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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	ESN364-HF-204

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ogeda S.A.
Sponsor organisation address	47 Rue Adrienne Bolland, Gosselies, Belgium, 6047
Public contact	Clinical Trial Disclosure, Ogeda S.A., astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Ogeda S.A., astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

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

Arm title	Fezolinetant

Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

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

End point description:

The HF Severity Score by method 2 takes into account moderate and severe HF during a given time period and was calculated as follows
HF Severity score = [(number of moderate HF/day × 2) + (number of severe HF/day × 3)]

The severity of HFs was clinically defined as follows:
- Moderate: Sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets.
- Severe: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).
Higher scores indicate worse symptoms. There is no maximum score since the score was participant-dependent for both number and severity.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

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

End point description:

The weekly HF frequency was calculated as number of mild, moderate and severe hot flashes over the week.
- Mild: sensation of heat without sweating/dampness. If at night, participant didn't wake up but later notices damp sheets or clothing.
- Moderate: Sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets.
- Severe: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).
Higher number of hot flashes is worse.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

End point title	Percentage of Participants With >=70% Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

End point title	Percentage of Participants With >=80% Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 4

Comparison groups	Placebo v Fezolinetant

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

End point title	Percentage of Participants With >=90% Reduction in the Weekly Hot Flash Score From Baseline to Weeks 4, 8 and 12

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 4

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 12

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

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 8

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

Notes:

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

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

End point title	Percentage of Participants With >=50% Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to

	Weeks 4, 8 and 12

End point description:

The weekly HF frequency of moderate and severe HF was calculated as number of moderate and severe HF over the week.
- Moderate: Sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets.
- Severe: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).
Higher number of HF indicates worse symptoms.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 4

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

End point title	Percentage of Participants With >=70% Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to Weeks 4, 8 and 12

End point description:

The weekly HF frequency of moderate and severe HF was calculated as number of moderate and severe HF over the week.
- Moderate: Sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets.
- Severe: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).
Higher number of HF indicates worse symptoms.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 4

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

Notes:

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

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 12

Comparison groups	Placebo v Fezolinetant

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

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 8

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

Notes:

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

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

End point title	Percentage of Participants With >=90% Reduction in the Weekly Frequency of Moderate and severe HF From Baseline to Weeks 4, 8 and 12

End point description:

The weekly HF frequency of moderate and severe HF was calculated as number of moderate and severe HF over the week.
- Moderate: Sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets.
- Severe: Sensation of intense heat with sweating, causing disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., removing layers of clothes, open the window, or get out of bed).
Higher number of HF indicates worse symptoms.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 8

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

Notes:

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

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

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

End point description:

The HFRDIS was a 10-item scale which measured a woman’s perceptions of the degree to which HF interfere with 9 daily life activities (work, social activities, leisure, sleep, mood, concentration, relations with others, sexuality, enjoying life); the 10th item measures interference with overall quality of life. This scale was modeled after items on the Brief Pain Inventory and Brief Fatigue Inventory both of which assessed the extent to which pain or fatigue interfere with daily life. Participants were asked to rate the extent to which HF had interfered with each item during the previous 4-week time interval using a 0 (do not interfere) to 10 (completely interfere) scale. Overall mean score was calculated as sum of items/number of available items. Higher score indicate a higher interference.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 8: Work

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [32]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	-1.42

Notes:

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

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Week 4: Leisure Activities

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [33]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	-1.31

Notes:

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

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 8: Leisure Activties

Comparison groups	Placebo v Fezolinetant

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

Notes:

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

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 12: Leisure Activties

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

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 4: Sleep

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Week 4: Concentration

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

Notes:

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

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Week 4: Mood

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Week 12: Mood

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

Notes:

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

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Week 8: Relations With others

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

Week 12: Sexuality

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

Notes:

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

Statistical analysis title	Statistical Analysis 25

Statistical analysis description:

Week 4: Enjoyment of Life

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

End point description:

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

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Week 4: Quality of Sleep

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [65]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.423
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.308
upper limit	3.539

Notes:

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

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Week 8: Quality of Sleep

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [66]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.291
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	3.251

Notes:

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

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Week 12: Quality of Sleep

Comparison groups	Placebo v Fezolinetant

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Week 12: Behaviour Following Sleep

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

Notes:

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

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

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

End point description:

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

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Week 12: Psychological

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

Notes:

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

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Week 8: Psychological

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 12: Physical

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

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 4: Vasomotor

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Week 12: Total Symptom Score

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

Notes:

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

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

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

End point description:

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

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:	
Week 8: Work/School	
Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [90]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	-1.3

Notes:

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

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Week 8: Social Life	
Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [91]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	-1.1

Notes:

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

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Week 4: Social Life	
Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [92]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.4

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

Notes:

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

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 12: Work/School

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [93]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.8

Notes:

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

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Week 12: Social Life

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [94]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.7

Notes:

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

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 4: Global Functional Impairment

Comparison groups	Placebo v Fezolinetant

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

Notes:

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

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Week 4: Family Life/Home Responsibilities

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

Notes:

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

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Week 8: Family Life/Home Responsibilities

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

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

End point description:

The SDS was a composite of 3 self-rated items designed to measure the extent to which 3 major sectors in a participant's life are impaired by panic, anxiety, phobic, or depressive symptoms. The participant rates the extent to which his/her 1- work/school, 2- social life, and 3- family life are impaired by his/her symptoms. In addition to the 3 items, the participants were asked two questions
Days Lost: On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities?
Day Unproductive: On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced?

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 4, 8 and 12

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Week 4: Days Unproductive

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.052 [104]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0

Notes:

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

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Week 8: Days Unproductive

Comparison groups	Placebo v Fezolinetant
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 [105]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0

Notes:

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

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 12: Days Lost

Comparison groups	Placebo v Fezolinetant

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

Notes:

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

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

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

End point description:

Change From baseline in plasma concentration of LH was reported.

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change From baseline in plasma concentration of E2 was reported.

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Follicle-Stimulating Hormone (FSH)

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

End point description:

Change From baseline in plasma concentration of FSH was reported.

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change From baseline in plasma concentration of SHBG was reported.

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Leptin

End point title	Change From Baseline in Plasma Concentration of Leptin

End point description:

Change From baseline in plasma concentration of leptin was reported.

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Concentration of Insulin

End point title	Change From Baseline in Plasma Concentration of Insulin

End point description:

Change From baseline in plasma concentration of insulin was reported.

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

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

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

Week 15 (n=43, n=42)	-0.0047 (± 0.6102)	-0.0095 (± 0.4023)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Plasma Concentration of Glycated hemoglobin (HBA1c)

End point description:

Change From baseline in plasma concentration of HBA1c was reported.

Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and week 12

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants with Adverse Events (AE's)

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug, & which does not necessarily have to have a causal relationship with treatment. An AE can therefore be any unfavorable & unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with use of a medicinal product (mp) whether or not considered related to the mp. An AE is considered "serious" if it results in death, is life-threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly or birth defect, requires in participant hospitalization or leads to prolongation of hospitalization, hospitalization for treatment/observation/examination caused by AE is to be considered as serious, discontinuation due to increases in liver enzymes, other medically important events. TEAE: An AE observed from first dose date up to end of study. Safety population.

End point type	Secondary

End point timeframe:

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

Treatment (trt)

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change from baseline in plasma concentration of BALP was reported.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and week 12

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change from baseline in plasma concentration of CTX was reported.

ITT population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and week 12

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study drug until end of the study (Up to week 15)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Fezolinetant
Reporting group description: Participants received 90 mg fezolinetant capsules orally, BID for a period of 12 weeks.	
Reporting group title	Placebo
Reporting group description: Participants received fezolinetant matching placebo capsules orally, BID for a period of 12 weeks.	

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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Notes: