notes:

[16] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

| Statistical analysis title | Statistical Analysis (Week 8) |
|----------------------------|-------------------------------|
| Comparison groups          | Fezolinetant v Placebo        |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 448                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[17]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | MMRM                        |
| Parameter estimate                      | LS mean difference          |
| Point estimate                          | -16.15                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -22.38                      |
| upper limit                             | -9.92                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 3.17                        |

Notes:

[17] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 4) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 448                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[18]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | MMRM                          |
| Parameter estimate                      | LS mean difference            |
| Point estimate                          | -19.03                        |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -24.95                        |
| upper limit                             | -13.11                        |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 3.01                          |

Notes:

[18] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 20) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[19]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -19.04                         |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -25.4                      |
| upper limit          | -12.68                     |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 3.23                       |

Notes:

[19] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 16) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[20]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -15.92                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -22.6                          |
| upper limit                             | -9.25                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.39                           |

Notes:

[20] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 24) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[21]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -16.55                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -22.96                         |
| upper limit                             | -10.13                         |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.26                           |

Notes:

[21] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 12) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 448                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[22]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | MMRM                           |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | -15.91                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -22.18                         |
| upper limit                             | -9.64                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.19                           |

Notes:

[22] - The LS Means, SE and p-values came from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline value as covariates, treatment group by week and baseline value by week as interaction terms.

### **Secondary: Number of participants with percent reduction of $\geq 50\%$ in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24**

|                 |   |
|-----------------|---|
| End point title | Number of participants with percent reduction of $\geq 50\%$ in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24 |
|-----------------|---|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness but was able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. FAS population.

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

End point timeframe:

Baseline, weeks 1, 4, 8, 12, 16, 20 and 24

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Fezolinetant    | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 226             | 226             |  |  |
| Units: Participants         |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Week 1                      | 95              | 33              |  |  |
| Week 4                      | 148             | 100             |  |  |
| Week 8                      | 149             | 117             |  |  |
| Week 12                     | 154             | 106             |  |  |

|         |     |     |  |  |
|---------|-----|-----|--|--|
| Week 16 | 140 | 107 |  |  |
| Week 20 | 149 | 101 |  |  |
| Week 24 | 137 | 104 |  |  |

## Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 8) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[23]</sup>   |
| P-value                                 | = 0.003                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 1.798                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 1.231                         |
| upper limit                             | 2.637                         |

Notes:

[23] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 12) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[24]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.421                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.653                          |
| upper limit                             | 3.568                          |

Notes:

[24] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis (Week 16) |
| Comparison groups                 | Fezolinetant v Placebo         |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 452                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[25]</sup> |
| P-value                                 | = 0.002                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.812                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.248                       |
| upper limit                             | 2.642                       |

Notes:

[25] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 4) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[26]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 2.386                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 1.636                         |
| upper limit                             | 3.499                         |

Notes:

[26] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 20) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[27]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.403                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.645                          |
| upper limit                             | 3.53                           |

Notes:

[27] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 1) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[28]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 4.377                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 2.792                         |
| upper limit                             | 7.005                         |

Notes:

[28] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 24) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[29]</sup>    |
| P-value                                 | = 0.002                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 1.815                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.249                          |
| upper limit                             | 2.647                          |

Notes:

[29] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

### **Secondary: Number of participants with percent reduction of $\geq 75\%$ in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24**

|                 |   |
|-----------------|---|
| End point title | Number of participants with percent reduction of $\geq 75\%$ in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24 |
|-----------------|---|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness but was able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. FAS population.

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

End point timeframe:

Baseline, weeks 1, 4, 8, 12, 16, 20 and 24

| End point values            | Fezolinetant    | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 226             | 226             |  |  |
| Units: Participants         |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Week 1                      | 35              | 5               |  |  |
| Week 4                      | 90              | 39              |  |  |
| Week 8                      | 104             | 69              |  |  |
| Week 12                     | 110             | 66              |  |  |
| Week 16                     | 104             | 67              |  |  |
| Week 20                     | 109             | 66              |  |  |
| Week 24                     | 106             | 67              |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis (Week 1) |
|---|-------------------------------|
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[30]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 8.361                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 3.49                          |
| upper limit                             | 24.82                         |

Notes:

[30] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

| Statistical analysis title              | Statistical Analysis (Week 4) |
|---|-------------------------------|
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[31]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 3.177                         |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 2.065   |
| upper limit         | 4.958   |

Notes:

[31] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 8) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[32]</sup>   |
| P-value                                 | < 0.001                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 1.936                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 1.318                         |
| upper limit                             | 2.858                         |

Notes:

[32] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical ANalysis (Week 24) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[33]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.099                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.427                          |
| upper limit                             | 3.103                          |

Notes:

[33] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis (Week 16) |
| Comparison groups                 | Fezolinetant v Placebo         |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 452                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[34]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 2.02                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.373                       |
| upper limit                             | 2.987                       |

Notes:

[34] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 20) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[35]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.283                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.547                          |
| upper limit                             | 3.389                          |

Notes:

[35] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 12) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[36]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.298                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.563                          |
| upper limit                             | 3.4                            |

Notes:

[36] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

**Secondary: Number of participants with percent reduction at 100% in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24**

|                 |  |
|-----------------|--|
| End point title | Number of participants with percent reduction at 100% in the frequency of moderate to severe VMS from baseline at weeks 1, 4, 8, 12, 16, 20 and 24 |
|-----------------|--|

End point description:

The frequency of moderate to severe VMS was the number of moderate to severe VMS per 24 hours. A daily frequency per week was derived by taking the mean of the data over 7 days. Moderate VMS was defined as sensation of heat with sweating/dampness but was able to continue activity. Severe VMS was defined as sensation of intense heat with sweating, caused disruption of activity. FAS population.

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

End point timeframe:

Baseline, weeks 1, 4, 8, 12, 16, 20 and 24

| End point values            | Fezolinetant    | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 226             | 226             |  |  |
| Units: Participants         |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Week 1                      | 0               | 0               |  |  |
| Week 4                      | 18              | 8               |  |  |
| Week 8                      | 35              | 17              |  |  |
| Week 12                     | 49              | 22              |  |  |
| Week 16                     | 50              | 27              |  |  |
| Week 20                     | 47              | 27              |  |  |
| Week 24                     | 50              | 24              |  |  |

**Statistical analyses**

|   |                               |
|---|-------------------------------|
| Statistical analysis title              | Statistical Analysis (Week 4) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[37]</sup>   |
| P-value                                 | = 0.049                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 2.365                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 1.037                         |
| upper limit                             | 5.878                         |

Notes:

[37] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 8) |
| Comparison groups                       | Fezolinetant v Placebo        |
| Number of subjects included in analysis | 452                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[38]</sup>   |
| P-value                                 | = 0.009                       |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 2.257                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 1.239                         |
| upper limit                             | 4.259                         |

Notes:

[38] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 12) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[39]</sup>    |
| P-value                                 | < 0.001                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.562                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.506                          |
| upper limit                             | 4.485                          |

Notes:

[39] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 16) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[40]</sup>    |
| P-value                                 | = 0.005                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.088                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.262   |
| upper limit         | 3.52    |

Notes:

[40] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 20) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[41]</sup>    |
| P-value                                 | = 0.013                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 1.928                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.159                          |
| upper limit                             | 3.624                          |

Notes:

[41] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis (Week 24) |
| Comparison groups                       | Fezolinetant v Placebo         |
| Number of subjects included in analysis | 452                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[42]</sup>    |
| P-value                                 | = 0.001                        |
| Method                                  | Regression, Logistic           |
| Parameter estimate                      | Odds ratio (OR)                |
| Point estimate                          | 2.385                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 1.422                          |
| upper limit                             | 4.098                          |

Notes:

[42] - Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of VMS at baseline as a covariate. An odds ratio of > 1 indicated a favorable response in the fezolinetant group.

## Secondary: Number of participants with Treatment Emergent Adverse Events (TEAEs)

|                 |   |
|-----------------|---|
| End point title | Number of participants with Treatment Emergent Adverse Events (TEAEs) |
|-----------------|---|

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 this treatment. An AE can be any unfavorable &

unintended sign, symptom, or disease temporally associated with the use of medicinal product (MP) whether considered related to MP. A TEAE was defined as an AE observed after starting administration of study intervention and up to 21 days after the last dose of study intervention. Safety Analysis set (SAF) consisted of all randomized participants who received at least one dose of study intervention,

|                            |           |
|----------------------------|-----------|
| End point type             | Secondary |
| End point timeframe:       |           |
| From first dose to week 27 |           |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Fezolinetant    | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 226             | 226             |  |  |
| Units: Participants         |                 |                 |  |  |
| number (not applicable)     | 147             | 138             |  |  |

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose to week 27

Adverse event reporting additional description:

SAF population

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

### Dictionary used

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

|                    |       |
|--------------------|-------|
| Dictionary version | v25.0 |
|--------------------|-------|

### Reporting groups

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

Reporting group description:

Participants received fezolinetant 45 mg up to 24 weeks of treatment and a safety follow-up visit 3 weeks after the EOT visit.

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

Reporting group description:

Participants received placebo matched to fezolinetant up to 24 weeks of treatment and a safety follow-up visit 3 weeks after the end of treatment (EOT) visit.

| Serious adverse events                               | Fezolinetant     | Placebo         |  |
|--|------------------|-----------------|--|
| Total subjects affected by serious adverse events    |                  |                 |  |
| subjects affected / exposed                          | 10 / 226 (4.42%) | 8 / 226 (3.54%) |  |
| number of deaths (all causes)                        | 0                | 0               |  |
| number of deaths resulting from adverse events       | 0                | 0               |  |
| Vascular disorders                                   |                  |                 |  |
| Haematoma  |                  |                 |  |
| subjects affected / exposed                          | 0 / 226 (0.00%)  | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Surgical and medical procedures                      |                  |                 |  |
| Hernia hiatus repair                                 |                  |                 |  |
| subjects affected / exposed                          | 1 / 226 (0.44%)  | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| General disorders and administration site conditions |                  |                 |  |
| General physical health deterioration                |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Psychotic disorder                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Hepatic enzyme increased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Spinal column injury                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Coronary artery dissection                      |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental impairment                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial aneurysm                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Enteritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ureterolithiasis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelocystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 226 (0.44%) | 0 / 226 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 226 (0.00%) | 1 / 226 (0.44%) |  |
| 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 %

| <b>Non-serious adverse events</b>                     | Fezolinetant      | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 52 / 226 (23.01%) | 49 / 226 (21.68%) |  |
| Nervous system disorders                              |                   |                   |  |
| Headache  |                   |                   |  |
| subjects affected / exposed                           | 20 / 226 (8.85%)  | 21 / 226 (9.29%)  |  |
| occurrences (all)                                     | 34                | 27                |  |
| General disorders and administration site conditions  |                   |                   |  |
| Fatigue   |                   |                   |  |
| subjects affected / exposed                           | 13 / 226 (5.75%)  | 1 / 226 (0.44%)   |  |
| occurrences (all)                                     | 15                | 1                 |  |
| Infections and infestations                           |                   |                   |  |
| COVID-19  |                   |                   |  |
| subjects affected / exposed                           | 30 / 226 (13.27%) | 29 / 226 (12.83%) |  |
| occurrences (all)                                     | 30                | 29                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 18 March 2022 | Revised Synopsis and Section 4.1 to clarify that participants who discontinue IP early will remain in the study and continue to complete the electronic daily VMS diary and electronic patient-reported outcome (ePRO) assessments as scheduled through week 24, and be monitored for AEs, SAEs and concomitant medications through week 27. Revised Figure 1 Study Schema footnote '*' to clarify that AEs, SAEs and concomitant medications will be monitored continuously from informed consent until the last study-related activity at week 27 for all participants, including participants who discontinue IP early. For participants who discontinued IP early, their week 27 visit can be conducted virtually. Intake of caffeinated beverages will be monitored continuously from informed consent until the safety follow-up visit (i.e., 3 weeks from the last dose). Revised Table 1 SOA footnote 'a' to clarify that participants who discontinue IP early will be monitored for AEs, SAEs and concomitant medications through week 27. Revised Table 1 SOA footnote 'r' to clarify that AEs, SAEs and concomitant medications will be monitored continuously from informed consent until the last study-related activity at week 27 for all participants, including participants who discontinue IP early. For participants who discontinue IP early, their week 27 visit can be conducted virtually. Intake of caffeinated beverages will be monitored continuously from informed consent until the safety follow-up visit (i.e., 3 weeks from the last dose). |
| 18 March 2022 | Revised Section 7.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information to clarify that all AEs and SAEs will be collected for all participants, including participants who discontinue IP early, from signing of the ICF through week 27 at the time points specified in the SOA. Revised Section 8.1 Discontinuation of Individual Participants from Study Treatment to clarify that participants who discontinue IP early will be monitored for AEs, SAEs and concomitant medications through week 27. Revised Section 8.2 Discontinuation of Individual Participant(s) from Study to clarify that all participants who discontinue study treatment will remain in the study to complete the electronic daily VMS diary and ePRO assessments as scheduled through week 24. Participants who discontinue IP early will be monitored for AEs, SAEs and concomitant medications through week 27.<br>Added bullet point to inclusion criterion #3 for hysterectomy without oophorectomy and who meet the biochemical criterion of menopause (FSH > 40 IU/L).  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported