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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	2693-CL-0312

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way, Northbrook, Illinois, United States, 60062
Public contact	Clinical Trial Transparency, Astellas Pharma Global Development, Inc., 60062 8008887704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Transparency, Astellas Pharma Global Development, Inc. (APGD), 60062 8008887704, 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	20 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

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)	447
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fezolinetant

Arm description:

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

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

Dosage and administration details:

Tablet administered orally once daily for 24 weeks.

Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

Tablet administered orally once daily for 24 weeks.

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

Baseline characteristics

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

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

End points

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

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

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

Statistical analyses

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, week 24

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

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Fezolinetant v Placebo
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, week 24

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

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Fezolinetant v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	0.7

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

Statistical analysis title	Statistical Analysis (Week 1)
Comparison groups	Fezolinetant v Placebo

Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	-1.61
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Week 20 (n= 184, 172)	-0.98 (± 0.06)	-0.62 (± 0.06)		

Statistical analyses

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

Notes:

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

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

Notes:

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

Statistical analysis title	Statistical Analysis (Week 8)

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

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

Notes:

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

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

Notes:

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

Statistical analysis title	Statistical Analysis (Week 16)
Comparison groups	Fezolinetant v Placebo

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

Statistical analysis title	Statistical Analysis (Week 16)
Comparison groups	Fezolinetant v Placebo

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

Notes:

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

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

Notes:

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

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

Notes:

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

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

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

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug, which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable &

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

End point type	Secondary

End point timeframe:

From first dose to week 27

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose to week 27	
Adverse event reporting additional description:	
SAF population	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	v25.0

Reporting groups	
Reporting group title	Fezolinetant
Reporting group description:	
Participants received fezolinetant 45 mg up to 24 weeks of treatment and a safety follow-up visit 3 weeks after the EOT visit.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to fezolinetant up to 24 weeks of treatment and a safety follow-up visit 3 weeks after the end of treatment (EOT) visit.	

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported